PHYSICAL THERAPY AND CHIROPRACTIC USE IN SURVIVORS OF CHILDHOOD CANCER: IMPACT ON HEALTH-RELATED QUALITY OF LIFE

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ABSTRACT

The purpose of this study was to examine prevalence of physical therapy (PT) and chiropractic use in survivors of childhood cancer and which factors are associated with the use of these services. In addition, the health-related quality of life (HRQOL) of survivors with musculoskeletal and neurological chronic conditions who reported using either PT or chiropractic was compared to those survivors with the same conditions who did not use either service. This study was a secondary analysis of the Childhood Cancer Survivor Study (CCSS) and included a subset of 9289 survivors who completed both the baseline and 2003 follow-up questionnaires. In addition to those two measures, the Medical Outcomes Short Form-36 (SF-36) was used to measure HRQOL. The sample consisted of 4708 (51%) males and 4581 (49%) females who were an average age of 31 years old and were predominantly White (89%). More childhood cancer survivors reported using chiropractic (12.3%) than PT (9.3%). Survivors who were older, female and had health insurance were most likely to use PT or chiropractic. Survivors who had a grade three or four musculoskeletal or neurological chronic condition were more likely to use PT, as were those survivors who had been diagnosed with CNS tumors, soft tissue sarcomas, or bone cancer. Chronic disease status, diagnosis, and treatment type were not associated with chiropractic use. Survivors with musculoskeletal or neurological chronic conditions who reported using either PT or chiropractic reported poorer HRQOL.
compared to those who did not use either service. Mediation analysis revealed PT
mediated the relationship between chronic condition and HRQOL.
DEDICATION

I lovingly dedicate this dissertation to my daughter, Morgan. Although this work often took time away from her, she always understood and never complained. I thank my husband, Cole, for encouraging me to pursue my dreams and for his patience through this long process. My father and stepmother, Charles and Linda Martin, were always supportive of me and proud of my accomplishments, and I will forever be grateful to them for their love, encouragement, and support. Finally, this dissertation is dedicated in loving memory to my mother and best friend, Dagmar, who inspired this dissertation.
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CHAPTER 1

INTRODUCTION

Five-year survival rates for all childhood cancers have risen from 62.9% in 1975 to 80% currently (Ries, et al., 2007). These increases in childhood cancer survival rates can be attributed to improved treatment modalities and have shifted the paradigm of care from one of cure to a long-term emphasis on treatment-related morbidity and health-related quality of life (HRQOL). Current treatments that incorporate systemic therapy (e.g., intrathecal chemotherapy with or without cranial radiation) have resulted in gains in survival that leave young cancer survivors with potentially over 60 years of productive life remaining, (Gaynon, et al., 2000; Harms & Janka-Schaub, 2000; Maloney, Shuster, Murphy, Pullen, & Camitta, 2000; Pui, Campana, & Evans, 2001; Pui, Relling, & Downing, 2004; Pui, Sandlund, et al., 2004; Schrappe, et al., 2000; Silverman, et al., 2001; Smith, Ries, Gurney, & Ross, 1999).

Although more effective treatments for childhood cancer have dramatically improved survival rates, this success has not come without a cost. Improved prognosis has been accompanied by the occurrence of late, treatment-related complications, known as late effects (Garre, et al., 1994; Oeffinger, Eshelman, Tomlinson, Buchanan, & Foster, 2000; Stevens, Mahler, & Parkes, 1998). Two common late effects experienced by childhood cancer survivors include musculoskeletal and neurological late effects.
Childhood cancer survivors have a documented risk for developing musculoskeletal late effects with over 10% of survivors in the Childhood Cancer Survivor (CCSS) cohort reporting musculoskeletal late effects (Oeffinger, et al., 2006). Due to treatment, childhood cancer survivors are affected by musculoskeletal late effects such as impaired bone maturation and osteonecrosis (Chollet, Britton, Neel, Hudson, & Kaste, 2005; Crofton, et al., 2000; Karimova, et al., 2007; Kaste, et al., 2006), decreased bone mineral density (Arikoski, Voutilainen, & Kroger, 2003; Crofton, 2009; Kaste, et al., 2001; Nysom, et al., 2001), decreased peripheral muscle strength and ankle dorsiflexion (Hartman, van den Bos, Stijnen, & Pieters, 2008), muscle atrophy (van Brussel, et al., 2006), and pain (Hudson et al., 2003).

Both treatment and diagnosis are associated with musculoskeletal late effects. Cranial radiation (Arikoski, et al., 2003; Crofton, 2009) and treatment with corticosteroids and methotrexate (Athanassiadou, et al., 2006; Mandel, Atkinson, Barr, & Pencharz, 2004) may impair bone mineralization. Radiation and chemotherapy during childhood, which is a vulnerable period of growth and organ development, can also have detrimental effects on the musculoskeletal system (Hewitt, Weiner, & Simone, 2003). Treatment regimens, such as chemotherapy, radiation, and/or surgery, used in the management of acute lymphoblastic leukemia (ALL), lymphomas, brain tumors, Wilm’s tumor, and sarcomas make survivors particularly vulnerable to musculoskeletal effects (Hewitt, et al., 2003).

