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Advances in cancer treatments have increased the overall five-year survival rate for children and adolescents with cancer to almost 85% (Howlader et al., 2014). However, the use of intensive treatment modalities to improve survival rates has jeopardized health-related quality of life (HRQOL) of survivors of childhood cancer. Survivors of childhood cancers are likely to experience serious or life-threatening late effects (Berk & Meyers, 2015) which can continue into adulthood (Bassal, 2006; Oeffinger et al., 2006). Late effects refer to various health problems in physical, mental, and social domains that occur after completion of cancer treatment (National Cancer Institute, 2016). Several studies of adults with cancer have identified associations between symptom clusters and poor patient outcomes, typically HRQOL (Dodd, Miaskowski, & Paul, 2001a; Kim, Barsevick, Beck, & Dudley, 2012; Miaskowski et al., 2006). There are few studies, however, examining the relationship of symptom clusters and HRQOL in survivors of childhood cancer.

The purpose of this study was to examine the impact of late effects on HRQOL in survivors of childhood cancer. This project investigates the association between subgroup membership based on the impact of late effects on HRQOL using cluster mixture modeling. The revised Dynamic Symptoms Model (Brant, Dudley, Beck, & Miaskowski, 2016) was used as a theoretical framework, which is focused on the relationship between predictors and symptom experience. St. Jude Lifetime Cohort (SJLIFE) study data were used for this analysis. The study participants were diagnosed with childhood cancer and

were treated between 1962 and 2002 at the St. Jude Children's Research Hospital; 3,129 participants were eligible for this study.

Using mixture modeling, a person-centered approach was used. The participants were young adult survivors (the mean age at the time of the survey was 31.0 years), were diagnosed with cancer during childhood (mean age of cancer diagnosis was 8.45 years), and were long-term survivors (mean time since cancer diagnosis was 28.10 years). Participants had various types of cancer including leukemia, lymphoma, sarcoma, and central nervous system tumors. Two distinctive subgroups were identified: the "high symptom cluster" group and the "low symptom cluster" group. Among all participants, pain was the most prevalent symptom (75.5%), and disfigurement (55%) and sensation abnormalities (31.1%) were higher. Several variables were associated with the high symptom cluster. Participants who were more than 40 years old at the time of the survey, female, non-Hispanic white, had less education, were unmarried, and had lower annual income were more likely to be in the high symptom cluster group. Participants who were in the high symptom cluster group reported lower physical and psychosocial HRQOL compared to those in the low symptom cluster group. Several socioeconomic and clinical variables affected HRQOL among participants in this study. In particular, use of certain types of chemotherapy (e.g., cisplatin, carboplatin, or oxaliplatin) was associated with poorer physical HRQOL and better psychosocial HRQOL.

The current study identified symptom cluster groups among young adult survivors of childhood cancers and found meaningful predictors that affect symptom cluster membership and HRQOL outcomes. The findings of this study provide information for

health care providers regarding treatment effects and subsequent HRQOL in children with cancer. These findings could be used as a basis for designing an intervention for individuals in the high symptom cluster group. Future research should include children with cancer who are in the various survivorship periods in order to better understand the relationships between symptom clusters and HRQOL across time.

PHYSICAL AND PSYCHOLOGICAL LATE EFFECTS ON HEALTH-RELATED QUALITY OF LIFE IN LONG-TERM SURVIVORS OF CHILDHOOD CANCER

by

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Approved by

Robin Bartlett
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To My Husband (Haewoong Park), My Father, and Mother for Their Endless Love

APPROVAL PAGE

This dissertation written by HYEWON SHIN has been approved by the following committee of the Faculty of The Graduate School at The University of North Carolina at Greensboro.

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CHAPTER I

INTRODUCTION

Advances in cancer treatments have increased the overall five-year survival rate in the U.S. for children and adolescents with cancer to almost 85% (Surveillance, Epidemiology, and End Results Program, 2010). For example, the five-year survival rate for leukemia, the most common type of cancer in children and adolescents, was 48% in the years 1975 to 1979, but increased to 84% during the years 2003 to 2009 (Ward, DeSantis, Robbins, Kohler, & Jemal, 2014). These remarkable improvements have spurred interest in health-related quality of life (HRQOL) of childhood cancer survivors. Children and adolescents view life differently than adults because they are in different developmental periods, so it is important to understand what quality of life (QOL) means from their perspective (Clarke & Eiser, 2004).

Researchers have examined the prevalence of symptoms or the associations between symptoms and HRQOL in survivors of adolescent cancer (Fernandez-Pineda et al., 2016; Huang et al., 2013; Maurice-Stam, Oort, Last, & Grootenhuis, 2009). Most of the literature reports that survivors of childhood and adolescent cancer have had similar or better QOL than healthy control groups. However, subgroups of survivors report significant psychological distress and poor QOL (Maunsell, Pogany, Barrera, Shaw, & Speechley, 2006; Zeltzer et al., 2008). Adolescent and young adult survivors of childhood cancer are affected by several factors known to reduce QOL, including late effects, low

income, type of cancer, and gender. Female survivors of childhood cancer and adolescent cancer reported lower QOL than male survivors (Maunsell et al., 2006; Zebrack, Yi, Petersen, & Ganz, 2008). Thus, identifying factors related to QOL in survivors of childhood cancer is important in order to help them make effective survivorship plans and achieve optimum health and wellness (Lipscomb, Gotay, & Snyder, 2007). To achieve these goals, data were obtained from the St. Jude Life Cohort Study (SJLIFE). The SJLIFE data were collected from St. Jude Children's Research Hospital and included a large sample size and various variables and health outcomes of childhood cancer survivors, making it an ideal choice for examining these important issues.

Cancer Diagnosis during Childhood and Adolescence

During adolescence, an individual establishes a personal identity, peer relationships and family roles (Mavrides & Pao, 2014). Cancer diagnosis during adolescence is a substantial stressor affecting typical development (Ramini, Brown, & Buckner, 2008). Adolescence is a critical developmental period, so cancer diagnosis during this period can have significant psychosocial impacts during and after cancer treatment. These psychosocial impacts include symptoms of depression, anxiety, post-traumatic stress disorder, distorted self-image, lower self-esteem, and limited social relationships (Essen, Enskär, Kreuger, Larsson, & Sjödén, 2000; Hewitt, Weiner, & Simone, 2003; Panel & Reuben, 2004; Seitz et al., 2010; Zebrack & Chesler, 2001). In order to understand cancer effects during adolescence, and how these effects might be manifested later in life, examining nationwide, longitudinal data can be useful. The National Cancer Institute (NCI) funded a nationwide study in the U.S for childhood

cancer survivors. The project, called the Childhood Cancer Survivors Study (CCSS), is a 26-institution retrospective cohort study including more than 14,000 childhood cancer survivors who were diagnosed between 1970 and 1986, and includes 4,000 of their siblings as a control group (Robison et al., 2009). Several researchers have used CCSS data and found that survivors experienced late effects, psychological symptoms, activity limitations, and functional impairments compared to healthy siblings (Fernandez-Pineda et al., 2016; Florin et al., 2007; Huang et al., 2013; Hudson et al., 2013). In particular, more than 75% of survivors reported at least one late effect, including physical symptoms such as organ damage, obesity, pain, learning problems and secondary cancer (Huang et al., 2013; Hudson et al., 2013). These late effects could affect survivors' HRQOL.

Also, children or adolescents who are diagnosed with cancer need to stay at the hospital where their treatment protocol is based, with stays ranging from several months to a year, which can cause isolation from their peers or school, preventing them from feeling like a "normal" child or adolescent. These survivors, who navigate several developmental tasks during adolescence, might have difficulty forming social relationships, social identity, and achieving physical and cognitive maturation compared to "normal" adolescents (Hudson et al., 2003; Woodgate, 1999). Adolescent cancer survivors report that being independent from their parents is difficult since their parents become overprotective of them after cancer diagnosis (Hokkanen, Eriksson, Ahonen, & Salantera, 2004). Moving toward independence from parents during adolescence is a typical developmental task of this period.

Social support could aid in coping with a cancer diagnosis and treatment in children with cancer. In particular, mothers and peers play an important role (Haluska, Jessee, & Nagy, 2002; Kyngäs et al., 2001; Woodgate, 2006). Previously known friends, who were friends before children or adolescents were diagnosed with cancer, can give greater social support than friends who are made after cancer diagnosis (Woodgate, 2006). This might be because close peers play a role as "shield-peers" when adolescents who have cancer participate in a friends' gathering. The cancer survivors might have concerns when comments about their changed appearances are voiced (Larouche & Chin-Peuckert, 2006).

Adolescence is a period during which individuals experience rapid physical, cognitive, and psychosocial changes (Kim, Koh, & Leventhal, 2005). Adolescents can better understand their prognosis, treatment, and complications than children who have experienced cancer. During adolescence, cognitive abilities transform from concrete operations to formal operations (Inhelder, 1958). Having formal operational functions helps adolescents think abstractly and better understand their treatments and possible complications. This advanced cognitive development in adolescents may engender more anxiety or worry about cancer treatment, complications, and prognosis than would be seen in younger children.

Several studies using the Childhood Cancer Survivor Study (CCSS) and the St. Jude Lifetime Cohort (SJLIFE) study data have made significant contributions to the childhood cancer survivorship literature for those between 0 and 19 years old at the time of their cancer diagnosis (Huang et al., 2013; Hudson et al., 2013; Ness et al., 2013).

Unlike adult cancer patients, survivorship plans for children and adolescent cancer patients need to address unique developmental tasks. Through the current study, subgroups of survivors of childhood cancer will be identified taking into account developmental characteristics, predictors, and consequences of subgroup membership. Individualized survivorship plans, focused on the unique challenges and needs of those surviving childhood cancer, have the potential to improve quality of life for these individuals.

Definitions of Survivors of Childhood Cancer

There are various definitions for survivors of childhood cancer. Researchers have used "young adult survivors of childhood cancer" (Oeffinger et al., 2004; Zebrack, Casillas, Nohr, Adams, & Zeltzer, 2004), "adolescent and young adult survivors of childhood cancer" (Nathan et al., 2013), "adolescent survivors of childhood cancer" (Brinkman et al., 2016), and "survivors of childhood and adolescent cancer" (Mertens et al., 2001; Mulrooney et al., 2009). In 2005-2006, the National Cancer Institute (NCI) addressed survivors of childhood cancer care needs, and identified their cancer characteristics and outcomes of treatment. Many researchers use the definition of adolescent and young adult (AYA) patients as those who were diagnosed with cancer between 15 and 39 years of age. However, this age group includes various types of cancer that may often occur in adults as well as adolescents and children. The types of cancer are different based on an individual's age of cancer diagnosis; for example, the broader age range, extending to 39 years old, includes breast cancer, thyroid cancer, cervical sarcoma, and colorectal carcinoma, common types of cancer for adults (Bleyer,

2007). Acute lymphoblastic leukemia, brain and central nervous system (CNS) tumors, neuroblastoma, and non-Hodgkin's lymphoma are the most common in children, whereas Hodgkin's lymphoma, thyroid carcinoma, brain and CNS tumors, and testicular germ cell tumors are most common in adolescents. Common in both children and adolescents are non-Hodgkin lymphoma, Hodgkin lymphoma, acute lymphocytic leukemia, and bone tumors (Ward et al., 2014).

Late effects and treatment effects might be different based on type of cancer or type of treatment. Thus, it is important to make distinction between different types of cancer based on an individual's age. The Surveillance, Epidemiology, and End Results (SEER) program by NCI defined AYAs as between 15 and 29 years of age because those in this age group have similar biological characteristics. Also, adolescents and adults have different developmental tasks. When survivorship plans are made, it is better to base plans on the unique developmental needs of the individual. Thus, in defining those who were diagnosed during childhood, it is important to consider the age range of persons in that category based on epidemiological findings as well as developmental characteristics. Key terms for the current study were defined.

1) Survivor: In 1986, the National Coalition for Cancer Survivorship (NCCS) used the term "survivors," because at that time cancer was considered a disease to fight. In 2006, the same institution defined the term as a person who had been free of cancer for five years, or someone who was living with cancer (Rowland, Hewitt, & Ganz, 2006). Moreover, NCI used a broader concept of survivor: "An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family

members, friends, and caregivers are also impacted by the survivorship experience and are therefore included in this definition" (NCI website, Office of Cancer Survivorship, 2016). The definition offered by NCI, which includes a broad period from cancer diagnosis to the end of life, was chosen for this research. Cancer diagnosis during childhood might bring dramatic life changes, and the impact persists even after completion of treatment. In addition, survivors of childhood cancer often have a long life after completion of cancer treatment. When clinicians consider survivorship care plans for survivors of childhood cancer, it is necessary to consider the survivors' lives after treatment.

2) Survivors of childhood cancer: Survivors of childhood cancer are defined as those who are diagnosed with childhood-specific cancers and both undergoing cancer treatment or after cancer treatment is complete. In this current study, the term "survivors of childhood cancer" refers to individuals who were diagnosed with cancer when less than 19 years old. Using SJLIFE data, the focus of this study is on survivors between 0 and 19 years old.

3) Late effects: Late effects refer to various health problems including physical, mental, and social aspects of these problems that occur after cancer diagnosis or after completion of cancer treatment. These may be associated with cancer or cancer treatment (NCI, 2016). In this study, symptoms or complications of treatment are interchangeably used with the term "late effects."

Late Effects after Cancer Treatment

Survivors of childhood cancer have experienced a serious, life-threatening disease, and the late effects of their cancer treatment can continue into adulthood (Bassal, 2006; Berk & Meyers, 2015; Oeffinger et al., 2006). The reported late effects include various symptoms such as fatigue and pain, psychological symptoms, and cognitive/memory loss (Arpawong, Oland, Milam, Ruccione, & Meeske, 2013; Larsson, Mattsson, & von Essen, 2010; Meeske, Patel, Palmer, Nelson, & Parow, 2007). According to the SJLIFE study, long-term survivors of childhood cancer suffer from one or more symptoms including pain, cardiac and pulmonary symptoms, learning/memory problems, anxiety, depression, and/or somatization (Huang et al., 2013). In this current study, the impact of late effects of cancer and cancer treatments on HRQOL in survivors of childhood cancer were examined. The late effect(s) or symptom(s) present as single or together. A symptom is defined as a subjective experience about changes in body functioning, sensation, or cognition (Harver & Mahler, 1990). Symptom clusters are defined as two or more related symptoms occurring concurrently, particularly when symptoms are statistically presented together in a group (Barsevick, 2007; Barsevick, Whitmer, Nail, Beck, & Dudley, 2006b; Kim et al., 2012).

Cancer Survivorships and Health-Related Quality of Life (HRQOL)

Considering the role of HRQOL in cancer survivorship is important. In the literature, researchers use QOL and HRQOL interchangeably (Arpawong et al., 2013; Huang et al., 2013; Larsson et al., 2010). Cancer survivorship is a broad concept that includes quality of life. The NCI (2016) emphasized that cancer survivorship research

should incorporate the physical, psychosocial, and economic conditions of survivors after cancer diagnosis and treatments, and it needs to focus on health and life beyond cancer diagnosis and treatments. It also seeks to both prevent and control adverse health outcomes, such as having poorer HRQOL or secondary malignancies. The "Healthy People" series provides ten years of national objectives in order to improve health of all Americans. Healthy People 2020 has a goal to increase the mental and physical HRQOL among cancer survivors (content C-14) (Healthy People, n.d.). In addition, the Children's Oncology Group (2013) has long-term follow-up guidelines for survivors of childhood and adolescent cancer. Although the guidelines consider issues regarding physical and emotional complications after cancer treatment, they do not provide any practical guidelines to measure QOL of survivors. Similarly, the Institute of Medicine (2007) suggested that QOL issues should be addressed in survivorship plans for survivors of adult cancer, yet practical guidelines are not employed. With consistent changes to the definition of HRQOL across time or based on the process of cancer treatment, it is important to regularly assess HRQOL for children with cancer (ranging in age from birth to 19 years old).

Symptom Clusters and Person-Centered Approaches

There have been few studies using symptoms clusters among survivors of childhood cancer. A few studies on adults with cancer have identified an association between experiencing symptom clusters and poor patient outcomes (Barsevick et al., 2006a; Dodd et al., 2001a; Kim et al., 2012; Miaskowski et al., 2006). Some symptom clusters identified in adults with cancer might be similar to the clusters identified among

survivors of childhood cancer. In order to understand the characteristics and the effects of symptom clusters on health outcomes among survivors of childhood cancer, several studies of symptom clusters in adults with cancer were reviewed. For example, Kim and colleagues used the effects of symptom clusters on health outcomes in adults with cancer patients (Kim et al., 2012). Patients reported various symptoms including pain, depressed mood, cognitive disturbance, fatigue, and insomnia, both while undergoing and after cancer treatment. These symptoms were divided into four groups including "all low symptoms," "high fatigue" and "low pain," "high pain," and "all high symptoms." Each subgroup showed differences in health outcomes such as physical performance and symptom burden. Patients in the "high symptoms" group showed the lowest physical performance across time. This finding is applicable for providing information to design interventions for the most vulnerable of groups that has all high symptoms. In addition, it is expected that survivors of childhood cancer might have several types of symptom cluster groups.

The majority of studies of adults with cancer have employed traditional variable-centered approaches such as factor analysis, correlation, and regression. These variable-centered approaches focus on patients' symptoms such as the identification of a pulmonary symptom group and a pain group. However, person-centered approaches are more interested in an individual who experiences symptoms. The subgroups can be categorized into an "all high symptom" subgroup and a "high physical symptoms and low psychological symptoms" subgroup. Thus, employing person-centered approaches could help to determine subgroup membership based on patients' symptoms and the

examination of the relationships between the subgroups and health outcomes (Miaskowski et al., 2006).

Variable-centered approaches describe associations among variables and require an assumption be met that the population is homogeneous regarding the relationships between variables (Laursen & Hoff, 2006). Person-centered approaches describe similarities and differences among individuals while considering how variables relate to each other (Laursen & Hoff, 2006), and assume that the target population is heterogeneous. In prior research, clusters based on reported symptoms have been identified using variable-centered approaches but not based on the individuals who experienced these symptoms using a person-centered approach (Dodd, Cho, Cooper, & Miaskowski, 2010; Masyn, 2013). Some researchers might consider these approaches opposite, but these approaches are complementary (Masyn, 2013). More recently, person-centered approaches, which employ some form of mixture modeling or cluster analysis, have shown great utility in the study of symptom clusters (Dodd et al., 2010; Miaskowski, Aouizerat, Dodd, & Cooper, 2007; Miaskowski et al., 2015). The person-centered approaches allow for the identification of subgroups of patients based on their levels of symptoms. A subgroup can be identified that is at high risk for a more severe symptom experience (Miaskowski et al., 2007).

Studying the impact of late effects on health behaviors beyond HRQOL using a person-centered approach is an important area for study. It could allow for better understanding of unique symptoms of childhood cancer survivors, so that targeted interventions can be developed for this group.

Purpose and Specific Aims

This study is a secondary data analysis using the SJLIFE data. The broad goal of this research is to investigate the impact of late effects on health outcomes (i.e., HRQOL) in survivors of childhood cancer. This project investigates the association between subgroup memberships based on effect of late effects on HRQOL using cluster mixture modeling.

The Specific Aspects of Aims are:

Aim A: to identify homogenous subgroups of survivors who share common profiles across multiple symptom classes including pain, cardiac and pulmonary symptoms, disfigurement, learning/ memory problems, and psychological symptoms (i.e., anxiety, depression, somatization, and global distress).

Aim B: to examine demographic and clinical factors as predictive of subgroup memberships.

Aim C: to find association between subgroup memberships and HRQOL.

Aim D: to examine the main effects of predictors on HRQOL while considering subgroup membership.

Hypotheses of Aims

Aim A. Several meaningful subgroups of survivors with heterogeneous symptom patterns will be identified (e.g., class 1: high psychological symptoms and high physical-related symptoms; class 2: low psychological symptoms and high physical symptoms; class 3: high psychological symptoms and low physical symptoms; and class 4: low psychological symptoms and low physical symptoms).

Aim B. Demographic or clinical factors will differentially predict subgroup membership. For instance, survivors who experienced amputation due to bone tumor might fall into a subgroup whose members report high physical symptoms and high psychological symptoms (class 1).

Aim C. Survivor membership in the subgroup high physical symptoms and higher psychological symptoms (class 1) will be associated with poorer physical aspects of HRQOL.

Aim D. Subgroup membership has a moderating effect on the relationship between sociodemographic or clinical factors and HRQOL. For example, survivors who belong to the high physical and psychological symptom group (class 1) will have lower income and poorer physical and mental HRQOL.

Dynamic Symptoms Model

A symptom is defined as a subjective experience about changes in body functioning, sensation, or cognition (Harver & Mahler, 1990). Symptom clusters are defined as two or more related symptoms occurring concurrently (Barsevick et al., 2006b; Kim et al., 2012). Survivors of childhood cancer are at risk of experiencing various symptoms (i.e., late effects) from their cancer treatment, and these symptoms could affect their health outcomes. With a focus on how to explain levels or clusters of symptoms with regard to health outcomes, the revised Dynamic Symptoms Model (Brant, Dudley, Beck, & Miaskowski, 2016) was chosen as a theoretical framework to guide this study. This model is revised from the symptom management model by the same authors (Brant, Beck, & Miaskowski, 2010). The Dynamic Symptoms Model consists of antecedents

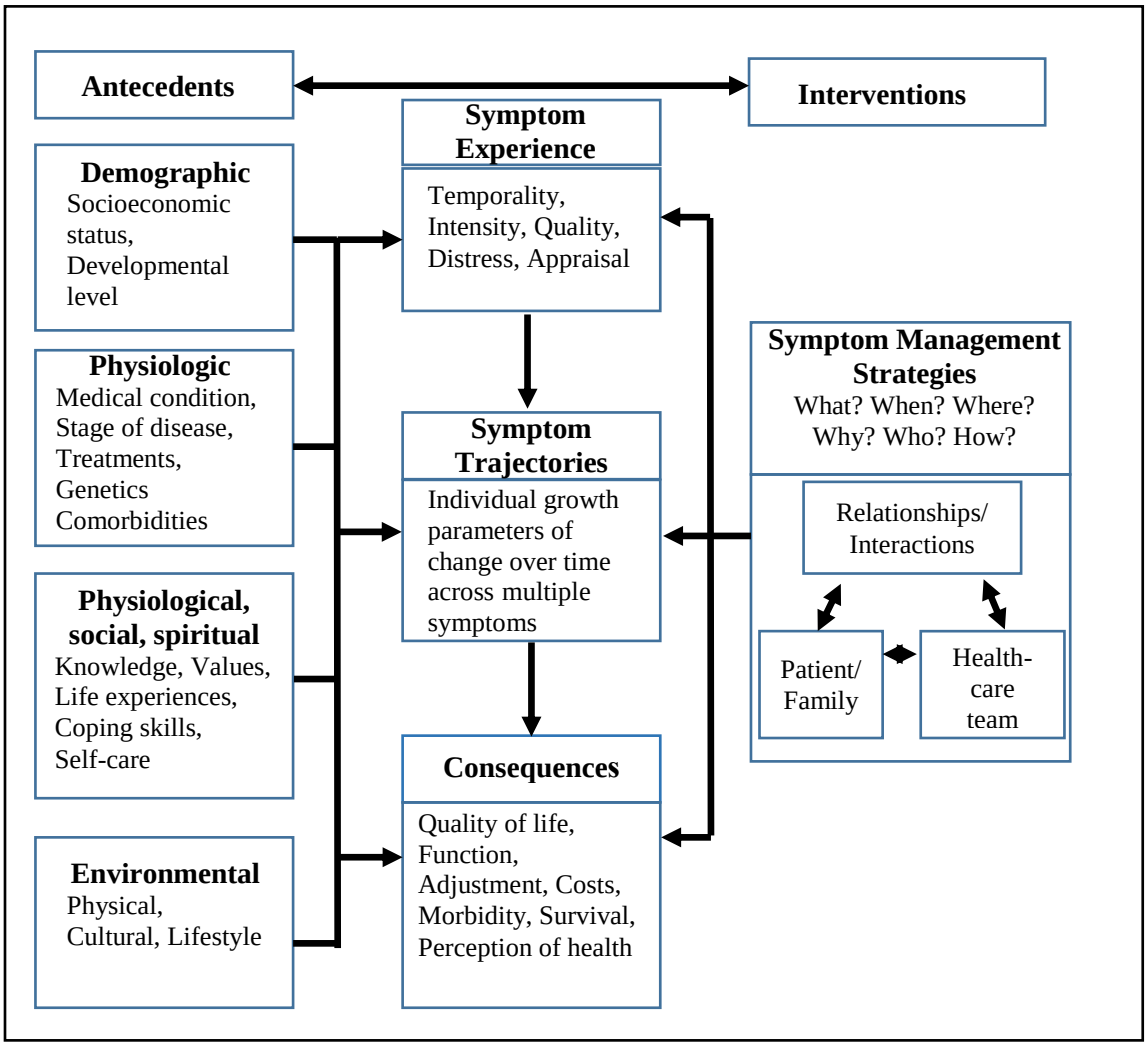
(e.g., age, medical conditions), consequences (e.g., quality of life, functioning), symptom experience over time (e.g., temporality, intensity, quality, and distress), and interventions (see Figure 1). Compared to the original model, the Dynamic Symptoms Model is parsimonious and comprehensively demonstrates the relationships among antecedents, symptoms, and consequences of health outcomes.