Neurological impairment is one of the most debilitating late effects among children whose cancer or cancer treatment involved the central nervous system (CNS)
many long-term survivors have permanent neurologic deficits that include motor dysfunction, tetraplegia or hemiplegia, ambulation difficulties, neuropathy, balance problems, coordination problems, and fine motor deficits (Aksnes & Bruland, 2007; Galea, Wright, & Barr, 2004; Gurney et al., 2006; Ilveskoski et al., 1996; Jenkin, Danjoux, & Greenberg, 1998; Lehtinen et al., 2002; Packer et al., 2003). Neurological damage resulting from cranial irradiation has been proposed as a contributing factor for motor impairment (Hovi, Era, Rautonen, & Siimes, 1993). Survivors of childhood cancer have been shown to experience coordination and motor control problems (Packer, et al., 2003), fine motor deficits (Lehtinen, et al., 2002), peripheral neuropathy (Aksnes & Bruland, 2007), paraparesis (Poretti, Zehnder, Boltshauser, & Grotzer, 2008), and monoparesis (Poretti, et al., 2008).

It has been ascertained that 73% of childhood cancer survivors reported developing at least one late effect by age 40, and 38% of survivors reported having three or more late effects (Oeffinger et al., 2006). In addition to ascertaining the prevalence of late effects experienced by childhood cancer survivors, these conditions have been graded for severity (Blaauwbroek, Groenier, Kamps, Meyboom-de Jong, & Postma, 2007; Geenen et al., 2007; Han et al., 2009; Oeffinger et al., 2000; Oeffinger et al., 2006). To determine the severity of late effects, scoring was based on the Common Terminology Criteria for Adverse Events (version 3), a scoring system developed through the National Cancer Institute by a multidisciplinary group and intended for use in scoring both acute and chronic conditions in patients with cancer and survivors of all ages (National Cancer Institute, 2006). The system grades conditions as mild (grade 1),
moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), and death (grade 5).

Musculoskeletal late effects that were included in order to grade musculoskeletal late effects include bone, spine scoliosis; cervical spine, range of motion; extremity, lower (gait/walking); extremity, upper (function); fracture; joint, function; local complication, device/prosthesis-related; lumbar spine, range of motion; muscle weakness; muscular/skeletal, hypoplasia; osteonecrosis; osteoporosis; and soft tissue necrosis. Neurological adverse events included in the grading of neurological late effects include: decreased fine motor coordination; seizure; tremor; neuropathy, motor; neuropathy, sensory; dizziness; involuntary movement; and ataxia (incoordination).

In studies that graded late effects, the prevalence of grade 3 or 4 late effect ranged from 10.8% to 39% (Blaauwbroek, Groenier, Kamps, Meyboom-de Jong, & Postma, 2007; Geenen, et al., 2007; Han, et al., 2009; Oeffinger, et al., 2000; Oeffinger, et al., 2006). Diagnoses associated with grade 3 or 4 late effects included brain tumors, bone tumors, CNS tumors, and Hodgkin’s disease (Geenen et al., 2007; Han et al., 2009; Oeffinger et al., 2006). Treatments associated with grade 3 or 4 late effects included radiation, chemotherapy, surgery, and hematopoietic stem cell transplantation (HSCT) (Geenen et al., 2007; Han et al., 2009; Oeffinger et al., 2006).

HRQOL includes areas of an overall quality of life, which are directly related to an individual's health, excluding such aspects as income, freedom, air or water quality (Kamphuis, et al., 2002). For the purposes of this study, HRQOL is conceptualized as the physical and mental health of childhood cancer survivors. Dividing health into physical and mental domains helps understand the influence of health status on HRQOL. Physical
health has been defined as comprising four aspects: physical functioning, physical role functioning, bodily pain, and general health (Ware, Kosinski, & Gandek, 2000). Mental health includes vitality, social functioning, emotional role functioning, and general mental health (Ware, Kosinski, & Gandek, 2000).

Two component summary scores capture the overall physical and mental health, the Physical Component Summary Scale (PCS) and the Mental Component Summary Scale (MCS) (Ware & Kosinski, 2001). The use of these summary scales, as opposed to all eight subscales, allows investigators to reduce the number of statistical tests necessary, while accounting for approximately 80% of the variance in the eight individual subscales (Ware & Kosinski, 2001). The PCS and MCS scores have commonly been used to report the HRQOL of childhood cancer survivors (Aksnes, et al., 2008; Nathan, et al., 2007; Ness, et al., 2008; Reulen, et al., 2007; Zeltzer, et al., 2008).

When normal functioning of the musculoskeletal or neurological system is impaired, limitations in physical function, and subsequently HRQOL, can result. Overall, survivors of childhood cancer report significantly poorer HRQOL than the general population (Grant, et al., 2006), and the effect of specific cancer diagnoses and treatments on HRQOL in childhood cancer survivors has been well-documented (Alessi, et al., 2007; Blaauwbroek, Stant, et al., 2007; Nathan, et al., 2007; Odame, et al., 2006; Punyko, et al., 2007; Zeltzer, et al., 2008).

Poor HRQOL is most prevalent among childhood cancer survivors whose cancer or treatment included an insult to the central nervous system (CNS) (Ness, et al., 2008). In addition, Speechley and colleagues (2006) reported that seven survivor diagnostic groups (i.e., CNS tumors, bone tumors, lymphoma, leukemia, soft tissue sarcoma, liver
tumor, and Wilm’s tumor) had considerably poorer mean physical component summary scores compared to an age- and sex-matched population sample with medium to large effect sizes. Other studies have also reported that survivors of CNS tumors (Maunsell, Pogany, Barrera, Shaw, & Speechley, 2008; Zeltzer et al., 2008), bone tumors (Blaauwbroek, Stant et al., 2007; Maunsell et al., 2008; Zeltzer et al., 2008), lymphoma (Zeltzer, et al., 2008), and soft tissue sarcoma (Zeltzer, et al., 2008) also reported lower HRQOL scores.