Several models have been used to explain the relationship between antecedents, symptoms and consequences. Compared to similar models such as the unpleasant symptoms model (Lenz, Suppe, Gift, Pugh, & Miligan, 1995) and symptom experience model (Armstrong, 2003), the Dynamic Symptoms Model provides a strong foundation for this project because it centers on antecedents of symptoms and articulates direct/indirect relationships between antecedents and consequences of symptoms. Parts of this theory are employed in this project. For example, a *demographic* factor (e.g., age, race, and gender) and a *physiologic* factor (e.g., medical condition, and types of treatment) under four categories of antecedents were used. Late effects (e.g., chronic conditions) were used as *symptom experiences*. The *distress* and *temporality* under *symptom experience* were also used. With regard to *consequences*, quality of life was used as the only outcome variable. In this model, intervention and symptom management strategies were not used. Using the Dynamic Symptoms Model, subgroups of survivors of childhood cancer who have symptom clusters were identified (aim A), demographic and clinical factors as antecedents of subgroup membership were examined (aim B), HRQOL differences between subgroup membership were examined (aim C), and the moderating

effects of subgroup memberships between demographic and clinical factors and HRQOL were examined (aim D).

Figure 1

Dynamic Symptoms Model



Note: Used by permission from the committee member (Dr. Dudley)

Literature Related to Dynamic Symptoms Model

Since the Dynamic Symptoms Model was released in 2016, there have been no reported studies that employed this theory. Therefore similar theories were reviewed that included the concepts of "antecedents" and "symptom clusters" and that examined how the Dynamic Symptoms Model was developed. Kim and colleagues used the Unpleasant Symptoms Model (Lenz et al., 1995) to predict the intensity of cluster symptoms in survivors of breast cancer using a longitudinal design (Kim, Barsevick, & Tulman, 2009). This theory indicates that multiple symptoms can occur at the same time and that various factors (e.g., situational, physiologic, and psychologic) affect symptoms. As a result, those authors identified two groups of predictors of symptom intensity: a psychoneurological symptom cluster and an upper gastrointestinal symptom cluster. Across time, age and treatment modality were consistently significant predictors of the upper gastrointestinal symptom cluster, and baseline physical performance status was a consistent significant predictor of the psychoneurological symptom cluster. For example, young women and women undergoing chemotherapy experienced more intense gastrointestinal symptoms. Patients with better physical performance status reported symptoms of low intensity. Thus, Kim and colleagues (2009) addressed the importance of assessing baseline physical performance status to decrease upper gastrointestinal symptom clusters in patients with cancer.

Outcomes that are considered within the unpleasant symptoms model include function, cognition, and physical performance. The theory is parsimonious and focuses primarily on symptoms and outcomes. However, categories under antecedents and

outcomes of this theory are not well defined (Brant et al., 2010). For example, the situational factors are not defined and performance is the only outcome using this theory. In addition, this theory can describe the relationship between symptoms and outcomes, but it does not address factors that can intervene to decrease patients' symptoms (Brant et al., 2010). The Kim et al. (2009) study showed the relationship between predictors of each symptom cluster; this finding might be helpful in determining which patient is vulnerable to experience a certain symptom cluster. However, as Brant et al. (2010) mentioned, since the definition of each antecedent is not well defined, this theory is not appropriate to use as the current study's framework.

The symptom experience model (Armstrong, 2003) is a complex design and includes detailed factors compared to the unpleasant symptom model. Brant and colleagues used the symptom experience model to explain the antecedents of symptoms and to examine the trajectories of symptoms including fatigue, pain, depression, distress, and sleep disturbance across time (Brant et al., 2011a). Although the symptom experience model does not include trajectories of symptoms, Brant and colleagues used this model to explain antecedents and symptom characteristics (e.g., frequency, intense, distress, and meaning). In addition, this model does not provide for the direct relationship between antecedents and consequences. After the completion of her study, Brant created a modified version of the symptom experience model that includes time trajectories for symptoms (Brant et al., 2010).

In her next study, Brant and her team used the modified version of the symptom experience model. That study's purpose was to examine the trajectories of six common

symptoms during chemotherapy across time (Brant et al., 2011b). Brant and colleagues considered symptoms as changing over time due to interaction with antecedents such as age, gender, or types of treatment. Employing the modified model, they sought to explain the trajectories of symptom clusters over time. Understanding a higher risk group of symptom clusters aids in the development of risk assessment tools and tailored interventions for patients undergoing cancer treatment (Brant et al., 2011b). Based on the modified model, Brant and colleagues created the Dynamic Symptoms Model in 2016 (Brant et al., 2016). The Dynamic Symptoms Model was used to guide the current study; it includes detailed explanations about each antecedent, and direct and indirect relationships between antecedents and consequences. In addition, this model reflects the characteristics of symptoms including a symptom experience factor (e.g., temporality and distress) and a symptom trajectory factor, along with consequences of the symptoms, such as quality of life.

Significance of the Study

This study includes several meaningful aspects that have the potential to improve HRQOL in survivors of childhood cancer. First, this study may fill gaps in symptom cluster identification and further elucidate their impact on HRQOL in survivors of childhood cancer. Several studies have identified subgroup membership of symptoms among adults with cancer, including breast, colon, prostate, or mixed disease groups of patients; however, there are few studies of survivors of childhood cancer. In addition, this study will test a recently developed theory, the dynamic symptoms model, to examine the relationships between demographics, symptom clusters, and quality of life. Using this

theory could help to identify antecedents that promote better HRQOL. Third, this study could provide critical information to the healthcare community that will enable providers to tailor individual survivorship plans for survivors of childhood cancer. HRQOL has multidimensional aspects; identifying symptom clusters associated with better HRQOL may be helpful for designing interventions for vulnerable groups that have severe and multiple symptoms. For example, if pain and fatigue are considered one cluster, targeting decreasing pain may attenuate fatigue as well. Another potential benefit of this study is that the identification of symptom clusters and their effects on HRQOL could be cost-effective for patients and clinicians. It may be possible to detect symptoms early and expect symptoms in advance, allowing for opportunities to reduce related symptoms.

CHAPTER II

REVIEW OF THE LITERATURE

The focus of the current study is to better understand symptoms and symptom clusters among survivors of childhood cancers, and the effect of the symptom clusters on survivors' HRQOL. This chapter examines the literature associated with several factors that are known to affect health-related quality of life (HRQOL) of those with childhood cancer. Assessment of HRQOL in survivors of childhood cancer is important in order to make meaningful survivorship plans. To obtain accurate information about HRQOL based on the survivors' developmental period, the literature was searched separately for adolescents and for children with cancer. Many studies include adolescents as childhood cancer survivors (including those 0 to 18 years old at time of cancer diagnosis). However, combining participants across this broad age range may mask the impact of unique developmental issues that may arise during a cancer diagnosis at vulnerable ages, especially during adolescence. Thus, the literature was searched separately for survivors of adolescent and childhood cancer. Large national studies were also included in order to compare findings with studies that reported relatively small sample sizes.

Late Effects after Cancer Treatment during Childhood and Adolescence

Cancer diagnosis and treatment during childhood and adolescence might result in various late effects. Most children diagnosed with solid tumors are treated with platinum drugs (cisplatin/carboplatin), and/or vinca-alkaloid (vincristine or vinblastine) drugs.

These solid tumors include osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma, and Wilms' tumor. Platinum drugs have complications including acute neuropathy within a short time after cancer treatment (Cavaletti, Alberti, Frigeni, Piatti, & Susani, 2011; Windebank & Grisold, 2008). Also, these drugs have long-term effects that are associated with increased risk of sensory and mobility impairments (Ness et al., 2013). Use of vinca-alkaloid drugs is related to peripheral neuropathy that occurs within several months after cancer treatment. The vinca-alkaloid drugs, often prescribed for a few years to those with acute lymphoblastic leukemia, can cause long-term effects such as mild neuropathy (Lehtinen et al., 2002; Ness et al., 2012; Ramchandren et al., 2009). The long-term effect of neuropathy has been found to be associated with an increased risk of motor impairment (Ness et al., 2013).

Anthracyclines are used in the treatment of various types of childhood cancers. Late cardiotoxicity can occur one year or more after completion of cancer treatment. This cardiotoxicity can include cardiac function abnormalities, dilated cardiomyopathy, and/or heart failure. The risk factors for cardiomyopathy were associated with accumulative doses of anthracyclines and included mediastinal irradiation, young age at exposure, female sex, and time passed after the treatment (Blanco et al., 2011; Mulrooney et al., 2009). Thirty years after treatment, survivors who were treated with a cumulative anthracycline dose ≥ 250 mg/m^2 had a cumulative incidence of congestive heart failure exceeding 7.5% (Mulrooney et al., 2009).

During the 1960s and 1970s, whole-brain radiotherapy was used for childhood leukemia cancer patients to decrease central nervous system cancer relapse. At present,

whole-brain radiotherapy is used only for patients with leukemia who are at high risk of CNS relapse (Pui & Howard, 2008). Survivors of childhood cancer who were treated with ovarian/uterine radiation and received high accumulating doses of alkylating agents or cyclophosphamide (2-3 g/m^2) are at high risk of premature menopause and less likely to become pregnant (Green et al., 2009, 2010; Sklar et al., 2006). Also, leukemia and lymphoma survivors who were treated with brain radiotherapy (dose of $\geq$ 30 Gy) have been found to have an increased risk of stroke compared to their healthy siblings (Bowers et al., 2006). Based on treatment benefits and risks identified over time, radiation treatments dosages and frequencies have been changed for children with cancer.

Findings from an analysis using the nationwide sample in the Childhood Cancer Survivor Study (CCSS) showed the prevalence of late effects and types of late effects experienced by childhood cancer survivors. Several researchers used CCSS data and identified various issues including late effects, health-related quality of life (HRQOL), health behaviors, mortality, and psychosocial effects (Hudson et al., 2003; Maunsell et al., 2006; Zebrack et al., 2002; Zeltzer et al., 2008). Based on the findings of these studies, it is clear that long-term survivors of cancer in childhood and adolescence have a high risk of chronic health conditions. For example, thirty years after cancer diagnosis, the expected rate of chronic health conditions was 73.4% (Oeffinger et al., 2006). In the same study, survivors had eight times increased relative risk of a serious chronic health condition compared to siblings who had not experienced cancer. Similarly, late effects commonly occur long after cancer diagnosis and treatment. According to a recent SJLIFE study, more than 90% of long-term (between 10 to 40 years after cancer diagnosis)

survivors of pediatric cancer suffer from one or more symptoms including pain, cardiac and pulmonary symptoms, learning/memory problems, anxiety, depression, and/or somatization (Huang et al., 2013).

Also, survivors who were treated for specific types of cancer have an increased risk for secondary cancer. Twenty years after cancer diagnosis during childhood, 20% of female survivors who were treated with chest radiotherapy were diagnosed with breast cancer (Bhatia, 2003). In addition, survivors who were treated with chest radiotherapy have a 20% increased risk of coronary artery disease two decades beyond the cancer diagnosis (Reinders et al., 1999). Also, a large cohort study in Britain among Hodgkin disease in childhood survivors found a risk of myocardial infection that was three times higher than in healthy populations (Swerdlow et al., 2007). Similarly, adult males who were treated for testicular cancer in childhood have an increased risk of cardiovascular complications such as hypertension, and they reported complications such as metabolic syndrome and obesity (Huddart et al., 2003; Nuver et al., 2005; van den Belt-Dusebout et al., 2007).

Fortunately, the incidence of late effects can be decreased with prevention strategies such as engaging in healthy behaviors, and the early detection of late effects could decrease their long-term consequences (Tonorezos & Oeffinger, 2011). As previously mentioned, these late effects could occur singly (one symptom) but could also occur concurrently as several symptoms referred to as symptom clusters. A few researchers started examining the concept of symptom clusters to explain relationships between symptoms and health outcomes among adults with cancer (Barsevick et al.,

2006a; Dodd, Dibble, et al., 2001b; Miaskowski et al., 2006). It is important to study symptoms clusters among childhood cancer survivors.

Initially, Dodd and colleagues identified symptom clusters of pain, fatigue, and sleep and their effects on functional health status among cancer patients undergoing cancer treatment (Dodd et al., 2001a). Other researchers identified symptom clusters in adults with various types of cancer (Barsevick et al., 2004; Brant et al., 2011b; Miaskowski et al., 2015) as well as a single type of cancer, including lung, breast, and prostate (Beck, 2012; Dodd et al., 2010; Gold et al., 2016; Legler, Davis, Potosky, & Hoffman, 2004). Symptom clusters varied depending on the characteristics of the symptom clusters. For example, researchers identified a psycho-neurological cluster (i.e., cognitive disturbance, depressed mood, fatigue, insomnia, and pain) (Kim, McDermott, & Barsevick, 2014), symptom experiences cluster (i.e., fatigue, sleep disturbance, depression, and pain) (Miaskowski et al., 2006), and clusters based on anxiety and depression scores (i.e., resilient, subsyndromal, delayed, and peak) (Gold et al., 2016).

To date, most studies on symptom clusters have been related to adults with cancer, but three studies examined symptom clusters in survivors of childhood cancer (Hockenberry, Hooke, McCarthy, & Gregurich, 2011; Mattsson, El-Khouri, Ljungman, & von Essen, 2009; Yeh et al., 2008). These three studies had relatively small samples (less than 150) of survivors of childhood cancer. The way symptom clustering was used varied among the studies: Mattsson et al. (2009) used psychosocial status clustering vitality, mental health, and anxiety and clustered into five groups (Mattsson et al., 2009). Hockenberry and colleagues (2011) used emotional and physical symptoms and clustered

symptoms into two groups including a group with fatigue and depression and a group with gastrointestinal (GI) symptoms and performance status. Yeh and colleagues identified five symptom clusters including symptoms related to sensory discomfort and body image; circulatory and respiratory system malfunction; fatigue, sleep disturbance, and depression; body image and eating difficulties; and gastrointestinal irritations and pain (Yeh et al., 2008).

Each group of researchers found several predictors that were related to each symptom cluster including gender, age, and type of cancer. For example, female survivors were linked to symptom clusters with worse psychosocial functioning (Mattsson et al., 2009) and fewer reported high GI symptoms and pain than male survivors (Yeh et al., 2008). Survivors who were older (current age between 16-19 years old) were associated with worse psychosocial functioning than survivors who were younger (13-15 years old) (Mattsson et al., 2009). Adolescent cancer survivors were linked to clusters with less activity and more sleep disturbance compared to child cancer survivors (10-12 years old) (Hockenberry et al., 2011). The cognitive ability of adolescents compared to children allowed them to understand their disease and recognize side effects of cancer treatment, which might have resulted in fatigue and sleep disturbances (Hockenberry et al., 2011).

Hockenberry et al.'s (2011) study included various types of childhood cancer. Survivors with a bone tumor were associated with a cluster including fatigue and depression, and survivors with solid tumors were linked to a cluster with GI symptoms (vomiting and nausea) and lower performance status (Hockenberry et al., 2011). Patients

with leukemia reported more distress from symptoms in clusters with fatigue, sleep disturbance, and depression than patients with solid tumors or lymphoma. These inconsistent results might have been related to individuals with different types of cancer and treatments. Patients who had solid tumors received repeated intensive chemotherapy in a short amount of time such as six months to one year, whereas leukemia and lymphoma patients typically had intensive chemotherapy for a longer period of up to two years. Thus, patients with solid tumors might have had cumulative chemotherapy effects and a propensity to gastrointestinal problems (Hockenberry et al., 2011). Also, the treatment of leukemia with drugs like corticosteroid medications could have affected survivors' mood and sleep patterns.

Two studies (Hockenberry et al., 2011; Mattsson et al., 2009) categorized symptoms as symptom clusters and examined predictors of symptom clusters, but Yeh et al. (2008) studied the impact of symptom clusters on physical functions. Among five clusters, only the cluster with GI symptoms and pain was associated with good functional status. It was unclear, however, how patients with pain reported good functional status. In the Yeh et al. (2008) study, parents answered questions about functional measurements for their children, so it might have affected results differently than if the child had been the respondent (Yeh et al., 2008). Also, although the measurement was considered a reliable measure of functional status (Yeh & Hung, 2003), it only included a single item (Yeh et al., 2008). In future studies, where possible, standardized measurements and instruments of functional status or HRQOL need to be obtained directly from adolescents or children. These three studies (Hockenberry et al., 2011; Mattsson et al., 2009; Yeh et

al., 2008) did not have a large enough sample size to generalize findings and the studies did not examine the relationship between symptoms clusters and HRQOL in survivors of childhood cancer. The current study examined the effect of both physical and psychological symptom clusters on HRQOL among survivors of childhood cancer.

The purpose of the current study that aimed to identify predictors of HRQOL is in line with the national cancer institute (NCI)'s research guidelines for cancer patients and the U.S. national guidelines to promote health and prevent diseases for Americans (i.e., healthy people 2020), and revealed predictors that could be used to prevent or maintain quality of life among survivors. Thus, before starting this current study, HRQOL-related literature was reviewed in order to better understand HRQOL. The aims for the literature review included (1) identify HRQOL status of survivors of childhood cancer; (2) identify factors that impact HRQOL among demographic or clinical variables; (3) examine other factors besides demographic or clinical variables thought to be significant predicators of HRQOL; and (4) identify appropriate HRQOL measurements for survivors of childhood cancer. This literature review focused on survivors of childhood cancer.

Health-Related Quality of Life

In 1948 the WHO defined health: "a state of complete physical, mental, and social well-being and not merely the absence of disease of infirmity" (WHO, 1948, p.1). In order to measure outcomes of health, health-related quality of life or quality of life has been used. As previously mentioned, the concepts of HRQOL and QOL have been used interchangeably in the literature. However, several researchers have made some distinctions. According to previous studies, quality of life has several key concepts.

Individuals have their own perspectives on QOL which depends on past and present experience and expected hope for the future. In a medical context, QOL is considered to have multidimensional aspects that combine to describe several functions (Aaronson et al., 1991). Also, QOL can include both subjective and objective health status in several domains (Testa & Simonson, 1996). Aaronson and Beckman (1987) defined QOL domains as consisting of four aspects: (a) functional status (e.g., self-care, mobility, physical activities, role activities), (b) disease-related and treatment-related physical symptoms (e.g., pain, nausea), (c) psychological functioning (e.g., anxiety, depression), and (d) social functioning.

HRQOL refers to focus on the impact of health and illness and is distinguished from the broader concept of overall well-being (Eiser, 2007). HRQOL is defined as a multidimensional construct that comprises several domains including physical, social, emotional, and cognitive functioning (Spieth & Harris, 1996). For this current study, HRQOL instead of QOL is used because of its focus on health-related well-being including multidimensional aspects of quality of life. Some researchers have developed HRQOL content and measurements based on this WHO definition while considering multidimensional aspects (Eiser & Morse, 2001; Varni, Seid, & Kurtin, 2001). In addition, the WHO supports a theory of QOL; "the individuals' perceptions in the context of their culture and value systems, in relation to their personal goals, standards, and concerns" (WHOQOL Group, 1994)(p. 24).

Historically, HRQOL research has been mostly limited to adult studies (Huebner, 1991; Veenhoven & den Buitelaar, 1993). However, in the 1990s, researchers began

studying children and adolescents' HRQOL (Gilman & Handwerk, 2001). Unlike adult cancer patients, children and adolescent cancer patients need detailed survivorship plans due to the unique developmental needs of their age. Also, after completion of cancer treatment, several complications can occur in these populations that do not apply to adults who have cancer. Clinicians must recognize that children and adolescents with cancer may have different views on life than adults, and thus it is important to understand what QOL means directly from children and adolescents' perspective (Eiser, 2007; Fayed, Schiariti, Bostan, Cieza, & Klassen, 2011).

Most of the literature reports that survivors of childhood and adolescent cancer have had similar or better QOL statuses compared to healthy control groups. However, a subgroup of survivors reported significant psychological distress and poor QOL (Maunsell et al., 2006; Zeltzer et al., 2008). Several factors are known to affect lower QOL. These include late effects, low income, gender, and type of cancer among survivors of childhood cancer. Late effects include physical symptoms, fatigue and psychological distress (Maunsell et al., 2006; Meeske et al., 2007; Zebrack et al., 2008). However, there is lack of study to examine the relationship between kinds of treatment variables and quality of life among long-term survivors of childhood cancer. Thus, identifying clinical factors related to HRQOL among this population is important to aid clinicians in their decision making and to help survivors understand their survivorship care plans. Further, this could help in the engagement of survivors in following their survivorship plans that will help them to achieve their optimum level of health across their lifespan.

Using appropriate HRQOL measurements for childhood cancer is essential to accurately measure QOL and to understand survivors' unique needs. HRQOL lacks a standard definition and various HRQOL measurements have been used for children and adolescents with cancer without considering their unique needs such as developmental tasks. For example, when children are become adolescents, they need to become independent. Thus, these studies revealed that the act of assessing HRQOL and providing opportunities for the patient to discuss their HRQOL can result in improvement of communication between patients and healthcare providers and increase patient satisfaction, and information gleaned about the patient's HRQOL can provide. Further, this information can aid providers in detecting complications early and it could also help clinicians in their clinical decision making regarding the patient's plan of care (Eiser, 2007; Varni, Burwinkle, & Lane, 2005). Thus, HRQOL concepts should be considered in the design of long-term survivorship care plans for survivors of childhood cancer.

HRQOL among Survivors of Childhood Cancer

HRQOL status as well as HRQOL-related factors among survivors of childhood cancer are described below.

HRQOL Status.

Overall, the majority of survivors of childhood cancer reported physical and psychological HRQOL scores similar to healthy control groups (Castellano-Tejedor et al., 2015; Chan et al., 2014; Larsson et al., 2010; Mannix, Feldman, & Moody, 2009; Mattsson, Ringner, Ljungman, & von Essen, 2007; Mort, Salantera, Matomaki, Salmi, & Lahteenmaki, 2011; Ruccione, Lu, & Meeske, 2013).