Cancer treatment type has also been associated with poor HRQOL of childhood cancer survivors. Blaauwbroek and colleagues (2007) reported that survivors who were treated with both chemotherapy and radiation therapy had more severe late effects and worse HRQOL than those treated with chemotherapy alone. Cranial radiation was also associated with more severe late effects and poorer HRQOL. Treatment with a combination of radiation, surgery, and chemotherapy followed by those with radiation and surgery and radiation only has also been reported to be associated with decreased HRQOL (Speechley, et al., 2006). Finally, Zeltzer and colleagues (2008) found that treatments with surgery, chemotherapy, and cranial radiation therapy were each associated with poorer HRQOL.

In addition to diagnoses and treatment factors, individual factors also predict decreased HRQOL in survivors. Age at diagnosis and time since diagnosis are both associated with HRQOL with those survivors who were older at diagnosis (Blaauwbroek, Stant et al., 2007; Stam, Grootenhuis, Caron, & Last, 2006; Zeltzer et al., 2008) and who had survived longer reporting worse HRQOL compared to population norms. Gender was also investigated in relation to survivors’ HRQOL. Several studies reported that
female survivors were most likely to report poorer HRQOL compared to males (Grant, et al., 2006; Langeveld, Grootenhuis, Voute, de Haan, & van den Bos, 2004; Shankar, et al., 2005; Speechley, et al., 2006; Stam, Grootenhuis, Caron, & Last, 2006).

In addition to the above mentioned factors, Zeltzer and colleagues (2008) also identified a number of other individual factors that contributed to poorer HRQOL for survivors of childhood cancer. These factors include older age at follow up, unemployment, lower annual household income, lower educational attainment, being Hispanic, and lack of health insurance. Langeveld and colleagues (2004) also identified lower educational attainment and unemployment as contributing to poorer HRQOL.

The use of specific health services may potentially improve the limitations imposed upon childhood cancer survivors who experience musculoskeletal and neurological late effects and thus improve their HRQOL. However, no literature currently exists that documents the relationship between the use of health services by childhood cancer survivors experiencing musculoskeletal and neurological late effects and HRQOL.

Physical therapy (PT) is the provision of health services that help restore function, improve mobility, relieve pain, and prevent or limit permanent physical disabilities of patients suffering from injuries or disease (Bureau of Labor Statistics U.S. Department of Labor, 2009). Rehabilitative services, such as PT are appropriate for individuals who have functional loss related to injury, disease, or the aging process. Often, the goals of PT intervention are to develop, maintain, and restore maximum movement and functional abilities. PT services are utilized regularly in the management of functional loss related to chronic disease including impairment of the musculoskeletal and neurological systems.
Clinical practice guidelines for childhood cancer survivors (Children's Oncology Group, 2008) recommend PT as part of the treatment regimen for survivors who have developed musculoskeletal or neurological late effects. However, no studies have investigated use of PT in childhood cancer survivors.

Few studies have examined the association between individual factors and PT use in the general population. Factors negatively associated with using PT services include older age, having no high school degree, Hispanic ethnicity, African-American race, and having no insurance (Carter & Rizzo, 2007). Hsieh and Dominick (2003) reported that in a population of patients with osteoarthritis, increased PT use was associated with greater disease severity. In a study involving 10-year breast cancer survivors, survivors who had more comorbidities were more likely to report using PT (van de Poll-Franse, et al., 2006).

While PT is part of mainstream health care, chiropractic is the largest, most regulated, and best recognized of the professions that have traditionally functioned outside of mainstream medical institutions and falls into the category of complementary and alternative medicine (CAM) (Meeker & Haldeman, 2002). Chiropractic is a health profession concerned with the diagnosis, treatment and prevention of mechanical disorders of the musculoskeletal system, and the effects of these disorders on the functions of the nervous system and general health (World Federation of Chiropractic, 2006). Chiropractic intervention is designed to correct spinal alignment and to relieve nervous system impingements (Evans & Rosner, 2005). Surveys indicate that patients frequently utilize chiropractors for the treatment of musculoskeletal complaints (Ernst, 2000).
A recent report from the Childhood Cancer Survivor Study (CCSS) examined chiropractic use within the context of CAM use and found that 12.1% of survivors reported seeing a chiropractor (Mertens, et al., 2008). Individual and diagnosis factors associated with increased use of CAM included older age at follow-up, female gender, education higher than high school graduation, having health insurance, and a diagnosis of bone cancer. Blacks were less likely to use CAM. In addition, survivors reporting major medical conditions and fair to poor health were more likely to use CAM. However, the specific factors that predicted chiropractic use were not examined in their global report.

In the general population, white race is associated with increased chiropractic use (Thaker & Pathman, 2004). In a study of correlates of use of different types of CAM by breast cancer survivors, only older age was associated with chiropractic use (Buettner, et al., 2006). In a comparative analysis of chiropractic and general practitioner (GP) patients in North America, Hurwitz and Chiang (2006) reported that patients who saw both a GP and chiropractor were younger, white, female, college educated, in the highest income quintile, and employed. They also were more likely to be in very good or excellent health and to have fewer chronic health conditions.

Both PT and chiropractic care improve musculoskeletal and neurological complications in the healthy population (Crawford, 1999; Hakkinen, Salo, Tarvainen, Wiren, & Ylinen, 2007; Hale, Hertel, & Olmsted-Kramer, 2007; Kohlbeck, Haldeman, Hurwitz, & Dagenais, 2005; Rubinstein, et al., 2007; Swanenburg, de Bruin, Stauffacher, Mulder, & Uebelhart, 2007), and in survivors of adult cancers (Gordon, Battistutta, Scuffham, Tweeddale, & Newman, 2005; Schneider, Dennehy, Roozeboom, & Carter, 2002; Schneider, Hsieh, Sprod, Carter, & Hayward, 2007). The use of PT or chiropractic
has also been associated with improved HRQOL in breast cancer patients and survivors and patients with cardiovascular disease, rheumatoid arthritis, and cerebral palsy (Buettner, et al., 2006; Choo, Burke, & Pyo Hong, 2007; De Backer, et al., 2008; Mustur & Vujasinovic-Stupar, 2007; Secor, Markow, Mackenzie, & Thrall, 2004; Segal, et al., 2003; Verschuren, et al., 2007; Wenban & Nielsen, 2005). These health services have the potential to ameliorate some of the limitations experienced by childhood cancer survivors as a result of musculoskeletal and neurological late effects, and subsequently, may also improve HRQOL.