However, nearly 20% of the survivors of childhood cancer reported lower psychosocial scores, a higher anxiety level, or having emotional distress than a healthy control group (Ander et al., 2016; Ruccione et al., 2013).

Risk Factors.

Risk factors for poor HRQOL among survivors of childhood cancer include type of cancer, type of treatment, chronic illness, late effects (e.g., symptoms), and patient demographics, including age and gender. For example, survivors of childhood central nervous system (CNS) tumors reported poorer psychological functioning than leukemia survivors (Meeske et al., 2007; Ruccione et al., 2013) and this was found to be negatively associated with the physical functioning of HRQOL (Chan et al., 2014). On the contrary, cancer diagnosis with leukemia was related to protective factors for better HRQOL. Leukemia survivors reported better overall QOL than survivors of other types of childhood cancer (O'Leary, Diller, & Recklitis, 2007), and better physical functioning than those with osteosarcoma (Mört et al., 2011). Leukemia or lymphoma, that were known to have higher survival rates compared to other types of cancer (Howlader et al., 2014), could be related to better HRQOL. Thus, survivors who have CNS tumors are considered more at risk for diminished HRQOL compared to survivors who have leukemia and lymphoma.

***Late effects*.** Potential complications from cancer treatment or late effects have been associated with poor physical functioning including obesity, vision impairment and hearing problems, symptoms (such as pain and nausea), and impaired neurocognitive functioning among survivors of childhood cancer (Arslan, Basbakkal, & Kantar, 2013;

Hocking, Hobbie, Deatrick, Hardie, & Barakat, 2015; Huang et al., 2013; Kazak et al., 2010; Mannix et al., 2009; Maunsell et al., 2006; Maurice-Stam et al., 2009; Rhee et al., 2014). In addition, several factors including fatigue, generalized pain, depression, posttraumatic distress, and sleep disturbance have been found to be related to lower psychological functioning among childhood cancer survivors (Gordijn et al., 2013; Meeske et al., 2007; Ruccione et al., 2013; Rueegg et al., 2013). A recent study examined HRQOL among survivors of adolescent cancer (who were diagnosed from ages 10 to 18 years) using CCSS data, and survivors who experienced disfigurement (e.g., scarring of head or neck) had two times the relative risk of poor HRQOL compared to survivors without disfigurement (Nolan et al., 2014).

Treatment intensity. There are inconsistent findings about the effect of treatment intensity on HRQOL. Treatment intensity indicates level of treatment from least to most intensive and includes treatment modalities based on types and stages of cancer (Werba et al., 2007). Higher treatment intensity has been negatively associated with poorer physical functioning aspect of HRQOL for survivors of child and adolescent cancer for those diagnosed between 10 to 21 years old (Bitsko, Stern, Dillon, Russell, & Laver, 2008; Nolan et al., 2014). Survivors of adolescent cancer who were treated with certain types of chemotherapy (i.e. alkylating agents) or radiation to the pelvis had 1.5 times relative risk of poor HRQOL (Nolan et al., 2014). Further, the intensity of treatment could impact patients' HRQOL and the burden on the patients' families (Kazak et al., 2010). In particular, survivors of childhood cancer who experienced one or more treatment modalities (e.g., radiation, chemotherapy and bone-marrow transplantation) or

experienced radiation therapy or bone marrow transplantation reported worse HRQOL than those treated with surgery only (Kazak et al., 2010). This finding is similar to nationwide studies using CCSS data on long-term survivors of childhood cancer and the participants. These survivors were nearly 20 years beyond their cancer diagnoses (Maunsell et al., 2006; Rueegg et al., 2013; Zeltzer et al., 2008). However, in another study, treatment intensity was not negatively associated with HRQOL among survivors of childhood cancer (Barakat, Marmer, & Schwartz, 2010; Ruccione et al., 2013). The Barakat et al. and Ruccione et al.'s studies included participants with a shorter-term survivorship period (i.e., 6 months to 20 months after cancer diagnosis), which is a shorter period than that of long-term survivors in the Barakat et al. and Ruccione et al. studies (Maunsell et al., 2006; Zeltzer et al., 2008).

According to the definition of late effects by the NCI, the complications of treatments could occur immediately or several years after a cancer diagnosis (NCI, 2016). Since studies on HRQOL in survivors of childhood cancer have used different HRQOL measurements, it is difficult to directly compare these studies' findings (Barakat et al., 2010; Maunsell et al., 2006; Rueegg et al., 2013). Treatment intensity ratings are objective measures, whereas HRQOL ratings are subjective measures and are influenced by multiple factors including emotions, perceptions about the cancer experience, and social support from family or friends (Ruccione et al., 2013).

Gender. Female survivors of adolescent cancer have reported poorer overall HRQOL (Ander et al., 2016; Canning, Bunton, & Talbot Robinson, 2014; Mattsson et al., 2009; Nolan et al., 2014). In particular, in Nolan and colleagues' study, female survivors

had two times relative risk of poorer HRQOL than male survivors. This gender factor is in line with three other studies using the CCSS data that included a nationwide sample of survivors of childhood cancer that received their cancer diagnosis less than 19 years old from CCSS (Maunsell et al., 2006; Zeltzer et al., 2008) and a nationwide sample in Hong Kong (Chan et al., 2014). Female survivors of adolescent cancer (who were diagnosed with cancer between 13 to 19 years old) were found to have higher anxiety levels than male survivors of adolescent cancer immediately after the cancer diagnosis. These anxiety levels decreased to a normal range within four years after the cancer diagnosis (Ander et al., 2016).

In addition, female survivors of childhood cancer are found to have higher psychological HRQOL than healthy siblings (Rueegg et al., 2013). However, gender difference on HRQOL has also been demonstrated in healthy populations. In one study, Mört and colleagues compared HRQOL status between survivors of childhood cancer and a healthy control group. The healthy females in the healthy control group reported lower HRQOL than males (Mört et al., 2011). On the contrary, in another study, gender and age were not associated with HRQOL. The participants were in the early survivorship period (20 months since cancer diagnosis) (Barakat et al., 2010). However, the previously mentioned studies included long-term survivors with an average of 15 years since their cancer diagnosis (Maunsell et al., 2006; Mört et al., 2011; Zeltzer et al., 2008). Thus, according to findings from the examination of large datasets, being a female survivor has a negative effect on HRQOL, short-term and long-term after cancer diagnosis.

Demographic factors in addition to gender. Demographic factors beyond gender have been found to be associated with HRQOL. Several demographic factors were negatively associated with HRQOL in survivors of adolescent cancer including unemployment status, living alone, and low household income (< $20,000) (Nolan et al., 2014). This finding is likely secondary to employment being such an important part of a young adult's life in order to provide financial support, development of a social life, and in order to identify roles in society (Blanc, 2004; Wanberg, 2012).

Protective Factors.

Factors related to better HRQOL in survivors of childhood cancer include time passed since cancer diagnosis, age, education level, subjective feelings such as optimism, happiness and self-concept, social support, and family functioning (Mannix et al., 2009; Ruccione et al., 2013; Spangler, 2009).

Time elapsed. Survivors of adolescent cancer (who were diagnosed with cancer between 13-19 years of age) have reported that their QOL improved with time following their cancer diagnosis (Ander et al., 2016; Jörngården, Mattsson, & von Essen, 2007; Larsson et al., 2010). For example, from six months to two years after cancer diagnosis, survivors demonstrated similar HRQOL to a healthy control group (Arpawong et al., 2013; Jörngården et al., 2007; Ruccione et al., 2013). However, 20% of the survivors had lower psychosocial functioning than the mean of the 'pediatric quality of life psychosocial functioning' measurement (Ruccione et al., 2013). On the contrary, in one study, survivors' HRQOL was lower when compared to a healthy control group in the same time period (Cantrell & Lupinacci, 2008). However, the Cantrell and colleagues

research had a comparatively smaller sample size (n = 35) than the other three studies that included more than 50 participants (Jörngården et al., 2007) and nearly 100 participants (Arpawong et al., 2013 & Ruccione et al., 2013). Generally, the studies with larger sample sizes reported that survivors' HRQOL was comparable to healthy control groups.

Interestingly, four years after cancer diagnosis, survivors reported higher HRQOL than a healthy control group (Ander et al., 2016; Larsson et al., 2010). Similarly, using a longitudinal design comparing survivors of adolescent cancer from six months to ten years after their cancer diagnosis with a healthy control group, the mental summary scores of HRQOL showed no change in this period, but the physical summary score of HRQOL improved over time (Ander et al., 2016). Overall, survivors of adolescent with cancer reported comparable or better physical or psychosocial HRQOL than the healthy control group. In order to confirm these findings, more research is necessary for survivors of childhood cancer between four to ten years after cancer diagnosis.

Age. The age of the adolescent (15-17 years old) has been shown to positively affect psychosocial HRQOL when compared to younger adolescents (younger than 15 years old) among survivors of childhood cancer (Ruccione et al., 2013). However, adult survivors of adolescent cancer (current age 35 and older) reported poorer physical HRQOL compared to younger survivors (current age 25 to 34 years old) (Nolan et al., 2014). This finding might be related to time passed since cancer diagnosis and occurrence of late effects. Ruccione et al.'s study only includes survivors within six months of completion of cancer treatment and Nolan et al.'s study includes survivors more than ten

years after treatment completion. Also, for survivors who early in their survivorship, late effects might not yet have occurred. Long-term effects of cancer treatment could occur decades after cancer diagnosis.

Education. Higher education level is also related to better HRQOL among survivors of childhood cancer. Survivors who had more than a high school education had better physical and psychological summary scores than survivors with less than a high school education in studies with larger sample sizes such as the CCSS or St. Jude Children's Research Hospital study (Huang et al., 2013; Nolan et al., 2014; Zebrack et al., 2002). Higher education might be related to using coping strategies that change negative thoughts about the past cancer experience to more positive thoughts. They might have learned these skills during their education.

Subjective feelings. Higher scores of a happiness measure have been associated with better QOL and fewer depressive symptoms, regardless of cancer treatment, in survivors of childhood cancer (Bitsko et al., 2008; Kazak et al., 2010). Also, some survivors of adolescent cancer (those who were diagnosed with cancer between 13-21 years old) have reported high optimism scores, which was associated with fewer physical symptoms (Mannix et al., 2009). Mannix and colleagues suggested that optimism may play a protective role by preventing painful thoughts and by supporting survivors to cope with their illness.

Perceived social support. Perceived social support from parents and clinicians predicted better psychosocial functioning among survivors of adolescent cancer (those who were diagnosed with cancer between 11 to 21 years old), but did not predict physical

QOL (Spangler, 2009). In particular, treatment-related variables including CNS radiation or bone marrow transplantation have been found to negatively affect physical QOL about three times as much as perceived social support. However, after controlling for the effects of CNS tumor diagnosis and treatment with CNS radiation, perceived social support from parents and psychiatrists did significantly predict better psychosocial HRQOL (Spangler, 2009). This finding indicated the importance of social support from family members and care providers after completion of cancer. Similarly, better family functioning scores and higher parental overprotection scores predicted better psychosocial QOL in survivors of childhood cancer (Barakat et al., 2010). Social support from parents and good communication between parents and their children during cancer treatment has been shown to help these children have better HRQOL (Yeh, 2002). Also, social support from close friends has had mediating effects on the physical functioning aspect of HRQOL (Spangler, 2009). This is due to fact that peer relationships become more important in adolescence. Adolescents spend more time with peers and value peers' opinions (Brown & Larson, 2009).

Ethnicity. There have been a few research studies examining the impact of ethnicity on HRQOL among survivors of childhood and adolescent cancer. However, with such few studies, it is unclear whether ethnicity plays a role in HRQOL, but studies do reveal some relationships (Arpawong et al., 2013; Mannix et al., 2009; Zeltzer et al., 2008). Better HRQOL has been reported among non-Hispanic White survivors of adolescent cancer (Arpawong et al., 2013; Mannix et al., 2009). Similarly, in 7,147 survivors of childhood cancer using the CCSS data, Hispanic cancer survivors reported

more somatization and overall distress scores (i.e., sum of somatization, symptoms of depression, symptoms of anxiety), and they reported poorer scores on the physical and social functioning subscales of HRQOL than non-Hispanic White cancer survivors (Zeltzer et al., 2008). Nolan and colleagues (2014) examined predictors on HRQOL using only survivors of adolescent cancer using the CCSS data (Nolan et al., 2014). They found that Hispanic or other races' cancer survivors (not non-Hispanic Black) have higher risk of poor HRQOL than non-Hispanic White cancer survivors (1.03 and 2.51 respectively). However, in two other studies, Hispanic survivors of adolescent cancer (Mannix et al., 2009) and childhood cancer (Ruccione et al., 2013) reported similar HRQOL to the norm, and they positively rated their overall health (Meeske et al., 2007). These two studies have small sample sizes, less than 100, as compared to the CCSS nationwide sample. Overall, Hispanic survivors of adolescent cancer reported comparable psychosocial functioning scores with the norm, but long-term Hispanic survivors of childhood cancer reported poorer psychosocial functioning and a higher distress level. Post-traumatic growth might explain why some survivors reported good psychological functioning. The cancer experience might be the traumatic event and higher psychosocial functioning could be related to posttraumatic growth (Zeltzer et al., 2008).

Post-traumatic growth occurs when individuals find meaning in traumatic events. As a result, these individuals have higher levels of functioning than which existed prior to the event (Linley & Joseph, 2004; Widows, Jacobsen, Booth-Jones, & Fields, 2005). Non-Hispanic White childhood cancer survivors reported greater post-traumatic growth (PTG) than Hispanic childhood cancer survivors that was positively related to

psychosocial functioning though negatively related to physical functioning (Arpawong et al., 2013). Despite this finding, of the 94 participants, 18% (n = 17) reported lower psychosocial functioning than the norm (Arpawong et al., 2013), and school and emotional functioning was lower in Hispanics than in non-Hispanic cancer survivors (Meeske et al., 2007). This might be related to the fact that Hispanics in the U.S. are generally of lower socioeconomic status than non-Hispanic whites.

Summary of Literature Review on HRQOL.

In this literature review, the current HRQOL status and factors that impact HRQOL among survivors of childhood and adolescent cancer were provided. Overall, except for subgroups of patients, survivors' QOL is comparable to healthy controls. However, the subgroup who experiences lower HRQOL should not be ignored. Ignoring this lower HRQOL in subgroups may lead to an aggravation of their HRQOL or negative impacts on their health outcomes. It is also necessary to think about whether standard HRQOL measurements are appropriate for survivors who are young adults or adolescents. Some researchers have questioned whether a survivor's good HRQOL score was related to measurement issues or to response bias. Thus, these researchers used interviews to verify the HRQOL measurements (Nightingale et al., 2011; Quinn, Huang, Murphy, Zidonik-Eddelton, & Krull, 2013).

In addition, O'Leary et al. (2007) measured self-deception enhancement (SDE) to examine whether survivors of childhood cancer were biased about their cancer-related experience (O'Leary et al., 2007). The SDE measures the possibility that high scoring individuals overestimated their positive attributes due to lack of insight or denial of

current problems. The survivors' mean SDE score was higher (7.5) than the norm (5.8) for both genders, thus 40% of the survivors (43 of 107) were identified as biased respondents. It is important to review the HRQOL measurements used most often for survivors of childhood cancer in order to determine if these measurements are appropriate.

HRQOL Measurement.

QOL assessment in pediatric oncology is an important piece of the cancer survivorship plan (Goodwin, Boggs, & Graham-Pole, 1994). This is because measures of QOL may generate clinical information that could help patients, their parents, and health professionals to make decisions about treatments or alternative therapies. Researchers used literature reviews to determine the best HRQOL measurements for their research purposes and participants' ages. According to Fayed and colleagues' review (2011), a most often used generic measurement of HRQOL is the Child Health Questionnaire, and three most often used measurements that are cancer-specific are the University of Minnesota Minneapolis-Manchester QOL Survey of Health, the PedsQL 3.0 cancer module, and the Pediatric Oncology Quality of Life Scale. Using a systematic review of survivors of childhood cancer, Anthony and colleagues report that the PedsQL-Cancer Module was the most commonly used cancer-specific instrument (Anthony et al., 2014). From these studies, there are no standard measurements for HRQOL in these populations. Thus, it is important to use a standardized measurement of QOL and to use more than one instrument in order to measure QOL comprehensively (Fayed et al., 2011). In addition, measurements should be chosen based on the research purpose (Anthony et al., 2014;

Eiser, 2007). Several researchers have suggested that in general, cancer-specific questionnaires are appropriate to use with cancer patients (Eiser, 2007; Fayed et al., 2011). In addition, generic measures are useful if the research questions intend to make comparisons between cancer survivors and the average population (Eiser, 2007). Several researchers have suggested that QOL is not hypothesized to be measure one dimension, thus, even if a subdomain of QOL has low internal consistency, it may be needed to be included in order to measure overall QOL (Cella & Tulsky, 1990; Goodwin et al., 1994).

Missing Content of Current HRQOL Measurements. Two studies found missing items in HRQOL measurement among young adult survivors of childhood cancer when surveying those between 17 and 37 years old (Nightingale et al., 2011; Quinn et al., 2013). The missing items included perceived sense of self, romantic relationships, fertility/sexual functioning, and spirituality. These unique aspects of HRQOL are needed to comprehensively measure HRQOL among young adult survivors. Researchers can include such items to supplement questionnaires when studying HRQOL. In the current study, SF-36 was used to measure HRQOL without adding supplement questionnaires. Future research should test HRQOL measurements that include these items.

Lack of Survivorship Care.

The earlier referenced Institute of Medicine (IOM) report suggests that all cancer survivors need to get follow-up care to monitor and prevent late effects and manage chronic conditions (Hewitt et al., 2003). In addition, cancer survivors are required to visit long-term follow-up (LTFU) clinics to detect late effects, provide information on health behaviors and access resources related to psychosocial, educational and socioeconomic

support (von der Weid & Wagner, 2003). The Children's Oncology Group's guideline for long-term follow-up care for survivors of childhood, adolescent, and young adult cancers emphasizes health care provider's need to be aware of these late effects and health outcomes (Children's Oncology Group, 2013).

However, according to a nationwide sample of 10,000 childhood cancer survivors using CCSS data, only 42% of survivors visited a hospital to get cancer-related medical treatment within the two years of the research period (Oeffinger & Hudson, 2004), and long-term survivors rarely attended LTFU clinics (Arvidson, Söderhäll, Eksborg, Björk, & Kreuger, 2006; Nathan et al., 2008, 2009). Moreover, non-attenders of long-term clinics were not aware of the necessity to visit clinics (Ford, Chou, & Sklar, 2013).

According to studies about long-term follow-up among childhood cancer survivors in Switzerland, socioeconomic levels, demographic characteristics, and health beliefs including susceptibility, severity of late effects, and benefits to health behaviors affected survivor's attendance rates at LTFU clinics. Also, perceived barriers were significantly associated with attendance at follow-up services (Michel et al., 2011). Younger survivors (less than 25 years old), single, and unemployed survivors with less than a high school education were more likely to attend LTFU clinics. Survivors who were diagnosed when older than 12 years and those who had more risks for complications after their treatments such as having a central nervous system tumor, those receiving radiotherapy, or those experiencing a cancer relapse, were more likely to attend LTFU (Michel et al., 2011).

There are also cultural differences among those attending LTFU. Racial/ethnic minority group members reported lower confidence in their ability to manage their survivorship care than did non-Hispanic White childhood cancer survivors. Minorities including African American and Hispanic childhood cancer survivors' hospital visits rate was 1.5 times lower than non-Hispanic white childhood cancer survivors (Oeffinger & Hudson, 2004). The NCI suggests that cultural differences or socioeconomic factors could lead to health disparities. To decrease health disparities, NCI emphasizes that researchers must identify factors related to disparities in order to develop culturally appropriate approaches for cancer survivors (NCI, 2006). The SJLIFE study includes various ethnic groups including non-Hispanic whites, non-Hispanic blacks, and Hispanics. In the current study their HRQOL based on ethnic differences is revealed.

Current Knowledge Gaps in HRQOL

Among survivors of childhood cancer, protective factors for HRQOL include family functioning, time since cancer diagnosis, subjective feelings such as happiness, optimism, and self-concept, and social support. Risk factors include gender, type of cancer and treatment, and late effects. Identifying these factors could be helpful in detecting vulnerable individuals who might have poorer HRQOL. There is lack of survivorship plans that include regular assessment of HRQOL in young adult survivors of childhood cancer and lack of comprehensive HRQOL instruments that evaluate unique characteristics of this population. The most commonly used measurements are the SF-36 and the Pediatric QL Generic Core Scale to assess multidimensional aspects of HRQOL, but these measurements are not sensitive to estimate developmental characteristics of

these populations. Additional items such as fertility/sexual function and romantic relationships might be added as supplemental questions to better understand HRQOL for these young adult survivors. Furthermore, it is necessary to choose measurements based on a study's research purpose.

More research is necessary on specific time periods after diagnosis among long-term survivors of childhood cancer. As demonstrated in this literature review, time passed since diagnosis was positively associated with improved HRQOL. Most studies focused on the time frame up to four years after cancer diagnosis (Arpawong et al., 2013; Jörngården et al., 2007; Larsson et al., 2010), or on long-term survivors of childhood cancer more than 10 to 15 years after cancer diagnosis (Huang et al., 2013; Mört et al., 2011; Spangler, 2009; Zeltzer et al., 2008). More research is necessary for those between four to ten years after cancer diagnosis in order to identify factors related to HRQOL status for this group. Also, among reviewed studies, most studies on HRQOL of survivors of childhood cancer used a cross-sectional design. There is a lack of study that has used a longitudinal design to know the individual change and longitudinal patterns of HRQOL after the completion of cancer treatment. Using a cross-sectional design cannot reveal the causal relationship between predictors and HRQOL. Thus, it is necessary to use a longitudinal design to find factors that are related to HRQOL across time.

After completing cancer treatment, survivors of childhood cancer are required to regularly visit long-term follow-up clinics to detect late effects, promote disease understanding, and to be provided with information and resources, including health behavior, psychosocial, and educational support (von der Weid & Wagner, 2003). During

follow-up care, regular assessment of HRQOL is necessary to understand an individual's subjective well-being status and to alter or modify future survivorship care plans for the survivors. Providing tailored interventions could improve HRQOL for those who have potential risk factors for poorer HRQOL. However, in order to tailor these interventions, a better understanding of factors associated with HRQOL among childhood cancer survivors is needed. This study addressed these gaps in the literature. In the next chapter a review of the methods used in this study are reported.

CHAPTER III

RESEARCH DESIGN AND METHODS

Design

The secondary analysis in this study was designed to examine the effects of symptom clusters on health-related quality of life (HRQOL) among survivors of childhood cancer. This study used a cross-sectional design to identify factors that are related to HRQOL. The dynamic symptom model (Brant et al., 2016) guided the choice of variables including antecedents and outcomes, as well as the analyses.

This overall study aim was to investigate the association between symptom subgroup membership and HRQOL among survivors of childhood cancer in the St. Jude Lifetime Cohort (SJLIFE) study after controlling for type of childhood cancer and treatment modalities as well demographic characteristics (see Figure 2). The SJLIFE data included individuals who were diagnosed with a variety of types of cancer and received various treatments. Prior research using clustering techniques on cancer symptoms has identified several distinct subgroups of adults with cancer (Dodd et al.,2010 ; Kim et al., 2012; Kim et al., 2014; Miaskowski et al., 2006). It was anticipated that using a similar technique with childhood cancer survivors would yield a similar outcome in terms of cluster structure. Key terms related to the analysis are defined below.

Subgroups (also called subgroup memberships, clusters or classes) were defined as groups of individuals who are similar in their patterns on the indicator variables (i.e.,

symptoms classes). Unlike traditional cluster analyses (such as hierarchical cluster analysis or *K* means cluster analysis) in which individuals are assigned to one and only one subgroup, mixture modeling is based on assigning subgroup membership for each individual based on the probability model. *Indicator variables* were defined as the variables analyzed to identify the subgroup membership. In this study, the indicator variables are binary, and indicate if the individuals experienced physical and psychological symptoms. These variables are illustrated by Y in Figure 2. *Mixture modeling* refers to a type of latent variable analysis in which the analyst strives to identify subgroup memberships. Two main forms of mixture modeling are latent class analysis (LCA: in which the indicator variables are binary - as in this study) and latent profile analysis (LPA: in which the indicator variables are continuous) (Masyn, 2013).

The approach outlined below yielded 1) identification of subgroups of survivors of childhood cancer based on symptoms, 2) associations between demographic and clinical predictors of symptom subgroup membership, 3) associations between subgroup membership and HRQOL, and 4) the moderating effects of subgroup membership between predictors and HRQOL. Four specific sub-aims follow:

Aim A: to identify homogenous subgroups of survivors who share common profiles across multiple symptoms including pain, cardiac and pulmonary symptoms, disfigurement, learning/ memory problems, and psychological symptoms (i.e., anxiety, depression, somatization, and global distress).

Aim B: to examine demographic and clinical factors as predictive of subgroup memberships.

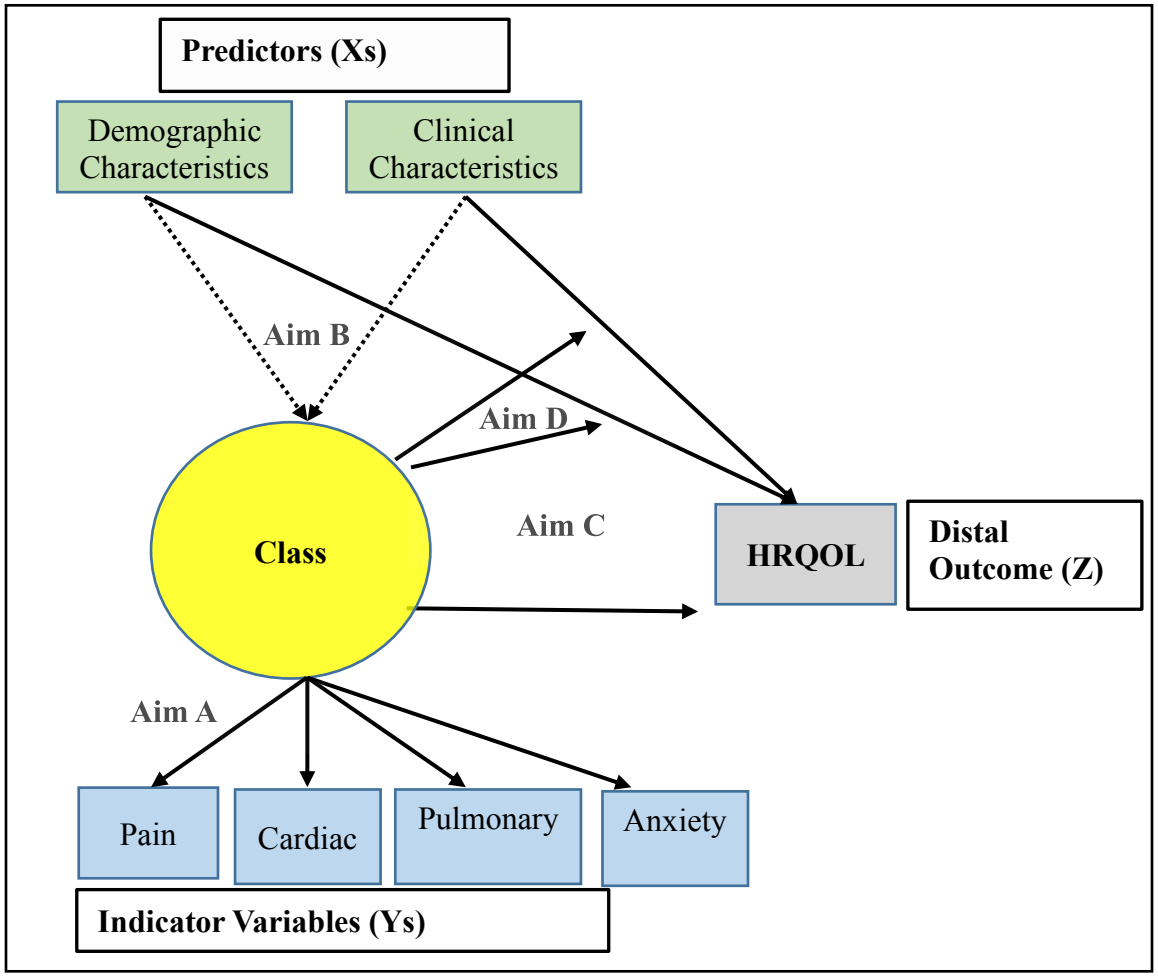
Aim C: to examine the differences of HRQOL as measured by two components of the SF-36 (physical function and mental function) between subgroup membership (identified above) and

Aim D: to examine whether the subgroup membership moderate the relationship between predictors and HRQOL.

Figure 2

Latent Class Moderation Analysis

Each figure shading based on Aim A, B, C & D
Class: a latent variable which holds class membership values for each participant
X: predictor variables which were categorical or continuous (e.g., gender, age, & type of cancer)
Y : indictor variables which were binary variables or continuous (e.g., pain, cardiac symptoms, pulmonary symptoms, & anxiety)
Z: a distal outcome (e.g. HRQOL) which were continuous



Note: Used by permission from Dr. Patrick Curran

Setting and Participants

Participants.

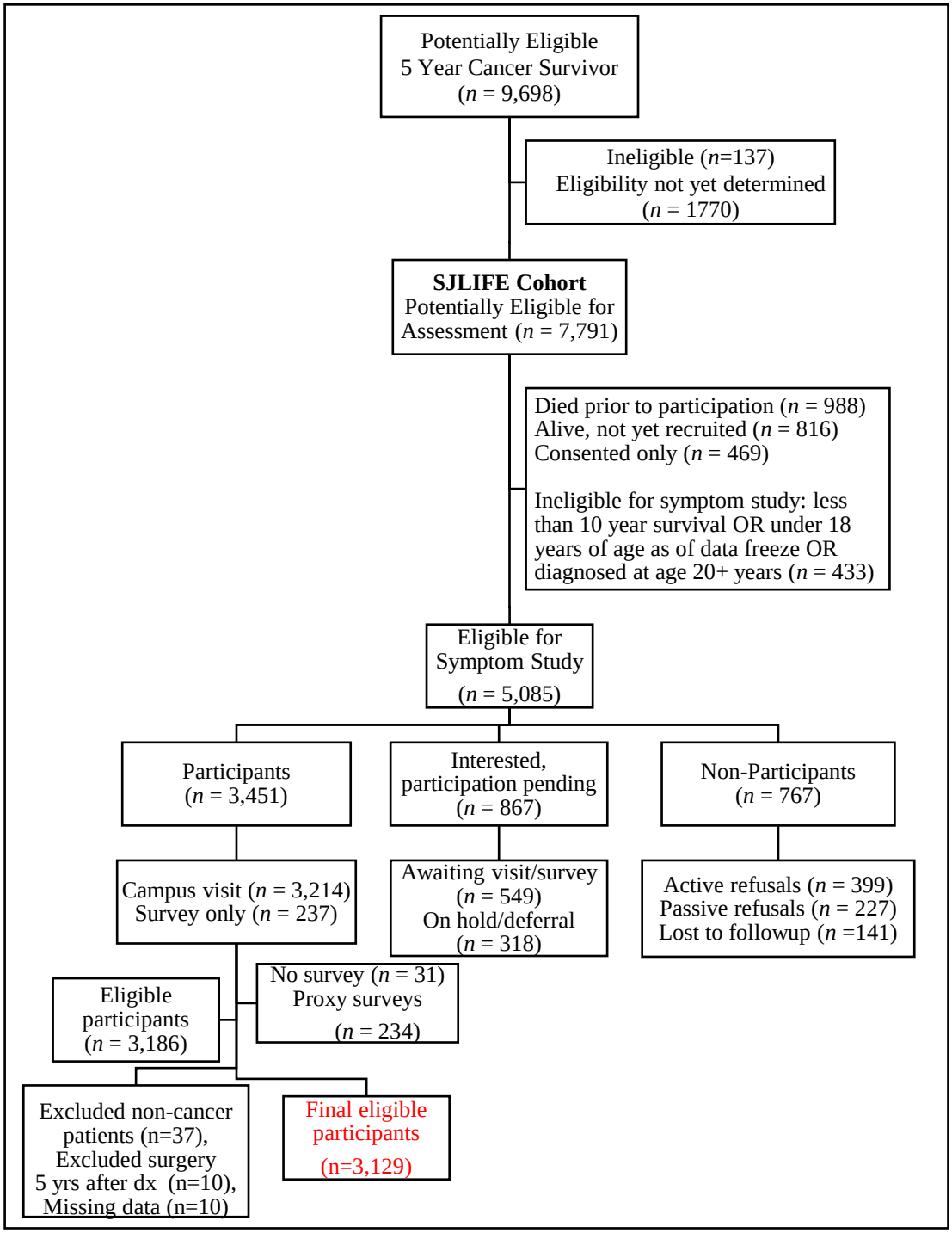
SJLIFE was established as a retrospective cohort with continuous enrollment to better understand health status and severity of long-term late effects of treatments for childhood cancer survivors (Hudson et al., 2011). Survivor participants were diagnosed with childhood cancer and were treated between 1962 and 2002 at St. Jude Children's Research Hospital. The SJLIFE study includes individuals who were 18 years or older at enrollment, and who had lived more than 10 years after cancer diagnosis.

Eligibility.

Inclusion criteria for the current study were : (1) diagnosis of childhood cancer treated at St. Jude Children's Research Hospital (SJCRH); (2) survival of more than 10 years since diagnosis; (3) 18 years or older at enrollment in the SJLIFE cohort study; and (4) between 10 and 19.9 years of age at that time of cancer diagnosis. The SJLIFE Study initiated enrollment of participants in November, 2007 (See. Figure 3. Project Consort).

Figure 3

Project Consort



Procedures

Data Information.

When the SJLIFE data were collected, participants were surveyed using SJLIFE questionnaires about demographics, symptom experiences, and patient outcomes (i.e., brief symptom inventory [BSI]-18 and the medical short form of outcome [SF-36]). Clinical variables (types of cancer, types of treatment, age at cancer diagnosis, and secondary cancer) were generated through St. Jude's medical records and SJLIFE research databases (Dr. Huang, personal communication, June 23, 2017).

Instruments.

Based on the Dynamic Symptoms Model (Brant et al., 2016), each instrument is represented below under either antecedents; symptoms; or consequences.

Antecedents.

a. Demographic variables

- Age at survey (years): 18-29, 30-39, ≥ 40
- Gender: male and female
- Race/ethnicity: non-Hispanic White, non-Hispanic Black, Hispanic, and Other
- Educational background: less than high school diploma, high school graduate/ General Education Development (GED), some college/training after high school, and more than college graduate
- Marital status: married and living with a partner/widowed/divorced/separated/single

- Employment status: currently employed (full/part time) and currently unemployed
- Insurance status: insured and uninsured
- Had difficulty obtaining health insurance: yes and no
- Annual household incomes: ≤ $39,999, $40,000-$79,999, and ≥ $80,000
- Annual personal incomes: none, $1 to ≤ $19,999, $20,000 to ≤ $59,999, and ≥ $60,000

b. Clinical variables

- Cancer diagnoses: All diagnoses related to pediatric cancers: Leukemia, Central nervous system tumors, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, Sarcoma, Embryonic tumors, Bone tumors, and others
- Time since diagnosis in years
- Age at diagnosis (years): 0-4 years, 5-9 years, ≥ 10 years
- Cancer treatment.
    - Chemotherapy: none; corticosteroids; Mercaptopurine/Thioguanine; Methotrexate; Erwinia-/ L-/ Peg-asparaginase; cisplatin/carboplatin/oxaliplatin; alkylating agents; anthracyclines; vincristine; other agents (all with yes/ no)
    - Radiotherapy: none; head/neck area; chest/lung area; pelvis/abdominal/urinary area; reproductive area (male/female); and other areas (muscle area)

- Surgery: yes (invasive surgery: that are only related to cancer-related treatment, includes surgery within 5 years since cancer diagnosis)

Symptom Perception.

c. Physical/ psychological symptoms

Physical and psychological symptoms in the SJLIFE study include nine physical symptoms and three psychological symptoms. From the comprehensive health questionnaire administered to the SJLIFE participants, 41 items measuring human organ impairment were categorized into nine physical symptoms (as indicators) and three psychological symptoms (as indicators). Each item has three response categories ("yes, the condition is still present," "yes, but the condition is no longer present," and "no"). Symptom presence was denoted if participants endorsed "yes, the condition is still present" for any item measuring that particular symptom. The physical symptoms included: cardiac symptoms (3 items); pulmonary symptoms (3 items); motor/movement problems (5 items); pain in head (3 items); pain in back/neck (2 items); pain involving sites other than head, neck, and back (7 items); sensation abnormalities (10 items); disfigurement (7 items); and learning/memory problems (1 item). Three psychological symptoms included: anxiety (6 items), depression (6 items), and somatization (6 items) based on the brief symptom inventory-18 (BSI-18). A summated item score of a particular symptom class was calculated and converted into an age and sex specific T-score; a score ≥ 63 was used to identify presence of a symptom class.

Consequences.

Health-related quality of life. The Medical Outcomes Short form-36 (SF-36) instrument was used to measure HRQOL. This measure is composed of 36 questions assessing functioning and well-being in physical, mental, and social dimensions of life (Ware, Kosinski, Dewey, & Gandek, 2000). This instrument has eight domains of HRQOL including physical functioning (10 items); role-limitation due to physical health problems (4 items); bodily pain (2 items); general health perceptions (5 items); vitality (4 items); social functioning (2 items); role-limitation due to emotional health problems (3 items); and general health (5 items). These eight domains can be summed into two measures: the physical component summary scores (PCS) and mental component summary scores (MCS). These two summary scores were used to evaluate overall physical and mental functioning of HRQOL. The sum of the scores was scaled from 0 to 100, with higher scores representing better HRQOL.

Data Management

Protection of Human Subjects.

The SJLIFE protocol and survey questionnaires were approved by the SJCRH Institutional Review Board (IRB). Informed consent was obtained from all participants before starting data collections. This current study was approved by University of North Carolina at Greensboro IRB (number: 16-0450) and was determined to be exempt from further review according to a regulatory category since this study used de-identified secondary data.

Data Safety and Monitoring.

The original survey documents are stored in a double-locked cabinet in the Department of Epidemiology and Cancer Control at St. Jude Children's Research Hospital. The electronic survey data were de-identified and stored on secured research servers at St. Jude Children's Research Hospital. In order to access the electronic survey data, an individual needs to get permission from the data management team and is required to use password and ID protected computers to access the research servers. Data analyses for this study were primarily conducted at St. Jude Children's Research Hospital. Follow up analyses were performed on SJLIFE de-identified data at the University of North Carolina at Greensboro.

Data Management and Analysis.

SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) and SPSS version 23.0 (SPSS INC., Chicago, IL) software were used in data preparation and management. Mplus version 8.0 (Phoenix Flow Systems, San Diego, CA) software was primarily used for data analyses. The samples were described using descriptive statistics. Frequencies were used for nominal level data, and means and standard deviations were calculated for continuous and interval data.

Data Cleaning.

The raw data consisted of data on all variables for 3,189 participants who met the inclusion criteria (see Figure # 3). A codebook was developed that included frequencies of all variables from the original survey data. The codebook included six sections (e.g., *section I. demographics*: types of cancer, gender, race, age at survey, age at enrollment,

years at diagnosis, live with whom, ever married, education, employment, home income, personal income, financial status at the end of the month, and had difficulty obtaining health insurance; *section II. symptom (indicator variable)*: hair loss, scarring on the body, walk with a limp, problems with double vision, abnormal sense of taste, arrhythmia, angina pectoris, chronic cough, emphysema, breathing problems, tremor, problems of balance, headache, body image, sensation, movement, cardiac problems, pulmonary problems, pain, memory, depression, anxiety, somatization, and HRQOL questionnaire using SF-36 ; *section III. treatment modalities*: chemotherapy (anti-tumor antibiotics, carboplatin, cisplatin, corticosteroids, cytarabin, doxorubicin, erwinia asparaginase, high dose methotrexate, L-asparaginase, mercaptopurine, oxaliplatin, thioguanine, and vincristine), radiation therapy (abdomen, breast, chest, eye, ear, female, male, GI hepatic, lung, muscle, oral, pelvis, urinary, and total body irradiation), surgery, and secondary cancer; *section IV. Psychological distresses (Brief Symptom Inventory-18); section V. health behaviors* (ever smoked, tobacco, marijuana/Hashish/Cannabis use, number of years use tobacco, drinking, vigorous exercise, moderate exercise, limited exercise, and sun protective behavior); and *section VI. Motivation* (four motivation behaviors, 10 social desirability, and five worry about cancer treatment complications). Section V and VI were not be used for the current project and will be used another project to examine moderated mediating effects using psychological factors among treatment variables, health behaviors, and symptoms in survivors of childhood cancer.

Variables were regrouped based on characteristics of participants such as types of cancer, race/ethnicity, and age at survey. Non-cancer patients (n = 37) were excluded as

were 10 patients who did not meet the inclusion criteria regarding their surgery history. At the beginning, 3,139 participants were used for the data analyses. Using Mplus, when the number of subgroups was chosen regarding Aim A, 10 participants were automatically deleted due to missing values. Thus, 3,129 participants were retained for this current study.

Analytic Approach for the Aims

The proposed analytical approach to accomplish the four sub aims of this study employed a four-phase model fitting process. It should be noted at the outset that the model fitting, especially in the first phase (aim A), required stepwise approaches for testing multiple models to arrive at the "best" model before going to the next phase. Model fitting relied on the recommendations of a number of methodologists for best practices in model fitting (Asparouhov & Muthén, 2014; Marsh, Lüdtke, Trautwein, & Morin, 2009; Masyn, 2013; Pastor, Barron, Miller, & Davis, 2007). Mplus (version 8.0) was used for the majority of the analyses such as finding the best model, conducting bivariate analyses, and conducting multivariable analyses. Given this overview, definitions of specialized terms used in the analyses, then the analytical plan for each sub aim, are provided.

Analyses for Aim A.

A strength of mixture modeling is that the modeling provides posterior profiles of membership in the subgroups instead of a rigid assignment of individuals to one and only one class (Masyn, 2013). Thus, the mixture model is more flexible in fitting models in which the data are not necessarily structured in a hierarchical fashion. In addition, the

mixture modeling also provides several probability-based tools for deciding on the number of classes to retain, tools which are not available in traditional hierarchical clustering methods. Finally, recent development in mixture modeling provides for the modeling of predictors of subgroup membership and distal outcomes (conditioned on subgroup membership) into a single joint model. This final point is an additional benefit of using mixture modeling in nonhierarchical data sets. There is considerable methodological work on this approach (Clark & Muthén, 2009; Vermunt, 2010; Wang, Hendricks Brown, & Bandeen-Roche, 2005). This mixture modeling provides a method for testing joint models which are homologous with the aims of this current study as in the model provided in figure 2. In figure 2 the LPA model (Aim A), a model of predictors of subgroup membership (Aim B), a model to examine the differences in distal outcomes based on subgroup membership (Aim C), and a model to examine the moderating effects of the subgroup membership on the relationship between predictors and HRQOL (Aim D) are presented.

The methodological issues that arise in this modeling have to do with the influences of the predictors and the outcomes on the analyses of subgroup memberships. It is common to see that subgroup memberships change with the addition of extra information contained in the predictors and outcomes, and such changes may undermine the validity of the initial mixture analyses. One solution is to use the Vermunt's three-step approach, which is implemented within Mplus software. This approach fixes subgroup membership by assigning individuals to the subgroup for which the posterior probabilities are highest. This discrete variable is then used as the indicator of group

membership (in place of the original indicators as shown in figure 2). The results of simulation using Vermunt's three-step approach indicated that this approach retains the validity of the original mixture model while providing for the benefits of testing hypotheses about predictors and outcomes of group membership.

The process of fitting the latent class model to the data was conducted by minimizing the likelihood function based on the number of clusters proposed. The process started with a baseline model with one cluster and then subsequently was expanded to two, three ... K clusters. At each model, a series of fit indices (AIC, BIC, and Sample size adjusted BIC) were examined and used to aid in the identification of the best model. In addition to these fit indices, the Lo Mendell Rubin test was used to test the hypotheses that the K number of classes provided a better fit that the K-1 model (Asparouhov & Muthén, 2014).

In addition to the fit indices, it was important to examine the size of the subgroups. For example, subgroups of less than 5% of the total sample may not have been reliable and thus size of subgroup is an important consideration in this phase of model fitting. Note that in cases with poor separation, these processes may not be definitive and one must rely on interpretability such as percent in each cluster (Marsh et al., 2009). Once the "best" model is obtained, the class membership becomes available for analyses either as a dependent variable or a predictor variable (see aim B and C).

Analyses for Aims B and C.

In addition to the methodological work concern of establishing the "best" model as described above, there has been considerable methodological work in the best ways to

examine predictors of subgroup membership and to examine outcomes of subgroup membership. One concern in this type of modeling is that by including predictors or outcomes of subgroup membership, the composition of the subgroups can shift (and thus introduce measurement error in the model and potentially invalidate the model developed in Aim A). The issue with regard to predicting distal outcomes based on cluster membership is related to circularity – the distal outcome inadvertently becomes an indicator variable at the same time it serves as an outcome variable.

To address this issue, Aspoarouhov and Muthén (2014) have summarized the work of a number of methodologists (e.g. Vermunt, Lanza, and Baak). These authors have explicated a strategy for the study of predictors and outcomes of subgroup membership and have implemented these strategies within Mplus. In Aim B and Aim C, the recommendations by Aspoarouhov and Muthén (2014) were followed and employed Vermunt's three-step approach. The Vermunt's three step approach can set up predictors and outcome variables separately. This work has been seen as a significant improvement over previous approaches which have built into a single modeling approach either the predictors of subgroup membership or employing subgroup membership as a predictor of distal outcomes.

Analyses for Aim D.

Whereas the test statistics for models Aim A through Aim C are provided as fit indices, the bootstrap Lo Mendell Rubin (model Aim A) regression coefficients for multinomial logistic regression (model Aim B) and tests of distal outcome means across groups (model Aim C), and the test for the moderating effect of group membership on the

association between clinical and demographic characteristics and distal outcomes (model Aim D) are accomplished using the Wald test. This test proceeds by constraining the regression coefficients of the predictors for each subgroup to be equal, and then testing the equality of these regression coefficients by examining differences in fit between the constrained and unconstrained model.

Reporting Methods of Aims

Aim A.

Aim A is to identify subgroup membership of survivors who share common profiles across multiple symptoms (See Figure 2). The methods described above for the critical step of identifying the number of subgroups that provide the best fit to the data were employed. Multiple models were contrasted by selecting indicator variables which provided the clearest separation between subgroups and the greatest homogeneity within groups.