**Significance**

Currently, there are an estimated 270,000 long-term survivors of childhood cancer of all ages in the United States (Hewitt, et al., 2003). As a result of cancer therapy, these survivors are at an increased risk for developing musculoskeletal and neurological late effects (Alvarez, et al., 2007; B. M. Brennan, Rahim, Adams, Eden, & Shalet, 1999; Hudson, et al., 2003; Maloney, et al., 2000; Nysom, et al., 2001; Nysom, et al., 1998; Oeffinger & Hudson, 2004; Schwartz, 2003), and survivors frequently have more than one late effect, with perhaps as many as a quarter of survivors experiencing one that is severe or life threatening (grade 3 or 4) (Garre, et al., 1994; Oeffinger, et al., 2000; Stevens, et al., 1998).

Musculoskeletal and neurologic late effects have the potential to disrupt physical performance and impair HRQOL. In the general adult population, musculoskeletal conditions are among the principal health concerns that patients seek referral for (Lin, et al., 2000). PT and chiropractic are two health services that may be readily available to
survivors who are experiencing musculoskeletal or neurological late effects, and use of these services may potentially improve HRQOL. No studies to date have examined use of PT in this population, and only one study reported use of chiropractic by childhood cancer survivors within the context of complementary and alternative medicine use (Mertens, et al., 2008). However, diagnosis, treatment, and demographic factors that were specifically associated with chiropractic use were not examined.

The increasing number of long-term childhood cancer survivors and their well-established risk of cancer-related morbidity strongly support the need for effective health promotion programs focusing on this medically vulnerable population (Hudson & Patte, 2008). Advance practice nurses forged their role in the long-term follow-up of childhood cancer survivors shortly after the need for continued care of this vulnerable population was identified (Children's Oncology Group, 2007), and Nurse Practitioners successfully lead comprehensive, long-term follow-up clinics for survivors of childhood cancer throughout the United States (Hewitt, et al., 2003; Hobbie & Hollen, 1993; Hollen & Hobbie, 1995). Therefore, nurses need the knowledge, skills, and attitudes that underlie the delivery of equitable health care to childhood cancer survivors. An ideal system of survivorship care would provide a range of direct services to survivors to identify, prevent, treat, and ameliorate late effects; bridge the realms of primary and specialty health care with education and outreach; coordinate medical care with educational and occupational services; and conduct research to better understand late effects and their prevention (Hewitt, et al., 2003). Nurses are well-suited to perform these services given the emphasis in nursing education and training on patient assessment, symptom management, psychosocial care, and care planning (Hewitt, Greenfield, & Stovall, 2006).
A more comprehensive body of knowledge regarding musculoskeletal and neurological late effects and health care services that can modify their impact on health-related quality of life is necessary in order to better inform health care practitioners on long-term follow-up care. Specifically, there is a need to delineate the influence variables such as cancer diagnosis, treatment type, and late effects severity have on the use of PT and chiropractic services and how these services may mediate the relationship between late effects severity and HRQOL. This knowledge is also necessary to inform researchers in the development of effective interventions to improve functioning in survivors with musculoskeletal and neurological late effects and subsequently improve HRQOL.

The results of this study would enlighten health care providers with regards to the individual, diagnosis, treatment, and late effect factors are likely to influence the use of PT and chiropractic services by childhood cancer survivors they may encounter in practice. Results of this study would inform health care providers as to whether or not PT and chiropractic services improve the HRQOL of survivors who use these services. Providers caring for childhood cancer patients have both the opportunity and the responsibility to play a critical role in prevention and risk reduction of morbidity from late effects following cancer and its treatment (Hudson & Patte, 2008), and this study will provide needed information for recommending health care services that emphasize health promotion strategies.
**Purpose of Study**

The purpose of this study is to describe the use of PT and chiropractic care in the CCSS cohort at the 2003 follow-up questionnaire and to describe the characteristics (i.e., demographic, diagnosis, treatment, and late effect severity) of those who report using PT or chiropractic in the previous two years. In addition, the HRQOL of childhood cancer survivors with grade 3 or 4 musculoskeletal and/or neurological late effect severity who report use of PT and/or chiropractic will be compared to those who did not use PT or chiropractic.

**Specific Aims**

The specific aims of this study are as follows: 1) Describe the frequency of and predictors of use of PT and/or chiropractic among childhood cancer survivors; 2) Describe the relationship between late effect severity and PT and/or chiropractic use; 3) Describe the relationship between diagnosis and PT and/or chiropractic use among childhood cancer survivors; 4) Describe the relationship between treatment and PT and/or chiropractic use among childhood cancer survivors; 5) Determine whether or not childhood cancer survivors with grade 3 or 4 musculoskeletal and neurological late effects who report PT or chiropractic use report better HRQOL than those with grade 3 or 4 musculoskeletal or neurological late effects who do not report PT or chiropractic use in the two years prior to the 2003 follow-up survey; and 6) Determine whether or not PT or chiropractic use mediates the relationship between musculoskeletal and neurological late effects and HRQOL.
Hypotheses

1. Childhood cancer survivors with grade 3 or 4 musculoskeletal or neurological late effects (measured at baseline) will be more likely to report use of PT, chiropractic, or both at the 2003 follow-up questionnaire when compared to those with grade 2 or lower musculoskeletal or neurological late effects.