Reporting method: This model was reported in several ways. The most salient report is a graph of the indicator means (proportions) across subgroups. Additional results in the form of fit indices that were used to justify the decision about the number of subgroups were provided. The AIC, BIC, and SSA BIC, and the Bootstrapped Lo Mendell Rubin Test (AIC: Akaike's Information Criterion, BIC: Bayesian Information Criterion, SSA-BIC: Sample-size-adjusted Bayesian Information Criterion) were employed.

Aim B.

Aim B is to examine demographic and clinical predictors of subgroup membership (See Figure 2). In this aim, predictors of subgroup membership were examined using the recommended Vermunt's three-step approach as discussed above. The analyses were focused on the main effects. Although the modeling could include interaction effects, this was not the focus on the current study. Thus, only the main effects were analyzed. Finding factors could provide a basis for refining the model and subsequent development of individualized interventions for vulnerable groups in an early period of cancer survivorship.

Reporting method: the analyses consisted of a series of simple logistic regression models in which class membership served as the binary outcome. These simple logistic models were followed by a multivariable logistic model in which those predictors which were associated with the *p* value of less than or equal to .001 were included as predictors. Multinomial regression analysis was conducted to address the issue of the dependent variable and subgroup membership if the numbers are greater than two. The primary reporting method is a table of values of the odd ratios accompanied by 95% confidence intervals.

Aim C.

Aim C is to examine the HRQOL differences between subgroup memberships (See Figure 2). The association between subgroup membership and the distal outcome of HRQOL was examined. As discussed above, the Vermunt's three-step approach within Mplus was used. It was expected that these analyses would include a multinominal

predictor variable (subgroup membership) and a continuous outcome variable (the medical short form - 36 [SF-36]). In Aim c, the analysis provided tests of mean differences of HRQOL across the classes comparable to analysis of variance.

Reporting method: The results of these analyses were reported in tabular form and may be thought of as a series of cross tabulation analyses with the chi-squared test statistic as the basis for hypothesis testing (See Table 6). Multivariable analyses were used to examine the relationships between predictors and the physical component summary HRQOL (PCS) (Table 7) and between predictors and the mental component summary HRQOL (MCS) (Table 8).

Aim D.

Aim D is to examine whether the subgroup membership moderate the relationship between predictors and HRQOL (See Figure 2). Using the Vermunt's three-step approach, the moderating effects of the symptom subgroups between predictors and HRQOL were examined. Common predictors between physical HRQOL and mental HRQOL were chosen and the Wald test was used to conduct hypothesis testing about the moderating effect of subgroup membership on the relationship between clinical and demographic predictors and the distal outcome.

Reporting method: The results of these analyses were reported (See Table 9).

Summary of Research Design and Methods

In this chapter, inclusion criteria of participants, settings, and measurements were provided. The measurements included antecedents (demographic variables and clinical variables), symptom perceptions, and consequences (HRQOL). Also, data management

and analysis plans for each research question were provided. In order to support better understanding about the four sub-aims, a diagram was provided. In the next chapter, findings of the statistical analyses and testing of each research question are described.

CHAPTER IV

RESULTS

The purpose of this study was to investigate the association between subgroup membership based on effect of late effects on HRQOL using cluster mixture modeling. This chapter reports the results of the statistical analyses used to evaluate the complex mixture model as outlined in the previous chapter. This chapter proceeds as follows: the report of the sample characteristics; the results of the initial mixture modeling (Hypothesis A); prediction of subgroup membership by demographic and clinical characteristics (Hypothesis B); tests of subgroup membership differences in physical and mental functioning (Hypothesis C); and a test of the association between clinical and demographic variables with physical and mental functioning as moderated by subgroup membership (Hypothesis D).

Sample Characteristics

This is a report of a secondary data analysis using SJLIFE cohort study data. The total sample size was 3,129 long-term survivors of childhood cancer. Table 1 shows the demographic and clinical characteristics of the survivors of childhood cancers in this study.

Demographic Variables.

The mean age of the study participants at the time of interview was 31.9 years (*SD* = 8.4 years) and the mean age at cancer diagnosis was 8.45 years (*SD* = 5.5 years).

The mean time since cancer diagnosis was 28.10 years (*SD* = 9.1). Among the participants, the percentage of males and females were similar at about 50%. Most participants were non-Hispanic White (*n* = 2,408, 79.8%) and the next largest population was non-Hispanic Black (*n* = 395, 13.1%). Most participants reported that they were college graduates (*n* = 2,055, 71.5%). In particular, 36% of survivors (*n* = 1,034) had more than a college degree. Half of the participants were married (*n* = 1, 298). Sixty seven percent of survivors (*n* = 2,057) currently work full-time or part-time. Most participants had insurance (*n* = 2,327, 77.7%), and most participants had no difficulty in obtaining insurance (*n* = 2,238, 75.4%). About forty percent of survivors had either low income ($1 to ≤ $19,999) or middle income ($20,000 to $59,999). In particular, about 13% of survivors (*n* = 381) had no income.

Clinical Variables.

Participants had various types of childhood cancer, which were categorized into four groups: leukemia, lymphoma, sarcoma, and central nervous system tumors. The number of patients who were diagnosed with each type of cancer were as follows: leukemia (*n* = 1,166, 37.3%), sarcoma (*n* = 1,029, 32.9%), lymphoma (*n* = 631, 20.2%), and central nervous system tumors (*n* = 303, 9.7%). Acute lymphoblastic leukemia, acute myeloid leukemia, and other types of leukemia were grouped as "leukemia." Hodgkin's lymphoma and non-Hodgkin's lymphoma were grouped as "lymphoma." Also, "sarcoma" included Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, neuroblastoma, Wilms' tumor, and bone tumors. Among participants, 15.4% of survivors (*n* = 425) experienced secondary cancer. Participants who experienced a surgery

accounted for 70.7% (*n* = 2,211), more than 70% of participants were treated with chemotherapy (*n* = 2,429), and 60% of survivors had been treated with radiotherapy (*n* = 1,819).

Several types of chemotherapy were used by more than 50% of the participants. These included: corticosteroids (*n* = 1,472, 47.1%), mercaptopurine/thiouguanine (*n* = 1,943, 62.1%), methotrexate (*n* = 1,608, 51.4%), anthracycline (*n* = 1,833, 58.7%), alkylating agents (*n* = 1,834, 59.2%), and vincristine (*n* = 2,124, 68.6%). Regarding radiotherapy, treatment in the head/neck area was the most prevalent (*n* = 1,537, 49.1%). Nearly 30% of participants received radiotherapy to other areas including chest/lung, pelvis/abdomen/urinary, and reproductive areas.

Table 1

Demographic, Clinical Characteristics of Survivors of Childhood Cancers

Variable	Total Sample (N=3,129)
	M (*SD*)
Age at interview [in year]	31.9 (8.4)
Age at cancer diagnosis (mean, SD) [in years]	8.45 (5.5)
Time since cancer diagnosis, (mean, SD) [in years]	28.10 (9.1)
	n (%)
Sex	
Male	1,583 (50.6)
Female	1,544 (49.4)
Race/ethnicity	
White, non-Hispanic	2,408 (79.8)
Black, non-Hispanic	395 (13.1)
Hispanic	144 (4.8)
Other	70 (2.3)
Educational background	
Less than high school diploma	261 (9.1)
High school graduate/ GED	556 (19.4)

Some college/ training after high school	1,021 (35.5)
College graduate/ Post graduate level	1,034 (36.0)
Marital status	
Married	1,298 (42.6)
Living with a partner/ widowed/ divorced/ separated/single	1,750 (57.4)
Employment status	
Currently employed (Full/part time)	2,057 (66.8)
Currently unemployed	1,034 (33.2)
Insurance status	
Insured	2,327 (77.7)
Uninsured	668 (22.3)
Had difficulty obtaining health insurance	
No	2,238 (75.4)
Yes	729 (24.6)
Annual personal income	
None	381 (12.7)
$1 to ≤$19,999	1,197 (39.9)
$20,000 to $59,999	1,103 (36.8)
≥$60,000	318 (10.6)
Annual household income	
≤$39,999	1,141 (43.7)
$40,000 to $79,999	853 (32.7)
≥$80,000	616 (23.6)
Cancer diagnosis	
Leukemia	1,166 (37.3)
Central nervous system tumor	303 (9.7)
Lymphoma	631 (20.2)
Sarcoma	1,029 (32.9)
Secondary cancer	
No	2,339 (84.6)
Yes	425 (15.4)
Chemotherapy	
Any chemotherapy	2,429 (77.6)
Corticosteroids	1,472 (47.1)
Mercaptopurine/Thioguanine	1,943 (62.1)
Methotrexate	1,608 (51.4)
Erwinia-/ L-/ Peg-asparaginase	1,017 (32.4)
Cisplatin/carboplatin/oxaliplatin	384 (12.3)
Anthracycline	1,833 (58.7)
Alkylating agents	1,834 (59.2)
Vincristine	2,124 (68.6)
Other agents	1,731 (55.3)

Radiotherapy	
Any radiotherapy	1,819 (58.3)
Head/neck area	1,537 (49.1)
Chest/lung area	931 (29.8)
Pelvis/abdominal/urinary area	1,005 (32.1)
Reproductive area	665 (21.3)
Muscle area	1,145 (36.6)
Invasive surgery	2,211 (70.7)

Note. Leukemia includes (Acute lymphoblastic leukemia, acute myeloid leukemia, & other leukemia); Lymphoma includes (Hodgkin's lymphoma & non-Hodgkin's lymphoma); Sarcoma includes (Ewing's Sarcoma, osteosarcoma, rhabdomyosarcoma, neuroblastoma Wilms' tumor, & bone tumors)

Subgroup Differences in Demographic and Clinical Variables.

The majority of the variables except race, surgery, and certain types of chemotherapy were significantly different between the two subgroup memberships, as shown below in table 2. The following analyses were conducted on the clusters in order to examine their differences. Cluster membership was used as the independent variable (with other demographic and clinical variables) in order to examine the differences between the symptom clusters on the demographic and clinical variables.

Table 2

Subgroup Differences in Demographic and Clinical Characteristics

Variable	High symptoms cluster	Low symptoms cluster	Test, Statistical Significance	
	n=888 (29.4%)	*n*=2,241 (71.6%)		
	M (*SD*)	M (*SD*)	*F*	*p*
Age at interview [in year]	33.45 (8.3)	31.33 (8.3)	2978.28	0.474
Age at cancer diagnosis (mean, SD) [in years]	9.02 (5.6)	8.24 (5.5)	2897.84	0.424
Time since cancer diagnosis (mean, SD) [in years]	29.26 (9.3)	27.69 (9.0)	81.62	0.0003
	n (%)	*n* (%)	$\chi 2$	*p*
Sex				
Male	382 (45.3)	1,201 (52.5)	13.02	<0.001
Female	461 (54.7)	1,083 (47.4)		
Race/ethnicity				
White, non-Hispanic	664 (81.8)	1744 (79.1)	5.27	.153
Black, non-Hispanic	104 (12.8)	291 (13.2)		
Hispanic	28 (3.45)	116 (5.3)		
Other	16 (1.97)	54 (2.5)		
Educational background				
Less than high school diploma	118 (15.3)	143 (6.8)	89.45	<0.001
High school graduate/ GED	186 (24.1)	370 (17.6)		
Some college/ training after high school	270 (34.9)	751 (35.8)		
College graduate/ Post graduate level	199 (25.7)	835 (39.8)		
Marital status				
Married	311 (36.9)	987 (43.2)	6.97	.008
Living with a partner/ widowed/ divorced/ separated/single	494 (58.6)	1,256 (54.9)		
Employment status				
Currently employed (Full/part time)	411 (48.8)	1,646 (72.0)	150.97	<0.001
Currently unemployed	418 (49.6)	616 (26.5)		
Insurance status				
Insured	590 (73.3)	1,737(79.3)	12.32	<0.001
Uninsured	215 (26.7)	453 (20.7)		
Had difficulty obtaining health insurance				
No	517 (65.5)	1,718 (79.1)	61.84	<0.001
Yes	272 (34.5)	453 (20.9)		
Annual personal income				

none	135 (16.7)	246 (11.2)	78.43	<0.001
$1 to ≤$19,999	397 (49.0)	800 (36.6)		
$20,000 to $59,999	225 (27.8)	878 (40.1)		
≥$60,000	53 (6.5)	265 (12.1)		
Annual household income				
≤$39,999	427 (61.4)	714 (37.3)	124.04	<0.001
$40,000 to $79,999	169 (24.3)	684 (35.7)		
≥$80,000	99 (14.2)	517 (27.0)		
Cancer diagnosis				
Leukemia	306 (26.3)	860 (37.6)	28.70	<0.001
Central nervous system tumor	105 (12.5)	198 (8.7)		
Lymphoma	202 (24.0)	429 (18.8)		
Sarcoma	230 (27.3)	799 (35.0)		
Secondary cancer				
No	613 (81.3)	1,717 (85.8)	10.19	.006
Yes	141 (18.7)	284 (14.2)		
Chemotherapy				
Any chemotherapy	676 (80.2)	1,753 (76.7)	4.36	.037
Corticosteroids	412 (48.9)	1,060 (46.4)	1.55	.213
Mercaptopurine/Thioguanine	328 (38.9)	858 (37.5)	0.50	.482
Methotrexate	428 (50.8)	1,180 (51.6)	0.17	.674
Erwinia-/ L-/ Peg-asparaginase	264 (31.3)	753 (32.9)	0.74	.390
Cisplatin/carboplatin/oxaliplatin	122 (14.5)	262 (11.5)	5.19	.023
Anthracycline	542 (64.3)	1,291 (56.6)	15.32	<0.001
Alkylating agents	543 (65.0)	1,291 (57.0)	16.19	<0.001
Vincristine	587 (70.1)	1,537 (67.9)	1.76	.185
Other agents	472 (56.0)	1,259 (55.1)	0.21	.647
Radiotherapy				
Any radiotherapy	570 (67.7)	1,249 (54.8)	42.34	<0.001
Head/neck area	497 (59.0)	1,040 (45.5)	44.66	<0.001
Chest/lung area	310 (36.8)	621 (27.2)	27.20	<0.001
Pelvis/abdominal/urinary area	325 (38.6)	680 (29.8)	21.91	<0.001
Reproductive area	216 (25.6)	449 (19.6)	13.17	<0.001
Muscle area	364 (43.2)	781(34.2)	21.57	<0.001
Invasive surgery	613 (72.7)	1,598 (69.9)	2.35	.125

Note. Leukemia includes (Acute lymphoblastic leukemia, acute myeloid leukemia, & other leukemia); Lymphoma includes (Hodgkin's lymphoma & non-Hodgkin's lymphoma); Sarcoma includes (Ewing's Sarcoma, osteosarcoma, rhabdomyosarcoma, neuroblastoma Wilms' tumor, & bone tumors)

Results of Hypotheses Testing

This section outlines the results of hypotheses testing and findings. In most analyses, the Vermunt-three step approach using Mplus software program was employed.

Hypothesis A.

The hypothesis of Aim A stated that several meaningful subgroups of survivors with heterogeneous symptom patterns will be identified. This hypothesis was supported. Two distinctive groups based on ten symptoms were identified: a group with high symptoms and a group with low symptoms. These clusters were named the "high symptom cluster" and the "low symptom cluster." In order to determine the best number of symptom clusters, Mplus was used. As previously mentioned in the methodology section, a series of fit indices (AIC, BIC, and Sample sized adjusted BIC) were used to identify the best model. The lowest values of each score were used as criteria to choose the best fit model (Asparouhov & Muthén, 2014).

When a four subgroup membership was chosen, the BIC (Bayesian Information Criterion), CAIC (Consistent Akaike information criterion), and SSA-BIC (Sample-size-adjusted Bayesian Information Criterion) were the lowest. However, when the two-subgroup membership was chosen, the CLC (Classification likelihood criterion) and ICL-BIC (Integrated classification likelihood with BIC approximation) were also the lowest, and entropy was the highest (see Table 3). Figure 4 (Summary of Model Fit) showed the values of AIC, BIC, CAIC, SSA-BIC, CLC, and ICL-BIC. The two subgroups were chosen based on this result. Choosing the best cluster solution is perhaps the most demanding aspect of mixture modeling.

The decision to choose the two-group solution was based on three criteria. The first was the pattern of decline (and rebound in the various fit statistics). With this criterion in mind researchers might choose either a two- or four-group solution. As can be

seen in Table 3, the BIC begins to rebound in the five-class solution, indicating that the four-class solution is a viable one, whereas the CLC rebounds at the two-class solution. Thus by these indices a solution between two and four classes seems viable. The second criteria is the Lo Mendell Rubin test, which shows that the four-class solution is also viable. The final criterion (and perhaps the most important criterion) is the interpretability of the class solution. Interpretability is not clear-cut, but may vary from research team to research team. Perhaps the clearest evidence for interpretability comes from the pattern of symptoms across the two-class solution which is discussed in the next section. The research team (committee members and author of this dissertation) decided to proceed with the two-cluster solution since this was indicated by the fit indices and the Lo Mendell Rubin test, and because this solution was deemed the most interpretable.

Table 3

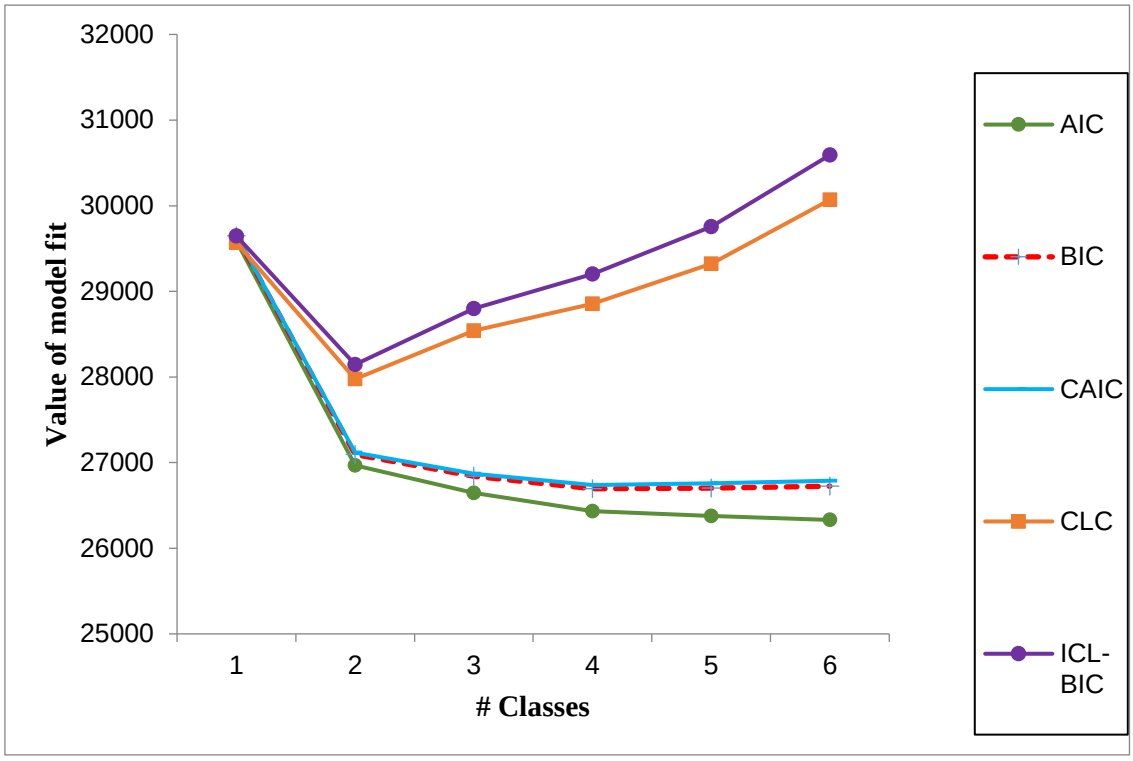
Goodness of Fit for Models Based on Different Numbers of Groups

C	#P	LL	AIC	BIC	CAIC	CLC	Entropy	ICL-BIC	*p* LMR (BLRT)
1	10	-14783.80	29587.60	29648.08	29658.08	29567.60	*NA*	29648.08	NA
2	21	-13463.26	26968.51	27095.53	27116.53	**27976.24**	**0.758**	**28145.26**	**.0000**
3	32	-13291.09	26646.18	26839.73	26871.73	28541.59	0.715	28799.14	**.0000**
4	43	-13174.60	26435.20	**26695.28**	**26738.28**	28856.40	0.711	29202.48	**.0000**
5	54	-13134.44	26376.87	26703.49	26757.49	29320.65	0.697	29755.27	**.0137**
6	65	-13100.40	**26330.81**	26723.96	26788.96	30069.23	0.655	30592.39	.1573

Note. C=Classes; #P=number of parameters; LL=Loglikelihood; AIC= Akaike's Information Criterion; BIC= Bayesian Information Criterion; CAIC= Consistent Akaike information criterion; CLC=Classification likelihood criterion; ILC-BIC=Integrated classification likelihood with BIC approximation; p LMR (BLRT)= p values for the Lo Mendell Rubin likelihood and the bootstrap likelihood ratio test for K vs. K -1 classes.

Figure 4

Summary of Model Fit



A. Pattern of symptom experience across the two clusters. The pattern of symptoms in each subgroup was shown using both a scatter plot (Figure 5) and a table (Table 4) representing this result. When the four-subgroup membership was chosen, there was overlap between the ten symptoms, but in the two-subgroup solution, a clear distinction was shown between the levels of symptoms. Table 4 shows the pattern of symptom experience across the two clusters in long-term survivors of childhood cancer using Mplus. These means are a second representation of the means provided in the figure. Among all participants, pain was the most prevalent symptom (n = 2, 362, 75.5%) and half of participants had disfigurement (n = 1, 690, 55.0%). Also, sensation

abnormalities were highly prevalent (*n* = 972, 31.1%), and learning/memory problems were endorsed by 749 participants (24.3%). Several symptoms were reported by less than 20% of participants, including motor/movement symptoms (*n* = 508, 16.3%) and cardiac symptoms (*n* = 471, 15.1%). Also, survivors who experienced psychological symptoms showed less than 20% prevalence, which included anxiety, depression, and somatization. There were significant differences between the two subgroup memberships (high symptoms cluster and low symptoms cluster) in each of the ten symptoms.