2. Childhood cancer survivors most likely to report use of PT and/or chiropractic will have been diagnosed with bone tumors or CNS malignancies, will be white race and female gender, have been older at follow-up, and have higher educational attainment, current health insurance, and higher household income.

3. Among childhood cancer survivors with grade 3 or 4 musculoskeletal and neurological late effects, those who report use of PT and/or chiropractic will report higher mean values on the Physical Component Summary score and the Mental Component Summary score, as well as the physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health subscales of the SF-36 when compared to those not receiving PT or chiropractic.

4. PT and/or chiropractic use will mediate the relationship between grade 3 or 4 musculoskeletal and neurological late effects and HRQOL (i.e. physical health and mental health) in childhood cancer survivors who use those services.
Definition of Terms

The following terms were operationally defined as follows for the purpose of the study:

Musculoskeletal Late Effect Severity: The presence and severity of musculoskeletal late effects as reported by survivors in the baseline questionnaire (http://www.stjude.org/SJFile/ccss_baseline.pdf). Musculoskeletal late effects include: bone, spine scoliosis; cervical spine, range of motion; extremity, lower (gait/walking); extremity, upper (function); fracture; joint, function; local complication, device/prosthesis-related; lumbar spine, range of motion; muscle weakness; muscular/skeletal, hypoplasia; osteonecrosis; osteoporosis; amputation; and soft tissue necrosis.

The musculoskeletal late effects will be operationalized as the grade of severity according to the Common Toxicity Criteria, Version 3 (CTCvs3) developed by the National Cancer Institute (National Cancer Institute, 2006). The system grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), and life-threatening or disabling (grade 4). Only musculoskeletal late effects that occurred subsequent to the cancer diagnosis or its treatment were included.

Neurological Late Effect Severity: The presence and severity of neurological late effects as reported by survivors in the baseline questionnaire (http://www.stjude.org/SJFile/ccss_baseline.pdf) and verified through medical record abstraction. Neurological late effects include: decreased fine motor coordination; seizure; tremor; neuropathy, motor; neuropathy, sensory; dizziness; involuntary movement; and ataxia (incoordination).
The neurological late effects will be operationalized as the grade of severity according to the Common Toxicity Criteria, Version 3 (CTCvs3) developed by the National Cancer Institute (National Cancer Institute, 2006). The system grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), and life-threatening or disabling (grade 4). Only neurological conditions that occurred subsequent to the cancer diagnosis or its treatment were included.

*Physical Therapy Use:* Physical therapy is the provision of services in circumstances where movement and function are threatened by injury, disease or the process of aging with the goal is to develop, maintain, and restore maximum movement and functional ability throughout the lifespan (American Physical Therapy Association, 2001). Physical therapy use is defined as any self-reported physical therapy visit in the two years prior to the 2003 follow-up questionnaire (http://www.stjude.org/SJFile/ccss_fu2.pdf). A self-reported visit to a physical therapist was measured by question A1 from the 2003 follow-up questionnaire.

*Chiropractic Use:* Chiropractic care addresses disorders of the musculoskeletal system and how these aberrations may impinge upon the nervous system, subsequently affecting general health (Evans & Rupert, 2006). Chiropractic use is defined as any self-reported visit to a chiropractor in the two years prior to the 2003 follow-up questionnaire (http://www.stjude.org/SJFile/ccss_fu2.pdf). A self-reported visit to a chiropractor was measured by question A1 from the 2003 follow-up questionnaire.

*Health-Related Quality of Life (HRQOL):* HRQOL includes areas of an overall quality of life, which are directly related to an individual's health, excluding such aspects as income, freedom, air or water quality.
The Medical Outcomes Study Short Form-36 (SF-36) (Ware & Sherbourne, 1992) was used to measure health-related quality of life (questions E1-22 and F1-14 in the 2003 follow-up questionnaire) (http://www.stjude.org/SJFile/ccss_fu2.pdf). Composite summative scores (i.e., PCS and MCS) reflecting overall mental and physical health-related quality of life will be calculated as aggregate mental and aggregate physical and mental component summary scores. The mean scores of these components encompass all subscales of the SF-36. The PCS is composed of physical functioning, role limitations by physical problems, bodily pain, and general health. The MCS is composed of role limitations by emotional problems, vitality and energy, social functioning, and mental health. Summary scores have some methodological features that make them more advantageous for clinical research. These features include smaller confidence intervals (CIs), the elimination of floor and ceiling effects, simpler analysis by reducing the number of statistical tests required, and avoiding the problem of multiple testing.

**Assumptions of Study**

For the purpose of this study, the following assumptions are made:

1. Children diagnosed with cancer survive to adulthood.
3. Childhood cancer survivors or their guardian or spouse have accurately reported use of physical therapy and/or chiropractic and HRQOL.
4. Data collected for the Childhood Cancer Survivor Study (CCSS) are reliable and valid.

**Theoretical Framework**

The study will be guided by the KRW (Kang, Rice, & Weaver) Integrative Model of Biobehavioral Interactions (Rice, personal communication, June, 2007) which is a comprehensive conceptual model that views health outcomes (or conversely disease outcomes) as the result of interactions of individual, psychosocial, environmental, and behavioral factors on biological responses. The interactions of these factors are typically cumulative either from multiple factors acting together at one point in time or one or more factors acting together over a period of time. The cumulative effects influence biological responses which, in turn, affect health outcomes. Figure 1 diagrams the full model, and Figure 2 is a diagram of the conceptual model guiding this study.