Figure 5

Pattern of Symptom Experience across the Two Clusters (using a graph)

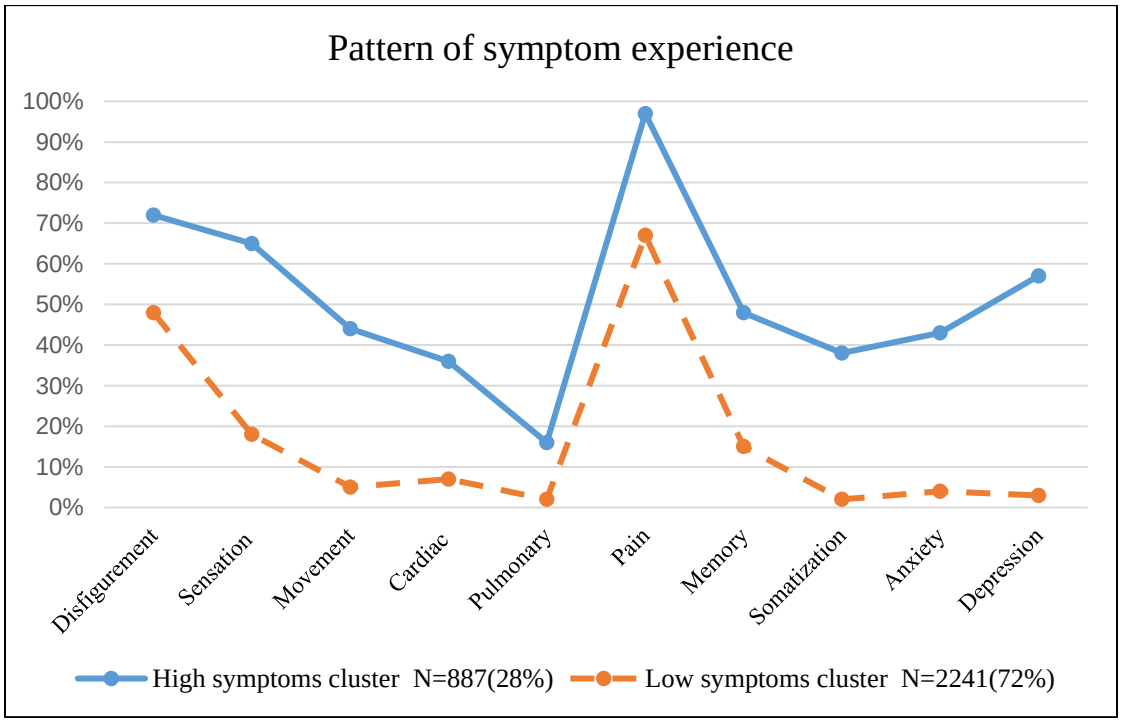


Table 4

Pattern of Symptom Experience across the Two Clusters (using a table)

Individual Symptom Group	Prevalence *n* (%)				
	Total Sample	High symptoms cluster	Low symptoms cluster	$\chi 2$	*p*
	N = 3,129	*n*=888 (28.4)	*n*=2,241 (71.6)		
Cardiac symptoms (yes/no)	471 (15.1)	315 (37.4)	156 (6.9)	448.29	<.0001
Pulmonary symptoms (yes/no)	183 (5.9)	145 (17.4)	38 (1.7)	271.92	<.0001
Motor/movement problems (yes/no)	508 (16.3)	396 (47.1)	112 (4.9)	801.14	<.0001
Pain (yes/no)	2362 (75.5)	821 (97.4)	1541 (67.4)	298.73	<.0001
Sensation abnormalities (yes/no)	972 (31.1)	569 (67.5)	403 (17.7)	713.06	<.0001
Disfigurement (yes/no)	1690 (55.0)	591 (71.7)	1099 (48.8)	127.79	<.0001
Learning/memory problems (yes/no)	749 (24.3)	399 (48.3)	350 (15.5)	353.13	<.0001
Anxiety (cutoff: 63)	368 (12.1)	336 (40.9)	32 (1.4)	884.60	<.0001
Depression (cutoff: 63)	465 (15.2)	387 (47.0)	78 (3.5)	884.50	<.0001
Somatization (cutoff: 63)	554 (18.1)	506 (61.4)	48 (2.2)	1426.16	<.0001

Note. Prevalence of symptoms in the total sample was calculated. The prevalence of symptoms in each subgroup (high and low symptom cluster) were calculated separately. The total sample's symptoms prevalence were different from the sum of the high symptom cluster and the low symptom cluster.

Hypothesis B.

Hypothesis B stated that demographic or clinical factors would differentially predict subgroup membership. This hypothesis was supported. Bivariate analyses were used to examine the relationships between each demographic and clinical variable and subgroup memberships. Most variables were significant in each subgroup, except for

race. After conducting bivariate analyses between all demographic and clinical variables and symptom variables, 18 statistically variables were chosen for multivariable analysis. Table 5 (Associations of symptom subgroups with demographics and clinical variables) represents this result.

B1. Demographic characteristics as predictors of cluster membership (using bivariate analyses). Participants who were more than 40 years old at the time of survey were 1.92 times (95% CI [1.49, 2.48]) as likely to be in the high symptom cluster group compared to participants between 18-29 years old at the time of the survey. Participants who had survived more than 30 years since cancer diagnosis were 1.45 times (95% CI [1.20, 1.75]) as likely to be in the high symptom cluster group compared to participants who had survived between 10 to 29 years since cancer diagnosis. Participants who were diagnosed with cancer when they were more than 10 years old were 1.35 times (95% CI [1.09, 1.68]) as likely to be in the high symptom cluster group compared to participants who were diagnosed with cancer at less than four years old.

Female participants were 1.41 times (95% CI [1.17, 1.71]) as likely to be in the high symptom cluster group compared to male participants. White non-Hispanic participants were more likely to be in the high cluster group compared to other races including Black non-Hispanic and Hispanic participants, but this is not statistically significant. However, education level had an effect on symptom cluster membership. Those with less education were more likely to be in the high symptom cluster group. For example, patients with less than a high school diploma were 3.90 times (95% CI [2.78,

5.48]) as likely to be in the high symptom cluster group compared to participants with the highest education level (more than college education).

Participants who were living with a partner, widowed, divorced, separated, or single were 1.30 times (95% CI [1.07, 1.58]) more likely to be in the high symptom cluster compared to participants who were currently married. Participants who were currently unemployed were 3.36 times (95% CI [2.75, 4.10]) more likely to be in the high symptom cluster group compared to participants who were currently employed. Participants who had difficulty obtaining health insurance were 2.27 times (95% CI [1.83, 2.81]) more likely to be in the high symptom cluster group compared to participants without difficulty obtaining health insurance.

Furthermore, lower annual household income was also related to more risk of being in the high symptom cluster group. Participants with an annual household income of less than $39,999 were 2.48 times (95% CI [1.98, 3.10]) more likely to be in the high symptom cluster group compared to participants with an annual household income of greater than $80,000. Annual personal income showed a similar risk pattern with the annual household incomes. In addition, participants who experienced secondary cancer were 1.48 times (95% CI [1.14, 1.92]) more likely to be in the high symptom cluster group compared to participants who did not experience secondary cancer.

B2. Clinical predictors of cluster membership (using bivariate analyses). Participants who were diagnosed with a central nervous system tumor (*OR*: 1.60, 95% CI [1.17, 2.20]) and lymphoma (*OR*: 1.39, 95% CI [1.08, 1.79]) were more likely to be in the high symptom cluster group compared to participants who were diagnosed with

leukemia. Participants who were treated with any type of chemotherapy were 1.28 times (95% CI [1.01, 1.62]) more likely to be in the high symptom cluster group compared to participants who were not treated with chemotherapy.

Regarding each type of chemotherapy, participants who were treated with anthracycline were 1.47 times more likely (95% CI [1.21, 1.79]) and those treated with alkylating agents were 1.49 times more likely (95% CI [1.25, 1.82]) to be in the high symptom cluster group compared to participants who were not treated with either of these agents. Participants who were treated with radiotherapy were statistically significantly different between the two symptom clusters. For example, patients who were treated with radiotherapy were 1.93 times (95% CI [1.58, 2.35]) more likely to be in the high symptom cluster group compared to participants who were not treated with radiotherapy. Specifically, among types of radiotherapy, participants who were treated with radiotherapy in the head or neck area showed the highest likelihood such that they were 1.91 times more (95% CI [1.57, 2.31]) likely to be in the high symptom cluster group compared to participants who were not treated with radiotherapy in the head or neck area. Participants who were treated in the chest or lung areas, or pelvis, abdominal, or urinary areas each showed 1.7 times greater likelihood of being in the high symptom cluster group compared to participants who were not treated in each of the same areas. The surgery variable was not statistically significantly different between the two symptom clusters.

Also, the modality of treatment was examined since most types of cancer were treated with a combination of treatments including chemotherapy, radiotherapy, and

surgery. The modality of treatment was regrouped for this analysis. Participants who were treated with only chemotherapy (reference group) were categorized into one group that was used as the reference group. Participants who were treated with chemotherapy and radiotherapy; chemotherapy and surgery; surgery only; or radiotherapy only were categorized into one group (middle group). Participants who were treated with three types of treatments including chemotherapy, surgery, and radiotherapy; and surgery and radiotherapy were categorized into one group (last group). It is expected that the last group has the highest risk of symptoms compared to the reference group that was only treated with chemotherapy. As expected, participants in the last group were 2.47 times (95% CI [1.74, 3.49]) more likely to be in the highest cluster symptom group compared to participants who were treated with chemotherapy alone. Participants in the middle group were 1.70 times (95% CI [1.20, 2.41]) more likely to be in the high symptom cluster group compared to those who were treated with chemotherapy alone.

B3. Demographic and clinical predictors of cluster membership (using multivariable analysis). Multivariable analyses were conducted using regression analysis. The results are presented in Table 5. Several variables were used, including participants' ages at that time of survey, gender, race, educational attainment, marital status, employment status, difficulty obtaining health insurance, annual personal income, alkylating chemotherapeutic agents, and head/neck area radiotherapy. These variables were statistically significantly different between the two symptom clusters. Survivors older than 40 years old at the survey had 2.16 times (95% CI [1.41, 3.32]) greater likelihood to be in the high symptom cluster group compared to survivors with younger

age (between 18 to 29 years old) at the time of the survey. Female patients were 1.37 times (95% CI [1.08, 1.75]) more likely to be in the high symptom cluster group compared to male patients. The ethnicity/race variable was not significant using the bivariate analysis, but it was statistically significant using multivariable analysis. For example, patients who were non-Hispanic White were 1.55 times (95% CI [1.13, 2.14]) more likely to be in the high symptom cluster group compared to other races/ethnicities (e.g., non-Hispanic Black and other races).

Those attaining the lowest level of education were more likely to be in the high symptom cluster group (OR: 2.77, 95% CI [1.84, 4.16]) compared to the reference group that has more than a college education. Unmarried survivors (e.g., living with partner, widowed, divorced, separated, or single) showed 1.50 times (95% CI [1.16, 1.94]) greater likelihood of being in the high symptom cluster compared to those currently married. Survivors with currently unemployed status were 2.58 times (95% CI [1.97, 3.38]) more likely to be in the high symptom cluster group compared to employed survivors. With regard to income, survivors who had lower annual personal income (none to ≤ $19,999) were 1.76 times (95% CI [1.12, 2.79]) more likely to be in the high symptom cluster group compared to survivors with the highest income level (≥ $60,000).

Regarding chemotherapy, alkylating agents was the only significant factor more likely to be found in the high symptom cluster group. For example, survivors who were treated with alkylating agents were 1.30 times (95% CI [1.00, 1.69]) more likely to be in the high symptom cluster compared to survivors who were not treated with that agent. Among types of radiotherapy, survivors who were treated with head or neck radiotherapy

were the only statistically significant type. Those receiving head or neck radiotherapy were 1.48 times (95% CI [1.12, 1.96]) more likely to be in the high symptom cluster compared to those not treated with head or neck radiotherapy.

Table 5

Associations of Symptom Subgroups with Demographics and Clinical Variables

	Bivariate analysis			Multivariable analysis		
	High symptom cluster vs. Low symptom cluster					
	OR	*p*	95% CI LL UL	OR	*p*	95% CI LL UL
Age at survey						
18-29 years	ref			ref		
30-39 years	1.48	<.0001	[1.19, 1.83]	2.04	<.0001	[1.49, 2.80]
≥ 40 years	1.92	<.0001	[1.49, 2.48]	2.16	<.0001	[1.41, 3.32]
Time since cancer diagnosis						
10-29 years	ref			ref		
≥ 30 years	1.45	<.0001	[1.20, 1.75]	1.21	.241	[0.88, 1.67]
Age at cancer diagnosis						
0-4 years	ref					
5-9 years	1.19	.185	[0.93, 1.53]			
≥ 10 years	1.35	<.0001	[1.09, 1.68]			
Sex						
Male	ref					
Female	1.41	<.0001	[1.17, 1.71]	1.37	.010	[1.08, 1.75]
Race/ethnicity						
White, non-Hispanic	1.23	.105	[0.96, 1.57]	1.55	.007	[1.13, 2.14]
Others	ref			ref		
Educational background						
Less than high school diploma	3.90	<.0001	[2.78, 5.48]	2.77	<.0001	[1.84, 4.16]
High school graduate/GED	2.16	<.0001	[1.66, 2.82]	1.97	<.0001	[1.42, 2.75]
Some college/ training after high school	1.45	.002	[1.15, 1.84]	1.45	<.0001	[1.09, 1.94]
More than college education	ref					
Marital status						
Married	ref			ref		
Living with a partner/ widowed/ divorced/ separated/single	1.30	.008	[1.07, 1.58]	1.50	.002	[1.16, 1.94]
Employment status						
Currently employed	ref					

Currently unemployed	3.36	<.0001	[2.75, 4.10]	2.58	<.0001	[1.97, 3.38]
Had difficulty obtaining health insurance						
No	ref					
Yes	2.27	<.0001	[1.83, 2.81]	2.09	<.0001	[1.62, 2.71]
Annual household incomes						
≤$39,999	2.48	<.0001	[1.98, 3.10]			
$40,000 to $79,999	0.87	.291	[0.66, 1.13]			
≥$80,000	ref					
Annual personal income						
None to ≤$19,999	2.49	<.0001	[1.81, 3.42]	1.76	.015	[1.12, 2.79]
$20,000 to $59,999	1.10	.593	[0.78, 1.55]	1.24	.339	[0.80, 1.92]
≥$60,000	ref			ref		
Second cancer						
No	ref					
Yes	1.48	.004	[1.14, 1.92]			
Cancer Diagnosis						
Leukemia	ref					
Lymphoma	1.39	.010	[1.08, 1.79]			
Central nervous system tumor	1.60	.004	[1.16, 2.20]			
Sarcoma	0.78	.035	[0.61, 0.98]			
Chemotherapy						
Any chemotherapy	1.28	.038	[1.01, 1.62]			
Corticosteroids	1.13	.213	[0.93, 1.36]			
Mercaptopurine/Thioguanine	1.07	.481	[0.88, 1.30]			
Methotrexate	0.96	.674	[0.80, 1.16]			
Erwinia-/ L-/ Peg-asparaginase	0.92	.390	[0.75, 1.12]			
	1.37	.023	[1.05, 1.80]	1.32	.138	[0.92, 1.89]
Cisplatin/carboplatin/oxaliplatin						
Anthracycline	1.47	<.0001	[1.21, 1.79]			
Alkylating agents	1.49	<.0001	[1.25, 1.82]	1.30	.050	[1.00, 1.69]
Vincristine	1.15	.185	[0.94, 1.41]	1.01	.935	[0.76, 1.36]
Other agents	1.04	.647	[0.87, 1.26]			
Radiotherapy						
Any radiotherapy	1.93	<.0001	[1.58, 2.35]			
Head/neck area	1.91	<.0001	[1.57, 2.31]	1.48	.006	[1.12, 1.96]
Chest/lung area	1.67	<.0001	[1.42, 1.96]	1.96	.297	[0.77, 2.31]
Pelvis/abdominal/urinary area	1.69	<.0001	[1.39, 2.06]	0.80	.476	[0.43, 1.48]
Reproductive area	1.50	<.0001	[1.21, 1.87]	1.02	.930	[0.67, 1.54]
Muscle area	1.57	<.0001	[1.30, 1.90]	1.18	.669	[0.55, 2.50]
Invasive surgery	1.18	.126	[0.96, 1.45]	1.32	.067	[0.98, 1.78]
Types of treatments						
Chemotherapy alone	ref					
Chemotherapy + Radiotherapy;	1.70	.003	[1.20, 2.41]			

Chemotherapy + Surgery; Surgery only; Radiotherapy only;			
Chemotherapy + Surgery+ Radiotherapy; Surgery + Radiotherapy	2.47	<.0001	[1.74, 3.49]

Note. Leukemia includes (Acute lymphoblastic leukemia, acute myeloid leukemia, & other leukemia); Lymphoma includes (Hodgkin's lymphoma & non-Hodgkin's lymphoma); Sarcoma includes (Ewing's Sarcoma, osteosarcoma, rhabdomyosarcoma, neuroblastoma Wilms' tumor, & bone tumors); OR=Odds ratio; CI=confidence interval; LL=low limit, UL=upper limit; ref=reference.

Hypothesis C.

It was hypothesized that cluster membership would be associated with more negative distal outcomes such that those in the high symptom group would show lower physical and mental functioning. This hypothesis was supported. Table 6 represents this result. Those in the high symptom cluster group reported a lower physical component summary score (M = 40.19, *SE* = 0.40) and a lower mental component summary score (M = 36.09, *SE* = 0.46) compared to the HRQOL scores of the low symptom cluster group.

Table 6

Difference in HRQOL for Each Class in Survivors of Childhood Cancers

	High symptom cluster (*n* = 888, 28.4%) *M* (*SD*)	Low symptom cluster (*n* = 2241, 71.6%) *M* (*SD*)	χ^2	*p*
Physical Component Summary	40.19 (0.40)	54.98 (0.16)	**1181.11**	**<.0001**
Mental Component Summary	36.09 (0.46)	53.08 (0.21)	**1070.90**	**<.0001**

C1. Demographic, clinical predictors, and physical HRQOL. Multivariable logistic analyses were conducted to examine the relationships between demographics, treatment variables, and HRQOL. HRQOL includes a physical component summary (PCS) and a mental component summary (MCS) score. Table 7 and Table 8 summarize the analysis results. Age at time of survey, educational background, employment status, having difficulty obtaining health insurance, annual personal income, two types of chemotherapy, and one type of radiotherapy showed statistically significant effects on PCS. Specifically, for a unit of change of age in survivors older than 40 at survey (compared to survivors from 18 to 29 years old at the time of survey), the PCS changed by -4.80 (95% CI [-6.11, -3.49], holding all other variables constant. Regarding education, for a unit of change of education in survivors with less than a high school diploma compared to survivors with more than a college education, PCS changed by -3.19 (95% CI [-4.64, -1.74]), holding all other variables constant. For a unit of change of unemployment status, the PCS changed by -2.39 (95% CI [-3.25, -1.53]), holding all other variables constant. For one unit of change of annual personal income from none to ≤ 19,999 compared to annual personal income ≥ $60,000, PCS changed by -1.77 (95% CI [-2.91, -0.63]), holding all other variables constant. With regard to chemotherapy, with one unit of change of using platinum chemotherapy (cisplatin/carboplatin/oxaplatin), the PCS changed by -1.51 (95% CI [-2.57, -0.45]), holding all other variables constant. Regarding radiotherapy, one unit of change of radiotherapy treatment in the muscle, the PCS changed by -2.39 (95% CI [-4.47, -0.31]), holding all other variables constant.

Table 7

Multivariable Associations of Demographic and Clinical Variables with PCS

PCS	β	*SE*	*p*	95% CI	
				LL	UL
Age at survey					
18-29 years	ref				
30-39 years	-2.18	0.45	<.0001	[-3.06, -1.30]	
≥ 40 years	-4.80	0.67	<.0001	[-6.11, -3.49]	
Time since cancer diagnosis					
10-29 years	ref				
≥ 30 years	-0.74	0.46	.107	[-1.64, 0.16]	
Sex					
Male	ref				
Female	-0.29	0.34	.391	[-0.96, 0.38]	
Race/ethnicity					
White, non-Hispanic	0.10	0.42	.807	[-0.72, 0.92]	
Other	ref				
Educational background					
Less than high school diploma	-3.19	0.74	<.0001	[-4.64, -1.74]	
High school graduate/ GED	-1.19	0.50	.018	[-2.17, -0.21]	
Some college/ training after high school	-0.54	0.40	.172	[-1.32, 0.24]	
More than college education	ref				
Marital status					
Married	ref				
Living with a partner/widowed/ divorced/ separated/single	0.43	0.36	.237	[-0.28, 1.14]	
Employment status					
Currently employed	ref				
Currently unemployed	-2.39	0.44	<.0001	[-3.25, -1.53]	
Had difficulty obtaining health insurance					
No	ref				
Yes	-1.48	0.42	<.0001	[-2.30, -0.66]	
Annual personal income					
None to ≤$19,999	-1.77	0.58	.002	[-2.91, -0.63]	
$20,000 to $59,999	-0.92	0.49	.060	[-1.88, 0.04]	
≥$60,000	ref				
Chemotherapy					
Cisplatin/carboplatin/oxaliplatin	-1.51	0.54	.005	[-2.57, -0.45]	
Alkylating agents	-0.71	0.36	.047	[-1.42, 0.00]	
Vincristine	0.60	0.40	.134	[-0.18, 1.38]	
Radiotherapy					
Head/neck area	0.03	0.39	.946	[-0.73, 0.79]	

Chest/lung area	1.51	0.77	.052	[0.00, 3.02]
Pelvis/abdominal/urinary area	-0.51	0.96	.598	[-2.39, 1.37]
Reproductive area	0.29	0.60	.634	[-0.89, 1.47]
Muscle area	-2.39	1.06	.025	[-4.47, -0.31]
Invasive surgery	-0.43	0.38	.256	[-1.17, 0.31]

Note. Leukemia includes (Acute lymphoblastic leukemia, acute myeloid leukemia, & other leukemia); Lymphoma includes (Hodgkin's lymphoma & non-Hodgkin's lymphoma); Sarcoma includes (Ewing's Sarcoma, osteosarcoma, rhabdomyosarcoma, neuroblastoma Wilms' tumor, & bone tumors); CI=confidence interval; LL=low limit, UL=upper limit; ref=reference.

C2. Demographic, clinical predictors, and mental HRQOL. Several variables showed statistically significant effects on the MCS in several categories including sex, education, marital status, employment status, difficulty obtaining health insurance, and two kinds of chemotherapies. Table 8 presents these results. For females, the MCS changed by -1.69 (95% CI [-2.47, -0.91]), holding all variables constant. For one unit change of education, the MCS changed by -1.91 (95% CI [-3.60, -0.22]), holding all variables constant. Interestingly, some types of chemotherapy showed positive effects on better mental health. For example, for one unit change of treatment with platinum drugs (cisplatin/carboplatin/oxaliplatin), the MCS changed by 1.60 (95% CI [0.33, 2.87]), holding all variables constant. For one unit change of treatment with alkylating agents, the MCS changed by 1.07 (95% CI [0.23, 1.91]), holding all variables constant. In a multivariable analysis, there were no significant effects between radiation therapy and MCS.

Table 8

Multivariable Associations of Demographic and Clinical Variables with MCS

MCS	β	*SE*	*p*	95% CI	
				LL	UL
Age at survey					
18-29 years	ref				
30-39 years	-0.23	0.51	.655	[-1.23, 0.77]	
≥ 40 years	0.73	0.73	.321	[-0.70, 2.16]	
Time since cancer diagnosis					
10-29 years	ref				
≥ 30 years	0.23	0.51	.655	[-0.77, 1.23]	
Sex					
Male	ref				
Female	-1.69	0.40	<.0001	[-2.47, -0.91]	
Race/ethnicity					
White, non-Hispanic	-0.27	0.51	.594	[-1.27, 0.73]	
Other	ref				
Educational background					
Less than high school diploma	-1.91	0.86	.026	[-3.60, -0.22]	
High school graduate/ GED	0.48	0.57	.403	[-0.64, 1.60]	
Some college/ training after high school	0.16	0.46	.725	[-0.74, 1.06]	
More than college education	ref				
Marital status					
Married	ref				
Living with a partner/ widowed/ divorced/ separated/single	-1.09	0.43	.011	[-1.93, -0.25]	
Employment status					
Currently employed	ref				
Currently unemployed	-1.73	0.52	.001	[-2.75, -0.71]	
Had difficulty obtaining health insurance					
yes	ref				
no	-1.02	0.48	.034	[-1.96, -0.08]	
Annual personal income					
None to ≤$19,999	-0.43	0.66	.519	[-1.72, 0.86]	
$20,000 to $59,999	-0.71	0.53	.180	[-1.75, 0.33]	
≥$60,000	ref				
Chemotherapy					
Cisplatin/carboplatin/oxaliplatin	1.60	0.65	.014	[0.33, 2.87]	
Alkylating agents	1.07	0.43	.012	[0.23, 1.91]	
Vincristine	-0.60	0.48	.214	[-1.54, 0.34]	
Radiotherapy					
Head/neck area	0.44	0.45	.325	[-0.44, 1.32]	
Chest/lung area	1.01	0.93	.282	[-0.81, 2.83]	

Pelvis/abdominal/urinary area	-0.21	1.13	.852	[-2.42, 2.00]
Reproductive area	-0.56	0.69	.416	[-1.91, 0.79]
Muscle area	0.51	1.28	.693	[-2.00, 3.02]
Invasive surgery	-0.32	0.47	.495	[-1.24, 0.60]

Note. Leukemia includes (Acute lymphoblastic leukemia, acute myeloid leukemia, & other leukemia); Lymphoma includes (Hodgkin's lymphoma & non-Hodgkin's lymphoma); Sarcoma includes (Ewing's Sarcoma, osteosarcoma, rhabdomyosarcoma, neuroblastoma Wilms' tumor, & bone tumors); CI=confidence interval; LL=low limit, UL=upper limit; ref=reference.