The KRW Integrative Model of Biobehavioral Interactions was developed by Drs. Duck-Hee Kang, Marti Rice, and Michael T. Weaver and builds on the earlier work of Selye (1976), Lazarus & Folkman (1984), and McEwen (1998) who developed conceptual or theoretical models to guide health-related research. Each of these models, however, has limitations. Selye’s model addresses the body’s biologic responses to stress to defend against negative health outcomes. However, its limitations are the non-specificity of the responses and the inadequacy of the model to explain the human stress response. It also fails to address the underlying psychological factors that might influence stress and coping responses.
Lazarus and colleagues proposed a cognitive theory of stress which addressed the interaction between external and internal components of the individual (Lazarus & Folkman, 1984; Lazarus & Launier, 1978). The interaction is an ongoing relationship between the individual and the environment, and according to Lazarus’ theory, the emphasis is on the meaning that an event has for the individual and not on the physiological responses. One’s view of a situation determines whether or not an event is experienced as stressful, making stress the consequence of appraisal (Lazarus & Folkman, 1984; Lazarus & Launier, 1978). The way an individual appraises an event determines the magnitude of the stress response, as well as the coping strategies he or she may employ in an effort to deal with the stress. How well a person is able to cope with stress determines whether or not the stress remains in their life. This theory adds to the understanding of stress through cognitive appraisal processes, but it does not address biologic aspects of the stress response.

Stress may be defined as a threat, real or implied, to the psychological or physiological integrity of an individual (McEwen, 2000). Based on Selye’s work, McEwen examined stress from the perspective of the adaptive physiological and behavioral responses and resulting health outcomes (McEwen, 1998). The body responds to stress by secreting hormonal and neurotransmitter mediators that set physiological responses of cells and tissues into motion. These mediators are essential for short-term adaptation, maintenance of homeostasis (allostasis), and survival. However, over longer time intervals, these mediators exact a cost (allostatic load) that can accelerate disease processes (McEwen, 2000). The term allostatic load refers to the wear and tear the body experiences due to repeated cycles of allostasis as well as the inefficient turning-on or
shutting off of these responses (McEwen, 1998; McEwen & Stellar, 1993). Perceived stress can be influenced by individual differences which can trigger physiologic and behavioral responses to the stress. While McEwen’s conceptualization involves biobehavioral interactions in response to chronic stress over time, it does not address cumulative effects of multiple factors occurring simultaneously over a relatively short period of time. Multiple factors occurring together can result in negative outcomes regardless of the period of time (Rice, personal communication, June, 2007).

The KRW Integrative Model of Biobehavioral Interactions addresses biobehavioral interactions that occur simultaneously or those that occur over a period of time. The model is comprised of six domains of factors: individual, environmental, psychosocial, behavioral, biological, and health outcomes. Individual factors are characteristics that are specific to each individual. The environmental domain involves social, cultural, or physical factors present in the milieu which surrounds and influences the individual or community. The psychosocial domain addresses the mental characteristics of an individual or group and the interdependent relationships of that individual or group as members of a community or society. Behavioral factors are observable responses or activities of an individual alone or in interrelationships with others. Biologic factors are responses that are involved in the organic functioning. The factors in the individual, environmental, psychosocial, and behavioral domains may interact with other factors within the same domain and/or across domains to affect biological factors or responses either directly or indirectly at one point in time or over a long period of time. When the alterations in the biological factors accumulate and reach critical levels, health outcomes will be compromised. Over time, biological responses and
health outcomes can in turn influence the individual, environmental, psychosocial, or behavioral domains (Rice, personal communication, June, 2007).

Figure 1: *The KRW Integrative Model of Biobehavioral Interactions*
As the diagram indicates, only the individual, biological, behavioral, and health outcome domains will be utilized from the original model for this study. According the conceptual framework, factors within the individual domain (diagnosis and treatment variables, individual variables) will influence the behavioral domain (i.e., PT and chiropractic use). In turn, the behavioral domain can influence the health outcome. The biological domain can also influence the behavioral domain and health outcome.
CHAPTER 2
REVIEW OF LITERATURE

This chapter provides discussions of literature pertaining to the factors that may influence the development of musculoskeletal or neurological late effects in childhood cancer survivors and health-related quality of life (HRQOL) in these survivors. The factors that influence the use of physical therapy (PT) and chiropractic in childhood cancer survivors will also be discussed, as well as the effect the reported use of these services has on improving survivors’ HRQOL.

Background

Over 12,000 children and adolescents younger than 20 years of age are diagnosed with cancer each year in the United States (Ries, et al., 2007). The incidence of all forms of childhood cancer in all races has risen from 12.9 in 1975 to 16.0 in 2004 for children 0 to 19 years of age (Ries, et al., 2007). For unexplained reasons, the incidence of childhood cancer is substantially higher for White children than for Black children (17.5 vs. 11.6), and males are more affected than females (18.7 vs. 16.2 for Whites and 11.9 vs. 11.2 for Blacks) (Ries, et al., 2007).

Health care treatment has changed greatly over the years, with greater reliance on combinations of modes of therapy (i.e., chemotherapy, radiation, surgery) and regimens of progressively reduced chronic toxicity (e.g., reductions in radiation dose), which are
intended to minimize the likelihood of late effects (Hewitt, et al., 2003). Most children with cancer diagnosed and treated prior to 1970 had little hope of being cured (Smith & Ries, 2002). Five-year survival rates for all childhood cancers have risen from 62.9% in 1975-1979 to 79.2% currently (Ries, et al., 2007), largely as a result of the development of intensive multimodal treatments.

Consistent with reports from survivors of adult cancers (Bower et al., 2006; Ganz et al., 2002; Ganz, Greendale, Petersen, Kahn, & Bower, 2003; Ganz et al., 2004), patterns of late effects have emerged among groups of childhood cancer survivors that have contributed to an appreciation of cancer as a chronic disease with implications for continuing health care (Hewitt, et al., 2003). These childhood cancer survivors will reach adulthood with a near-normal life expectancy and with a childhood background of complex and often intensive antineoplastic therapy (Schultz, Beck, Stava, & Vassilopoulou-Sellin, 2003). Two of the most common late effects that have the greatest potential to impact functioning of survivors are musculoskeletal and neurological late effects. Structural or physiologic impairment of these organ systems as a consequence of either the cancer or treatment intervention may alter normal organ system functioning. In turn, impaired functioning may limit the physical performance of the cancer survivor and thus interfere with health-related quality of life (HRQOL) (American Physical Therapy Association, 2001; Nagi, 1976; World Health Organization, 2002).

Musculoskeletal conditions, including pain, osteoporosis, spinal disorders, and muscle weakness, are major causes of severe long-term pain, physical disability, and decreased HRQOL in the general US adult population (United States Bone and Joint Decade, 2008). Musculoskeletal medical conditions were reported in 107.67 million

Musculoskeletal conditions are common late effects experienced by childhood cancer survivors, and may include decreased muscle strength, decreased flexion, osteoporosis, and pain. Disabilities involving the bone and muscle are reported in up to a third of survivors of various pediatric cancers (Bhatia & Landier, 2005). Decreased knee extension, ankle dorsiflexion strength, and lower-extremity strength have been reported in children with acute lymphoblastic leukemia (ALL) both during and after treatment (Gocha Marchese, Chiarello, & Lange, 2003; Hovi, et al., 1993). Childhood cancer survivors also have a 25-fold increased risk of developing osteoporosis, and 38% of survivors between the age of 12 and 32 years old had already developed osteoporosis or osteopenia (Gurney, et al., 2003). In addition, 10.2% of survivors surveyed in the Childhood Cancer Survivor Study (n=9535) reported experiencing chronic pain (Hudson, et al., 2003). Childhood cancer survivors who had been diagnosed with bone cancer were three times more likely to report chronic pain compared to survivors of other types of childhood cancer.

Neurological dysfunction can include a wide-range of disorders, thus making ascertaining prevalence in both the child and adult populations difficult. A recent analysis of late effects in a sample of childhood brain tumor survivors in the Childhood Cancer Survivor Study found that 49% of survivors reported a coordination problem and 26% reported a motor control problem (Packer, et al., 2003). Those survivors who received higher doses of radiation to the frontal region of the brain had an increased risk for developing motor problems. Lehtinen and colleagues (2002) found that 31% of a
group of 32 childhood leukemia survivors had fine motor deficits. Poretti and colleagues (Poretti, et al., 2008) found that 50% of their sample of 20 children with intraspinal tumors suffered from long-term neurological consequences, including either paraparesis or monoparesis. In addition, findings from a recent study indicated decreased motor performance in children with ALL, Wilm’s tumor, B-cell non-Hodgkin lymphoma, and malignant mesenchymal tumors, independent of the cumulative Vincristine dose (Hartman, van den Bos, Stijnen, & Pieters, 2006).

Musculoskeletal and neurological late effect prevalence, chronicity, and severity rates have not been consistently reported across studies (Alvarez, et al., 2007; Arikoski, et al., 1998; Barr, et al., 1998; Brennan, et al., 1999; Burger, et al., 2005; Crofton, et al., 2000; Galea, Wright, & Barr, 2004; Harila-Saari, Vainionpaa, Kovala, Tolonen, & Lanning, 1998; Hartman, et al., 2006, 2008; Kaste, 2008; Lehtinen, et al., 2002; Ness, Bhatia, et al., 2005; Ness & Gurney, 2007); therefore, the risk for musculoskeletal and neurological dysfunction remains poorly defined among childhood cancer survivors. The impairment imposed by the dysfunction of these two systems may result in limitations in emotional well-being (Hobbie, et al., 2000; Hudson, et al., 2003; Schwartz & Drotar, 2006; Yabroff, Lawrence, Clauser, Davis, & Brown, 2004) and physical performance (Dimeo, et al., 2004; Fialka-Moser, Crevenna, Korpan, & Quittan, 2003; Ness, Mertens, et al., 2005; Simmonds, 2002) and thus result in decreased HRQOL of childhood cancer survivors.

Understanding the associations between musculoskeletal and neurological late effect severity and the use of health services, such as PT and chiropractic, in childhood cancer survivors is not only important for members of the rehabilitation community but
for the nursing community specifically. Irreversible deficits in these two systems as the
result of childhood cancer and its treatment may not be amenable to medical intervention.
However, performance limitations and pain can be remediated or ameliorated with
compensatory and adaptive strategies provided by rehabilitation and/or complementary
health professionals. Interventions designed to address performance limitations and pain
may eventually improve HRQOL in childhood cancer survivors, and nurses may be the
key health care professionals for making recommendations for these interventions.
Registered nurses are involved in cancer-related ambulatory care visits, and nurses are
often involved in the provision of supportive care (Hewitt, et al., 2006).

Nursing encompasses autonomous and collaborative care of individuals of all
ages, families, groups and communities, sick or well and in all settings (International
Council of Nurses, 2000). Nursing includes the promotion of health, prevention of illness,
and the care of ill, disabled and dying people. Health promotion is defined by the
International Council of Nurses as strategies that allow populations to be healthy and
enable them to make healthy choices (International Council of Nurses, 2000). Because of
the multiple determinants of health, health promotion requires collaboration between the
community, health professionals and other sectors. Because of nursing’s focus on health
promotion and disease prevention, nurses are central to any interdisciplinary effort in
survivorship care.