Hypothesis D.

During the data analysis, the comprehensive relationships among predictors, symptom clusters, and HRQOL were examined. In particular, the moderating effect of the symptom clusters between predictors and quality of life were tested. These relationships were tested in order to more comprehensively understand the relationships between predictors, symptom clusters, and HRQOL among these survivors. Four common variables were found that demonstrated a statistically significant effect on both PCS and MCS. These variables included educational background (less than a high school diploma), difficulty obtaining health insurance, employment status, and two types of chemotherapy (cisplatin/carboplatin/oxaliplatin and alkylating agents). The Wald test was used to examine the moderating effects of symptom cluster membership on the relationship between these four predictors and both physical HRQOL and mental HRQOL using Mplus. The "omnibus" Wald test (in which all moderating effects were tested) was significant overall. Following this significant omnibus Wald test, individual tests were performed for each relationship. Table 9 presents the relationship between predictors and HRQOL in each symptom cluster. For example, for individuals in the high symptom cluster group who had less than a high school diploma, their educational level

had a stronger negative relationship with better physical HRQOL compared to individuals in the low symptom cluster group, whereas this educational level had a significant effect on mental HRQOL only in the high symptom clusters group. Regarding chemotherapy, use of alkylating agents had a significantly stronger impact on physical HRQOL for those in the high symptom cluster group compared to those in the low symptom cluster group. However, the alkylating agents had a significant effect on mental HRQOL only for those in the low symptom cluster group; the estimator was less than 1.0.

Table 9

Omnibus Wald Test Results of Coefficient Equality of Predictors on PCS and MCS

	High symptom cluster					Low symptom cluster				
PCS	β	*SE*	*p*	95% CI		β	*SE*	*p*	95% CI	
				LL	UL				LL	UL
Education										
≤ High school	-2.79	1.03	.007	[-4.81, -0.77]		-1.59	0.67	.017	[-2.90, -0.28]	
≥ College	ref									
Had difficulty obtaining health insurance										
No	ref									
Yes	-2.92	0.81	.0001	[-4.51, -1.33]		-0.93	0.36	.011	[-1.64, -0.22]	
Employment										
Currently employed	ref									
Currently unemployed	-5.33	0.81	.0001	[-6.92, -3.74]		-0.23	0.34	.497	[-0.90, 0.44]	
Chemotherapy										
Cisplatin/carboplatin/oxaliplatin	-0.25	1.01	.802	[-2.23, 1.73]		-0.99	0.49	.042	[-1.95, -0.03]	
Alkylating agents	-1.93	0.81	.017	[-3.52, -0.34]		-0.55	0.25	.029	[-1.04, -0.06]	

MCS	β	*SE*	*p*	95% CI		β	*SE*	*p*	95% CI	
				LL	UL				LL	UL
Education										
≤ High school	-3.01	1.44	.037	[-5.83, -0.19]		-0.49	0.83	.557	[-2.12, 1.14]	
≥ College	ref									
Had difficulty obtaining health insurance										
No	ref									
Yes	-1.38	0.94	.144	[-3.22, 0.46]		-1.29	0.39	.001	[-2.05, -0.53]	
Employment										
Currently employed	ref									
Currently unemployed	-2.54	0.94	.007	[-4.38, -0.70]		-0.97	0.41	.018	[0.17, 1.77]	
Chemotherapy										
Cisplatin/carboplatin/oxaliplatin	3.78	1.29	.003	[1.25, 6.31]		0.66	0.55	.227	[-0.42, 1.74]	
Alkylating agents	1.77	0.98	.070	[-0.15, 3.69]		0.77	0.33	.022	[0.12, 1.42]	

Note. CI=confidence interval; LL=low limit, UL=upper limit; ref=reference.

Summary of Results

The objective of this chapter was to report the results related to the research questions and hypotheses in the current study. A substantial sample (*n* = 3,129) was used for these analyses. A person-centered approach, Vermunt's three-step approach, was employed using Mplus software. All of the hypotheses were supported. The first hypothesis stated that there would be subgroup membership of survivors who shared common profiles across multiple symptoms associated with their childhood cancer and its treatments. This hypothesis was supported in that two different groups were identified: the high symptom cluster and low symptom cluster.

The second hypothesis stated that demographic and clinical variables would differentially predict subgroup membership. This second hypothesis was supported. Except for a few variables, most of the variables predicted subgroup membership of the symptom cluster. For example, survivors with lower education status, lower income, those who were unemployed, those of older age at the time of the survey (more than 40 years old), those with a longer time since the cancer diagnosis, and females were more likely to be in the high symptom cluster group. Regarding clinical variables, survivors with older age at cancer diagnosis (more than 10 years old), those who had experienced secondary cancer, were diagnosed with lymphoma or central nervous system tumors cancers, those treated with any type of chemotherapy, those treated with any radiotherapy, and those treated with a combination of therapies (chemotherapy, radiotherapy, and surgery) were more likely to be in the high symptom cluster group.

The third hypothesis stated that survivors who belonged to the high physical and psychological symptoms subgroups would have poorer HRQOL. This hypothesis was supported. Survivors who belonged to the high symptom cluster group showed lower physical summary and mental summary scores compared to survivors who belonged to the low symptom cluster group.

The fourth hypothesis stated that there would be mediating effects of symptom subgroup membership between demographic variables, clinical predictors and HRQOL. This hypothesis was supported. The results of this chapter will be discussed in the next chapter, including comparison of findings with other research findings, limitations of the current study, implications for clinicians, and recommendations for future study.

CHAPTER V

DISCUSSION

The purpose of this study was to identify subgroup membership among survivors of childhood cancer and to find factors related to HRQOL status. Chapter V provides an interpretation of the findings related to the four hypotheses. The Dynamic Symptoms Model was used as the theoretical framework to identify the relationship between sociodemographic variables, symptom clusters, and patient outcomes. Using mixture modeling, two symptom clusters were identified as a best-fitting model, and various sociodemographic and clinical factors related to symptom clusters and HRQOL were examined. Major findings about the relationships between predictors and each symptom cluster, and between predictors and HRQOL, were also examined. In addition, eight different types of chemotherapy and five different body areas of radiotherapy and their relationship with HRQOL were tested. In this chapter, these findings are compared and contrasted with prior research on symptom clusters in adult survivors of cancer and childhood cancer. Clinical, research, and nursing implications are presented and limitations for this study are discussed. Finally, future research recommendations are also addressed.

Few studies have examined symptom clusters and HRQOL among survivors of childhood cancer. The few studies that have been conducted included less than 150

participants (Hockenberry et al., 2011; Yeh et al., 2008). These prior studies examined sociodemographic and clinical factors in the context of symptom clusters. The current study included 3,129 participants. In the current project, detailed treatment information was examined, including several types of chemotherapy and radiotherapy of various body parts, in order to explore their relationships to symptom clusters and HRQOL among the childhood cancer survivors.

Overall, findings from this study suggest that participants who were older when they took the survey, those for whom more time has passed since their cancer diagnosis, were female, had a lower educational level, were unmarried, unemployed, and had lower incomes were more likely to be in the high symptom cluster group. In addition, participants who had experienced secondary cancer, had been diagnosed with CNS tumors or lymphoma, or had been treated with chemotherapy or radiotherapy were more likely to be in the high symptom cluster group. In this current study, the symptom clusters based on symptom levels were related to quality of life of survivors. For example, survivors who were in the low symptom cluster reported better physical HRQOL and mental HRQOL than survivors who were in the high symptom cluster group.

Several sociodemographic factors and clinical factors were found to be related to poorer HRQOL among survivors. Those who were older when they took the survey, had less than a high school diploma, were unemployed at the time of the survey, had a lower annual personal income (less than $19,999), and were treated with either chemotherapy or muscle radiotherapy were more likely to report poorer physical HRQOL. Survivors

who were female, had less than a high school diploma, answered "other" to the marital status questions (i.e., living with partner, widowed, divorced, separated, or single), were unemployed at the time of the survey, and had difficulty obtaining health insurance were more likely to report poorer mental HRQOL. However, being treated with certain chemotherapy (i.e., cisplatin/carboplatin/oxaliplatin, or alkylating agents) was associated with better mental health. Detailed information about predictors of symptom clusters and the relationship between predictors, symptom clusters, and HRQOL are reported below and compared with the findings from other studies.

Participant Demographics

There were 3,129 study participants who were treated for their cancer at St. Jude Children's Research Hospital and subsequently surveyed through the St. Jude Life Cohort Study (SJLIFE), included in this study. The study participants were nearly evenly distributed between the genders. Other studies on survivors of childhood cancer have reported similar rates of participation by both genders (Ameringer, Erickson, Macpherson, Stegenga, & Linder, 2015). In the current study, most participants were non-Hispanic White, 13 % were non-Hispanic Black, and nearly 5% were Hispanic. Ameringer's study included 72 participants with adolescent and young adult cancer: 79% non-Hispanic White and 10% non-Hispanic Black. Using the Childhood Cancer Survivor Study (CCSS) data, Nolan et al. studied HRQOL among survivors of adolescent cancer. With 2,064 cancer survivors participating, 92% were non-Hispanic White (Nolan et al., 2014). This race/ethnicity breakdown is similar to the current study.

In the current study, the majority of participants had obtained more than a high school diploma; more than one-third of the participants had a college degree or higher. These reported education levels are similar to other studies. Among 425 survivors of childhood cancer in Switzerland, more than 90% had obtained more than secondary education (Wengenroth et al., 2015). In a report using the CCSS data, 44% of participants had a college degree (Nolan et al., 2014). In another study of 170 survivors of childhood cancer, 73% had at least some college education (Badr et al., 2013).

In this study, half of the participants were married. In a different study, 25% (*n* = 7) of survivors of bone tumors were married (Barrera, Teall, Barr, Silva, & Greenberg, 2012). However, the mean age of those participants was 24 years, which is younger than the mean age of participants in the study reported here. Employed participants accounted for 66.8% of the sample at the time of the survey and they reported working full-time or part-time. This percentage is higher than Badr et al.'s study, which found that 52% of participants were employed (Badr et al., 2013). In the current study, most participants had insurance and had no difficulty obtaining health insurance. Twelve percent of participants had no personal income annually, and 40% of participants had incomes of less than $19,999 per year. Participants who earned between $20,000 and $59,999 per year made up 36% of the sample.

Leukemia and sarcoma were the most prevalent types of cancer reported, with lymphoma (20.2%) the next most prevalent. Central nervous system tumors accounted for less than 10% of reported cancers. In one study in Switzerland, leukemia was the most common cancer among children, and CNS tumor and lymphoma were each 8%

(n=32) (Wengenroth et al., 2015). The rate of survivors who reported CNS tumors in that study is similar to the current study, but lymphoma was less prevalent in the current study. If all of their categories including neuroblastoma, renal tumor, bone tumor, soft tissue sarcoma are categorized into a general sarcoma category (as in the current study), then the rate of sarcoma is similar between the two studies. In another study, Ameringer et al. included participants of older age at cancer diagnosis (mean 18.5 years), and leukemia and lymphoma were the most prevalent types of cancer in this age group (respectively 20% and 30%) (Ameringer et al., 2015). In the current study, fifteen percent of participants reported experiencing secondary cancer. Childhood cancer survivors who reported a relapse experience accounted for approximately 11% in other studies (Hsiao et al., 2017; Wengenroth et al., 2015).

In the current study, the majority of participants (77%) were treated with chemotherapy, and 60% of participants were treated with radiotherapy. In Wengenroth et al.'s study, most survivors received chemotherapy (81%, n = 344), more than half received surgery (59%, n = 252), and less than 20% had radiotherapy (17%, n = 74) (Wengenroth et al., 2015). The difference between the studies in percentage of participants receiving radiotherapy treatment might be related to the treatment era or type of cancer. For example, Wengenroth's participants were diagnosed between 1976 and 2005, and participants in the current study were diagnosed with cancer between 1962 and 2002. Radiation therapy is an essential treatment for childhood cancer survivors, but it can bring long-term complications. Physical body and tissues are still growing in children and adolescents, so tissues or organs can be sensitive to radiotherapy. The complications

or late effects from radiotherapy are associated with the treated organs, type of radiation administered, daily treatment, accumulated dose, and age at the time of treatment (Oeffinger & Hudson, 2004). It has been known that complications of brain radiotherapy are a decrease in cognitive function. In order to decrease complications, reduced dosages have been used with similar efficacy (Oeffinger & Hudson, 2004). Armstrong and colleagues studied long-term effects of radiation exposure using nearly 14,000 survivors from the childhood cancer survivor study (CCSS) data. They found that survivors who were treated with radiotherapy have an increased risk of late mortality (defined as death occurring 5 years after their cancer diagnosis), secondary cancer, obesity, pulmonary and cardiac dysfunction, and chronic conditions (Armstrong et al., 2010). In the current study there were more types of lymphoma and sarcoma that might have necessitated radiotherapy. Half of the participants were treated with head/neck radiotherapy. In addition, 70% of participants had invasive surgery that was related to their cancer or treatment within five years of their cancer diagnosis.

Discussion of Hypotheses

Hypothesis A.

Hypothesis A was supported in that two meaningful subgroups of survivors with heterogeneous symptom patterns were identified. Several risk factors were associated with the long-term complications of childhood cancer including type of cancer, age at the time of treatment, and whether or not they were receiving chemotherapy and radiation therapy (Oeffinger, Hudson, & Landier, 2009). Individuals were clustered based on their symptom patterns. Two distinctive subgroups were found that represent different patterns

of symptom clusters in survivors of childhood cancer. Survivors who are in the high symptom cluster reported high scores for both physical and psychological symptoms, and survivors in the low symptom group reported low scores for both sets of symptoms. These groups were named the high symptom cluster and the low symptom cluster.

Other studies of symptom clusters among adults with cancer have identified a similar number of clusters, usually between three and five. In addition, researchers have named clusters based on the unique symptoms of each cluster. For example, Kim and colleagues defined five symptom clusters using a longitudinal design. These five groups were the "constantly low symptom subgroup"; "gradually increasing symptom subgroup"; "start low with dramatic increase and decrease patterns subgroup"; "constantly high pattern subgroup"; and the "start high with dramatic increase and decrease pattern subgroup" (Kim et al., 2014). Also, Miaskowski and colleagues identified four symptom clusters based on patients' experiences with four highly prevalent symptoms (Miaskowski et al., 2006). Their four subgroups were high fatigue and low pain; all low symptoms (i.e., low fatigue and low pain); low fatigue and high pain; and all high symptoms (i.e., high fatigue and high pain). Yeh and colleagues identified five symptom clusters using a variable-centered approach in older Taiwanese children with cancer (Yeh et al., 2008). Their five symptom clusters were symptoms of sensory discomfort and body image; circulatory and respiratory system malfunction; fatigue, sleep disturbance, and depression; body image and eating difficulties; and gastrointestinal irritations and pain. Thus, researchers have identified several subgroups based on characteristics of each symptom cluster in survivors of cancer patients.

Hypothesis B.

Hypothesis B was supported in that demographic or clinical factors differentially predicted subgroup membership. The two groups are associated with different sociodemographic characteristics and clinical factors. Survivors who belong to the high symptom cluster group were older in age (i.e., more than 40 years old at the time of the survey); were older at the time of cancer diagnosis (i.e., more than 10 years old); were female; and had a lower level of educational attainment (i.e., less than a high school diploma). In addition, these groups included survivors who had a marital status other than married, such as divorced, single, widowed, or live with partner. Survivors who had no job, had difficulty obtaining health insurance, had a lower annual personal income of less than $19,999, and who had experienced secondary cancer were more likely to be in the high symptom cluster group.

Sociodemographic factors. In the current study, most variables (including sex, education, marital status, employment status, insurance status, annual personal income, annual household income, cancer diagnosis, secondary cancer, whether or not received and type of chemotherapy, and whether or not received and type of radiotherapy) were statistically significantly different between the high symptom cluster and the low symptom cluster. The variables of race, age at interview, age at cancer diagnosis, and experience with surgery were not different between the clusters. There are few studies that examine symptom clusters in survivors of childhood cancer (Ameringer et al., 2015; Erickson et al., 2013; Hockenberry et al., 2010, 2011; Yeh et al., 2008), so the current study's findings were also compared with studies of adults with cancer. As mentioned in

Chapter II, studies examining the potential for symptom clusters among cancer survivors began less than two decades ago, these have primarily been among those with adult cancers, and only a few studies have examined associations between experiencing symptoms and patient outcomes including functioning and quality of life (Barsevick et al., 2006b; Dodd et al., 2001a; Miaskowski et al., 2006).

Among demographic and clinical factors, employment was the only significant factor among four cluster symptom groups in breast cancer patients (Dodd et al., 2010). In particular, as might be expected, employed participants belonged to the low symptom cluster group rather than the moderate or high symptom cluster group (Dodd et al., 2010). A study examining symptom clusters in adult breast cancer patients showed that race was not statistically significantly different in the two subgroups (Kim et al., 2012), which was similar to the results in the current study. In Kim and Beck's study, marital status, employment status, and symptom management were not significantly different among subgroups prior to chemotherapy and/or radiation treatment or within a month after treatment. However, the differences in these variables are statistically significant among subgroups in the current study. This may be because of the time passed since treatments. The current study has long-term survivors' data regarding symptoms, but Kim and colleagues had short-term data regarding symptoms immediately following cancer treatment. Symptom frequencies or levels in cancer patients who have recently completed their treatments might be different from those who are long-term survivors and who are many years beyond their treatments.

***Clinical factors*.** Survivors who were diagnosed with lymphoma or a central nervous system tumor belonged to the high symptom cluster group. Oeffinger and colleagues' study supports that survivors who were treated for a central nervous system tumor and Hodgkin's lymphoma were considered as belonging to a high-risk group experiencing more late effects (Oeffinger et al., 2009). In the current study, survivors who were treated with either chemotherapy or radiotherapy were more likely to be in the high symptom cluster group. Invasive surgery was not associated with either symptom cluster group. Specifically, survivors who were treated with two different categories of chemotherapy including "cisplatin/carboplatin/oxaliplatin" and "alkylating" agents were more likely to be in the high symptom cluster group. Use of chemotherapy including bleomycin, busulfan, and cyclophosphamide have been shown to be related to pulmonary fibrosis (Kaplan et al., 1996; O'Driscoll et al., 1990), arguably resulting in symptoms that might be associated with those in the high symptom cluster in the current study. Similarly, in Armstrong et al. (2010)'s study, being given certain types of chemotherapy including cyclophosphamide, bleomycin, busulfan, carmustine, and lomustine was associated with increased pulmonary complications. These pulmonary complications could persist up to 25 years after cancer diagnosis (Armstrong et al., 2010). Also, use of anthracycline chemotherapy and radiotherapy are associated with cardiotoxicity (Adams & Lipshultz, 2005). Cardiac toxicity is a major cause of morbidity and mortality in survivors of childhood cancer. These serious symptoms likely would have resulted in high symptom cluster membership.

In the current study, most body areas of radiotherapy were associated with the high symptom cluster group. In particular, survivors who were treated with head or neck radiotherapy were most likely to be in the high symptom cluster compared to those receiving other body areas of radiotherapy. Survivors who were treated with radiotherapy may have late effects immediately after treatment or experience them many years later (K, C. Oeffinger et al., 2009). For example, survivors who were treated with radiotherapy showed three times greater likelihood of developing medical conditions and an eightfold increase in the likelihood of having severe health conditions (Armstrong et al., 2010). In a study that examined long-term effects of radiation exposures in childhood cancer survivors using CCSS data, survivors who were treated with radiotherapy showed late mortality, increased risk of developing secondary cancer, pulmonary, cardiac, and thyroid dysfunction, as well as increased risks for chronic health conditions (Armstrong et al., 2010). Use of radiotherapy is associated with long-term pulmonary toxicity and is consistent with membership in the high symptom cluster.

In the current study, the average time since cancer diagnosis was 23 years. Among the various body areas of radiotherapy reported by participants, head/neck and chest/lung radiotherapy were included in the analyses since a higher percentage of participants were treated in these areas of radiotherapy than in other body areas. The higher prevalence of brain radiotherapy is due to the fact that brain radiation is used to treat survivors who have a brain tumor, acute lymphoblastic leukemia, had and neck soft tissue sarcoma, and retinoblastoma in the head or neck (Oeffinger & Hudson, 2004; Reimers et al., 2003). Patients who were treated with brain radiation can develop

cognitive dysfunction. In particular, survivors who were treated with high dose brain radiotherapy showed a decrease in cognitive function. This decreased function was related to cancer survivors being less likely to graduate from high school, to gain employment, and to live independently from their parents (Reimers et al., 2003).

In the current study, one fourth of the long-term survivors experienced a memory/learning problem. This might be related to the treatment of brain radiotherapy. However, the percentage of participants in this study who had obtained a high school diploma was 90%, better than the U. S public high school graduation rate (83%) in the 2014-2015 academic year (National Center for Education Statistics, 2017). In the current study, one-third of participants were unemployed, lower than the 4.3% U. S unemployment rate in 2017 (United States Department of Labor, 2017). Some of these findings may be consistent with Reimers et al.'s (2003) findings that the effects of brain radiotherapy in brain tumor survivors were associated with cognitive function decrease. However, more research in this area is needed to better understand the unique effects of brain radiotherapy and the association with patients' outcomes.

In the current study, survivors who were treated with chest or lung radiotherapy were more likely to be in the high symptom cluster group. In another study, female childhood cancer patients who were treated with chest radiotherapy showed a 10-20% prevalence of breast cancer when they became young adults, older than 30 years (Kenney et al., 2004; Taylor, Winter, Stiller, Murphy, & Hawkins, 2007). Moreover, chest radiotherapy has also been associated with cardiovascular problems. For example, twenty years after radiotherapy in the chest area, 16% of survivors of Hodgkin's lymphoma

(median age: 25 years old) reported cardiovascular diseases (Hull, Morris, Pepine, & Mendenhall, 2003). The rate of lymphoma diagnosis was 20% and the rate of chest/lung radiotherapy was nearly 30% in the current study. Also, the percentage of participants who experienced secondary cancer was nearly 15%. So, the participants in the current study who were diagnosed with lymphoma might be at a higher risk of having cardiovascular problems and/or secondary cancer.

The relationships between a combination of therapies and symptom clusters were examined in the current study. Survivors who were treated with a combination of therapies (chemotherapy, surgery, and radiotherapy; surgery only; radiotherapy only) were more likely to be in the high symptom cluster group compared to survivors who were treated with only chemotherapy. This finding corresponds with common knowledge (of pediatric cancer treatment teams) that combination therapies or complex treatments may be associated with more (worse) symptoms and poorer functioning. Hsiao et al.'s study involved 201 participants of childhood cancer who had survived an average of six years since their cancer diagnosis. Among them, survivors who were receiving radiation therapy reported higher rates of late effects compared to those who did not receive radiation therapy (Hsiao et al., 2017). In Hsiao et al.'s study, the most prevalent symptoms were altered body image (31.5%), fatigue (14.9%), and memory/learning problems (12.5%). The current study includes long-term survivors of childhood cancer (such as 28 years after cancer diagnosis), and the most prevalent symptoms reported by participants were pain, disfigurement, and sensation abnormalities. In the current study, 55% of participants reported altered body image, which is higher than the 31.5% from

Hsiao's study. These findings provide support for the presence of the long-term nature of late effects in survivors of childhood cancer. One fourth of participants in the current study reported a memory/learning problem, which is higher than that of Hsiao's study. In this study, CNS tumor survivors reported more symptoms; this is similar to Hsiao's study results.

Using data from childhood cancer survivors (CCSS), 67% (n = 1,309) of survivors of adolescent cancer reported disfigurement (Nolan et al., 2014). This is higher than the current study, possibly because Nolan and colleagues included participants who were diagnosed with cancer only during adolescence, a developmental time when a focus on the body is great (Nolan et al., 2014). Long-term young adult survivors who were diagnosed with a brain tumor in childhood experienced late effects including ocular/visual impairment, seizure, and mobility disturbances of limb(s). Those neurological late effects were associated with poorer physical HRQOL (Blaauwbroek et al., 2007; Sato et al., 2014). Many survivors who were in the high symptom subgroup in the current study experienced somatization. Similarly, in the low symptom cluster group, pain symptoms, disfigurement and memory problems were higher than the other symptoms examined. Less than 5% of survivors in this group reported psychological symptoms, which is a lower prevalence compared to those in the high symptom cluster group.

Landier and colleagues (2012) reviewed literature to examine the prevalence of both late effects and screening tests of these effects (Landier et al., 2012). As a result, Landier and colleagues grouped symptoms into three categories based on the levels of

symptoms including high, intermediate, and low prevalence. Pulmonary dysfunction belonged to the high prevalence symptom group, and the prevalence of pulmonary dysfunction in this group was between 13% and 87% from the reviewed studies (Landier et al., 2012). In the current study, the prevalence of pulmonary symptoms was lower than in Landier's study. However, pulmonary complications are consistently noted as one of the common late effects in long-term survivors of childhood cancer.

Authors of a study in Finland that included children and young adult cancer survivors (n = 13,860) who were diagnosed with cancer before 35 years old examined cardiovascular late effects among long-term survivors (Kero et al., 2014). Survivors who were diagnosed between 0 and 19 years of age showed a 13 times greater risk of developing cardiomyopathy/cardiac insufficiency and were three times more likely to experience myocardial infarction compared to their siblings. Survivors who had acute lymphoblastic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, testicular malignancies, and CNS tumors demonstrated an increased risk of having cardiovascular problems (Kero et al., 2014). Even thirty years after cancer diagnosis, the cumulative incidences of cardiovascular problems continued in cancer survivors regardless of their age at cancer diagnosis (survivors who were either 0 to 19 or 20 to 34 years of age at cancer diagnosis) compared to their siblings (Kero et al., 2014). Thus, the 30-year cumulative incidence was about 2.5% for congestive heart failure, and less than 1% for cardiac ischemia in survivors of childhood cancer (Kero et al., 2014). The current study's participants have survived an average of 25 years since cancer diagnosis, and the rate of cardiovascular problems in participants was 15%, which was higher than Kero and

colleagues' findings. One area of further research could involve determining which diagnosis and what treatments contribute most to late effects and other subsequent negative outcomes for survivors.

Hypothesis C.

Hypothesis C supported the notion that survivor membership in the subgroup with high physical symptoms and higher psychological symptoms was associated with poorer physical aspects of HRQOL. Details about these associations follow.

***Symptom clusters and HRQOL*.** Survivors who were in the low symptom cluster group reported better physical and mental summary scores in HRQOL compared to survivors who were in the high symptom cluster group. The low symptom cluster group was chosen as a reference group since the number in this group was larger than that in the high symptom cluster group. The current study results related to other studies on symptom clusters among survivors of adult cancer.

Kim and colleagues identified several symptom clusters across time (Time 1, Time 2, and Time 3) in breast cancer patients who were undergoing chemotherapy or radiotherapy. Time 1 was prior to any treatments; Time 2 was within two days of treatments; and Time 3 was one month after completion of treatments (Kim et al., 2012). The researchers measured five psychoneurologic symptoms including depressed mood, cognitive disturbance, fatigue, insomnia, and pain. At Time 1, Kim and Beck identified four symptom subgroups including all low symptoms, high fatigue and low pain, high pain, and all high symptoms. In addition, the researchers examined the pattern of symptom clusters across time (Kim et al., 2012). In the current study, two groups were

identified: all high symptoms and all low symptoms. These categories were similar to those identified by Kim et al. In the current study, participants with higher physical symptoms showed higher psychological symptoms. In the current study, more types of symptoms were examined than in the Kim et al.'s study, including physical, psychosocial symptoms, and memory/learning symptoms, thus extending their findings.

Dodd and colleagues also examined symptom clusters and quality of life in breast cancer patients. Three time points were used: T1 (baseline-prior to treatment), T2 (end of cancer treatment), and T3 (about one year after at the start of chemotherapy) (Dodd et al., 2010). The researchers categorized the participants into four subgroups: all low symptoms, mild symptoms, moderate symptoms, and all high symptoms. The mild symptoms subgroup had mild fatigue and pain, and the moderate subgroup had a moderate level of pain, fatigue, sleep disturbance, and depression. Although each subgroup showed a distinctive category of symptoms across time, some of the subgroups included a small sample size. For example, at Time 1, the participants with mild symptoms included five participants; at Time 3, no one reported all low symptoms, and only three participants reported all high symptoms (Dodd et al., 2010). Identifying fewer than four subgroups might better explain symptoms at each time point. In the current study, a person-centered approach was used, which allowed each cluster to include subgroups of patients who share similar patterns of symptom experience. Each group included a substantial sample size, nearly 900 for the high symptom cluster group and nearly 2,200 for the low symptom cluster group. In order to meaningfully explain each cluster's characteristics, it is important to have sufficient sample size in each cluster.

In Dodd et al.'s study, participants who belonged to the "mild" and "moderate" subgroups reported significantly higher HRQOL scores compared to the "moderate" or "all high" subgroups (Dodd et al., 2010). This is similar to the current study findings that the high symptom cluster's members reported poorer HRQOL than those in the low symptom cluster. Dodd et al.'s study had three time points: T1 (before treatment), T2 (end of treatment), and T3 (one year after the first treatment). Interestingly, nearly a majority of participants (90%) remained in the mild symptom clusters at Time 2 and Time 3 in their study. This suggests that symptoms can have persistent effects to at least one year after cancer treatment.

Although the current study had at least five time points of data collection associated with the longitudinal design, only the T1 time point was examined for this project. For future research, important information might be gleaned by examining the data longitudinally to understand whether participants experienced similar symptoms across time and to clarify the symptom cluster effects on HRQOL in these survivors across time. This information could be critical in the development of survivorship plans for childhood cancer survivors.

Demographic, clinical variables, and HRQOL. Children with cancer might experience several symptoms related to their cancer or cancer-related treatment (Baggott, Dodd, Kennedy, Marina, & Miaskowski, 2009; Hockenberry & Hooke, 2007). These symptoms could impact the child's quality of life (Baggott et al., 2009). In the current study, several demographic factors were associated with poorer physical HRQOL. These variables were survivors who were older when they took the survey (more than 40 years),

had a lower educational level (less than high school diploma), were unemployed, and had lower annual personal income (less than $19,999).

In another study using CCSS data, survivors who were female, older at the time of survey, obese, living in a household with a lower income level (less than $20,000), were treated with alkylating agents, or were disfigured reported poorer physical HRQOL (Nolan et al., 2014). Researchers found that younger age at cancer diagnosis, such as less than 10 years old, was associated with poorer physical and mental HRQOL (Maurice-Stam et al., 2009; Mertens et al., 2014; Nathan et al., 2007; Ness et al., 2010). The "age at cancer diagnosis" variable was not included in multivariable analysis in the current study because the age at the survey and time after cancer diagnosis were related to the age of cancer diagnosis. Thus, several demographic variables were identified to have an impact on HRQOL in long-term survivors of childhood cancer.

In the current study, several clinical factors were associated with poorer physical HRQOL. Treatment variables (e.g., types of chemotherapy, types of radiotherapy) were used in the multivariable analysis in this study but type of cancer was not included in this analysis. These treatment variables are closely related to types of cancer, and use of these two variables at the same time could have resulted in multicollinearity problems. The use of platin drugs (cisplatin/carboplatin/oxaliplatin) was associated with poorer physical HRQOL. Being treated with muscle radiotherapy (with the exception of head/neck, chest/lung, pelvis/abdominal/urinary, and the reproductive area) was associated with poorer physical HRQOL. According to a literature review by Robinson and Carr, the medications cisplatin, carboplatin, and oxaliplatin were considered as contributing to high

and moderate emetic problems (Robinson & Carr, 2007). Children who experience vomiting might have electrolyte imbalances, dehydration, and weight loss (Robinson & Carr, 2007). Thus, use of platin drugs has the consequence of emetic problems in children with cancer and this could result in their poorer physical HRQOL.

There are other clinical factors that affect cancer survivors' physical HRQOL. In a study of 643 survivors of childhood cancer in Italy, survivors who were diagnosed with a CNS tumor were found to be 2.5 times more likely to report poorer HRQOL scores compared to survivors who were diagnosed with leukemia (Alessi et al., 2007). In addition, female survivors were more likely to report poorer HRQOL compared to male survivors. Survivors who were diagnosed with bone tumors, CNS tumors, and both Hodgkin disease and neuroblastoma were 18 times, three times, and two times more likely, respectively, to report ambulation problems compared to survivors who had leukemia (Alessi et al., 2007). In future work, it will be important to have separate analyses for male and female survivors to better understand gender effects related to HRQOL outcomes as this too could be important information for the development of survivorship plans for different groups of survivors.

In the current study, the relationship between symptom clusters and HRQOL were examined. Huang and colleagues' study examined the relationship between each symptom and HRQOL (Huang et al., 2013). All of the symptoms explained 60% of HRQOL, but demographic and clinical variables explained 15% of HRQOL in long-term survivors of childhood cancer (Huang et al., 2013). Symptoms seem to have more effect on HRQOL than sociodemographic factors. In Huang and colleagues' study as well as in

the current study, more symptom experiences were associated with poorer HRQOL. In future studies, researchers could determine whether to examine symptoms separately or use clusters based on their research purposes to better understand the relationship between these and patients' outcomes.

In the current study, survivors who were female, who had less education (less than a high school diploma), were unemployed, and unmarried reported poorer mental HRQOL. On the other hand, survivors who were treated with chemotherapy (cisplatin/carboplatin/oxaliplatin) or alkylating agents reported better psychosocial HRQOL. This might be related to the social supports they received as caregivers worked with them to help decrease the side effects of chemotherapy. As previously mentioned, in the current study, the two types of chemotherapy examined were highly emetic chemotherapies, and these drugs result in more than 90% of emetic problems (e.g., nausea, vomiting) (Robinson & Carr, 2007). However, there are few studies to examine the relationship between platin drugs and HRQOL. This is in need of further study. In the current study, radiotherapy did not affect mental HRQOL. However, in another study using CCSS data, survivors of adolescent cancer, other than non-Hispanic Whites, and survivors who had disfigurement in the head/neck area, reported statistically significantly poorer mental HRQOL (Nolan et al., 2014). In summary, in the current study, several demographic and clinical predictors were associated negatively or positively with physical and mental HRQOL in survivors of childhood cancer.

It is hypothesized that there are subgroup membership differences in physical and mental HRQOL. In the current study, the mean of physical HRQOL and the mean of

mental HRQOL were lower compared to the mean of physical and mental HRQOL in survivors who were in the high symptom cluster group. Using the same SJLIFE cohort data, Huang and colleagues examined HRQOL and symptoms in 1,667 adult survivors of childhood cancer (Huang et al., 2013). Huang and colleagues' study included survivors who attended a follow-up visit after being surveyed for the SJLIFE cohort study (not the same as the SJLIFE data used in the current study). In their study, survivors who experienced more symptoms reported poorer physical component summary scores (PCS) and mental component summary (MCS) scores in HRQOL. However, this study did not identify symptom clusters and symptoms that negatively affected HRQOL. This is similar to the current study's findings.

Researchers have used various cutoff scores to determine poor HRQOL. Two researchers used 40 (on the same instrument) as the cutoff score (Hudson et al., 2003; Zeltzer et al., 2008), whereas Norman et al. used 45 as the cutoff score to determine poorer PCS HRQOL as well as MCS HRQOL (Norman, Sloan, & Wyrwich, 2003). In the current study, when 40 was used as the cutoff score indicating poor HRQOL, the high symptom cluster group had slightly higher mean physical HRQOL and lower mean mental HRQOL. This suggests that survivors belonging to the high symptom cluster group reported poorer physical HRQOL and poorer mental HRQOL. In the low symptom cluster group, the mean physical HRQOL scores were higher than the cutoff score, which is 40, and the mental HRQOL scores were higher than the cutoff score, also 40. This suggests that survivors who are in the low symptom cluster group reported better physical and mental HRQOL. In another study, using CCSS data, researchers found that the

physical component summary HRQOL was 51.6 and mental component summary HRQOL was 41.4 for 674 female survivors of childhood cancer, and they found that physical summary scores were 53.2 and mental summary scores were 48.8 from 629 male survivors of childhood cancer (Maunsell et al., 2006). In both domains of HRQOL, males reported higher HRQOL than female survivors. It might be necessary to examine the effects of gender on HRQOL in long-term survivors of childhood cancer in a future study.

Hypothesis D.

The findings of this study supported the notion that subgroup membership has moderating effects between demographics/clinical variables and HRQOL. Details about these associations follow. There were moderating effects of symptom clusters between four variables and HRQOL. No prior studies have examined symptom clusters and moderating effects of subgroup membership between predictors and patient outcomes. Thus, the current study's findings were not compared with other studies regarding moderating effects. In the current study, when survivors had lower than a high school diploma and belonged to the high symptom cluster group, they had poorer physical HRQOL compared to survivors who were in the low symptom cluster group. Also, regarding treatment with alkylating agents, those in the high symptom cluster group had poorer physical HRQOL than those in the low symptom cluster group. Regarding mental HRQOL, unemployed survivors who were in the high symptom cluster had poorer mental health than those in the other cluster. Even with the same demographic characteristics or treatment variables, survivors in the high symptom cluster group reported poorer physical

and mental HRQOL. Future research is necessary to examine the mediating effects of symptom clusters and predictors in this population. Also, it is necessary to provide nursing interventions for survivors in the high risk group in order to improve both their physical and mental HRQOL.

Application of the Dynamic Symptoms Model

The Dynamic Symptoms Model (Brant et al., 2016) represents the hypothesized relationship between antecedents, symptoms, and outcomes. This theory also considers the levels of symptom experience and appraisal of symptoms. The current study found that there were significant relationships between sociodemographic factors, clinical factors, symptoms, and outcomes among survivors of childhood cancer. Overall, an antecedent directly affects a symptom experience or quality of life. In addition, an antecedent indirectly affects quality of life through the symptom experience. For example, the HRQOL status was different based on each symptom cluster group.

Considering antecedents, most demographic factors including age, gender, income level, and education were associated with the symptom experience. In addition, under the physiologic antecedent category, medical conditions (type of cancer), treatments, and comorbidities were associated with the higher symptom cluster group. In the current study, the existence of ten symptoms (yes or no) was used, and there was no information about the intensity of symptom or quality of symptoms. The consequences of the symptoms, such as quality of life, were different based on each symptom cluster. For example, an individual who belongs to the high symptom cluster group reported lower levels of physical and psychological HRQOL. To better understand the relationship

between antecedents and symptoms, it would be useful to have more information about treatment variables, such as using accumulative doses of treatments (e.g., chemotherapies or radiotherapies). Other antecedents, under the physiological, social, and spiritual or environmental categories, and their relationship to quality of life were not tested since these variables were not available in the current data set. However, future studies might test whether an individual's knowledge, values, coping skills, self-care, or cultural differences impact the individual's symptom experience or quality of life.

The existence of the symptom experience was used for this analysis, but use of additional characteristics of symptoms (e.g., temporality, intensity, quality, distress, and appraisal) could provide useful information related to HRQOL. For example, intensity of symptom, appraisal of symptoms, and symptom changes across time could provide detailed information that would be useful to guiding providers in care planning and for the development of survivorship care plans that could be tailored to the unique needs of the individual cancer survivor. Also, further study about the nuances of the associations of the various aspects of the model (antecedents, symptom experience, and quality of life) and survivor outcomes might provide more useful information to guide symptom management interventions.

This was a preliminary study using the dynamic symptoms model (Brant et al., 2016) as a way of understanding the symptom experience of childhood cancer survivors and associated long-term outcomes. This model is useful for understanding the relationships and trajectories from antecedents to symptoms to outcomes for survivors. However, in the future, this model might be further tested considering various

antecedents, symptom experiences, symptom trajectory, and symptom management interventions.

Limitations

Several limitations of this study should be noted. A cross-sectional design was used for the current study. This strategy did not allow for the explanation of the inferential relationships between predictors, symptoms, and HRQOL. Although the original SJLIFE data had five different time points, only the first time point of data was used for the current analysis. This choice was made because the first time point of data had the largest sample size, and it was necessary to preliminarily explore the relationships between symptom clusters and HRQOL in survivors of childhood cancer before examining data longitudinally. The Dynamic Symptoms Model was used as a theoretical framework, but symptom intensity and quality were not examined because that information was not available in the primary data set. Since the clinical factors were binary variables, the accumulative doses of chemotherapy or radiotherapy were not tested, which if available might have yielded detailed information about the effect of treatment variables for the individuals who were in the high symptom cluster group. This could be important information for treatment providers in designing the most effective treatment plan with the lowest incidence of poor outcomes for the survivor.

Regarding analysis, cluster analysis is an exploratory statistical procedure that requires researchers to make decisions about the number of clusters and names of the symptom clusters (Miaskowski et al., 2006). Although empirical guidelines were used to choose the best-fit model, a greater or lesser number of symptom clusters could have

explained the symptoms more accurately. The current sample is limited to survivors who were mostly middle-aged, non-Hispanic Whites, with a high level of educational attainment in the United States, which might be hard to generalize to childhood cancer patients who are from minority groups, of other races/ethnicities, and for those of lower education levels in developing countries. For future research, it might be helpful to examine a homogeneous survivor sample that is characterized by the same types of cancer, same types of treatment, and similar age at cancer diagnosis in order to identify more distinctive subgroups.

Implications

Implications for Research.

This study used a new statistical approach to identify symptom clusters experienced by survivors of childhood cancer. The larger sample from SJLIFE data allowed the use of clinically relevant variables within the latent class analysis (LCA) using mixture modeling to identify distinct symptom subgroups. A cross-sectional design was used for the current project. However, approximately 50% of SJLIFE participants have completed the HRQOL survey at more than two time points. In a future study it will be important to conduct longitudinal analyses to better understand the relationship of cancer treatments, symptoms, cluster membership and outcomes so as to better inform care planning for these survivors. Using a longitudinal design could provide further information for the development of survivorship plans.

The current study includes long-term survivors of childhood cancer, but future research might include those in various stages of cancer treatment, such as those

undergoing cancer treatment or shortly following completion of cancer treatment. Understanding symptom clusters in each stage of cancer treatment could provide information for researchers about designing symptom management interventions for the target group in a particular cluster, for example, the high symptom cluster. Childhood cancer survivors who were diagnosed with cancer between 0 to 19 years of age were used for data analysis in order to examine symptom clusters and HRQOL. However, it is possible that encompassing childhood and adolescence into one study group might mask the unique developmental differences of survivors of adolescent cancer. Although the age at cancer diagnosis was categorized into three different groups, this variable was not used in a multivariable analysis to avoid multicollinearity with time since cancer diagnosis. For future research, it may be necessary to examine symptom clusters and HRQOL in different age groups such as survivors of adolescent cancer.

Implications for Nursing Practice.

This study had a substantial sample size of participants. The heterogeneous cancer diagnoses, types of chemotherapy, and types of radiotherapy make the findings potentially generalizable for other childhood cancer survivors and patients. Findings from this study can provide the basis for investigation into the stability of clusters with survivors from different socio-economic groups, different types of cancer, and those who received different types of chemotherapies and radiotherapies.

Nurses need to pay attention to patients who experience high degrees of physical and mental symptoms associated with their cancer and treatments because these patients risk having a poor quality of life as a result. In the current study, most long-term

survivors of childhood cancer experience pain and disfigurement, and these complications are associated with poorer HRQOL. Also, a subgroup of participants experienced psychological symptoms including anxiety, depression, and somatization. In particular, survivors of brain tumors experienced poorer HRQOL compared to survivors of leukemia. Nurses need to be aware of and understand these symptoms and target populations who might have poorer health outcomes in order to provide effective nursing care. These study findings can help health care providers make tailored survivorship care plans for childhood cancer patients. Nurses need to consider nursing interventions designed to decrease treatment complications during cancer treatment. Also, it is important to provide resources to survivors such as counseling with mental health care providers, support groups with other cancer patients, and writing or music therapy to aid in the relief of psychological distress. These could all be in the form of a comprehensive survivorship care plan.

Implications for Clinicians.

This study included survivors who had received eight different types of chemotherapy and five different body areas of radiotherapy. Understanding the differential effects of treatment-related variables could help clinicians understand that when their patients have received certain types of chemotherapy and certain body areas of radiotherapy, they may be at a greater risk for being in a high symptom cluster, which could lead to poorer outcomes. Also, helping clinicians understand that symptoms often co-occur, and that physical and mental symptoms may be associated with each other, could aid these caregivers in providing the best treatments/interventions for their young

patients. For example, when a patient is in a cluster with more severe symptoms, clinicians might need to assess the prevalence of other symptoms in the same cluster. Also, clinicians could include family and friends as resources in the survivorship care plans in order to support survivors of childhood cancer to cope with cancer. Clinicians' insights and comprehensive assessments, as well as targeted interventions, could prevent or decrease symptoms for cancer patients, which could in turn result in improved outcomes for these survivors over their lifetime.

Conclusion

This study focused on the identification of symptom clusters and HRQOL in survivors of childhood cancer. Two distinctive subgroups were identified based on symptom experience. The mixture modeling was useful for identifying the subgroups. Using advanced statistical analysis such as mixture modeling with a person-centered approach helped in the identification of a high symptom cluster and a low symptom cluster. This statistical approach could be replicable for future studies that may involve identifying symptom clusters in various types of cancer or other types of illnesses.

In the current study, each subgroup shared unique common symptoms. Each subgroup had distinctive sociodemographic and clinical characteristics that were antecedent to the clusters and distinctive health outcomes. Survivors of childhood cancer who were in the high symptom cluster group experienced poorer physical and mental HRQOL outcomes. Findings from this person-centered approach to analysis provided clinically useful insights for health care providers and could lead to the development of symptom management interventions for the high-risk group that could help those in this

group to have better health outcomes. Future study should continue to identify factors that are related to symptom experiences and HRQOL for survivors of childhood cancer who are in the various cancer survivorship periods. This could lead to the design and testing of interventions to decrease symptoms and to increase HRQOL for these populations.

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