In some instances, nurses may be the best health care provider for providing
health promotion strategies to childhood cancer survivors because nursing has staked a
claim to be holistic in its approach to patients in its care (American Nurses Association,
2004). Childhood cancer survivors should be able to expect that this holistic approach
extends to and includes them. For optimal impact on HRQOL, nurses working with populations that are chronically ill, such as childhood cancer survivors, should recommend health services that emphasize wellness and health-promotion strategies (Pender, Murdaugh, & Parsons, 2006).

Recently released clinical practice guidelines (Children's Oncology Group, 2008) recommend PT as part of the treatment regimen for musculoskeletal and neurological conditions. For patients with musculoskeletal injuries and disabilities, physical therapy is the cornerstone of management (Barclay, 2007). The Children’s Oncology Group (Children's Oncology Group, 2008) does not currently recommend referral to chiropractors for any condition. Physical rehabilitation of cancer patients and survivors requires an interdisciplinary approach because of the variety of potential problems patients may face as a result of their cancer and its treatment (Kaplan, 2006). The role of the nurse on the rehabilitation team is pivotal because he or she typically functions as an extension of other members of the team and may assist with treatment interventions that the physical therapist begins (Kaplan, 2006).

PT is the provision of services in circumstances where movement and function are threatened by injury, disease or the process of aging with the goal is to develop, maintain, and restore maximum movement and functional ability throughout the lifespan. PT can enhance the functional dimensions of HRQOL (Smith, 1996) and is a regular component in the management of various (chronic) disorders, such as musculoskeletal disorders (Chartered Society of Physiotherapy, 2001; Gordon, et al., 2004; Pina, et al., 2003; Woolf, et al., 2004). A number of therapeutic modalities are available through PT, including exercise prescription (strength, motor control, stretching, and endurance),
manual therapy techniques like joint mobilization/manipulation, and soft tissue massage (Bureau of Labor Statistics U.S. Department of Labor, 2009). No studies to date have examined use of PT in childhood cancer survivors.

While PT is part of mainstream medical care, chiropractic is the largest, most regulated, and best recognized of the professions that have traditionally functioned outside of mainstream medical institutions and falls into the category of complementary and alternative medicine (CAM) (Meeker & Haldeman, 2002). Chiropractic care addresses disorders of the musculoskeletal system and how these aberrations may impinge upon the nervous system, subsequently affecting general health (Evans & Rosner, 2005), and studies report that chiropractic has been effective in improving HRQOL in the general population. The scientific literature regarding chiropractic use and HRQOL in cancer survivors is limited, though there is evidence that it is effective in improving HRQOL in adult breast cancer survivors (Buettner, et al., 2006; Secor, et al., 2004; Wenban & Nielsen, 2005).

Surveys indicate that individuals are more frequently utilizing chiropractors for the treatment of musculoskeletal complaints, and national guidelines in the United States, Australia, and United Kingdom recommend chiropractic for acute and chronic low-back pain (Bigos et al., 1994; Bogduk, 1999; Royal College of General Practitioners., 1999). Overall, estimates of the use of chiropractic services by the general population range from 3% to 18% (Dagenais & Haldeman, 2002), and about 90% of chiropractic patients are self-referred (Menke, 2003). Chiropractic patients are more likely than medical patients to be obese, have a higher level of education, have a higher household income, lack a regular doctor, have few chronic conditions, take few drugs, and be uninsured and
dissatisfied with health care (Hurwitz & Chiang, 2006; Kelner & Wellman, 1997). In a recent report for the Childhood Cancer Survivor Study, 12.1% of survivors reported seeing a chiropractor (Mertens, et al., 2008).

Both PT and chiropractic care have been shown to improve musculoskeletal complications both in the healthy adult population (Crawford, 1999; Hakkinen, et al., 2007; Hale, et al., 2007; Kohlbeck, et al., 2005; Rubinstein, et al., 2007; Swanenburg, et al., 2007) as well as for survivors of adult-onset cancers (Gordon, et al., 2005; Schneider, et al., 2002; Schneider, et al., 2007) and may have the potential to ameliorate some of the performance limitations that result from musculoskeletal late effects experienced by childhood cancer survivors and improve their HRQOL. There have been studies demonstrating that small percentages of the childhood cancer survivor population utilize physical therapy and chiropractic services. However, what factors predict their use have not been examined nor was the mediating effect these services may have on the relationship between musculoskeletal late effects experienced by survivors and their HRQOL.

Due to improved treatment modalities, the overall 5-year survival rate for childhood cancer survivors is now almost 80% (Ries, et al., 2007) resulting in an increased prevalence of childhood cancer survivors in the U.S. population. It is estimated that by 2010 one in every 250 to 400 adults between the ages of 21 and 44 years will be a survivor of childhood cancer (Twombly, 2001). This roughly translates into 2 to 3 survivors seen each year by primary care health care providers, with this number expected to increase to approximately 6 to 9 per year (Oeffinger, 2000). As the prevalence of childhood cancer survivors continues to increase, the need for long-term
medical follow-up and interventions to address or prevent late effects and to remediate functional limitations becomes more important. The Children’s Oncology Group currently recommends physical therapy referral for non-pharmacologic pain management, range of motion, strengthening, stretching, functional mobility, and gait training in childhood cancer survivors (Children's Oncology Group, 2008). However, not studies to date have examined the use of PT in childhood cancer survivors, and only one study to date have examined the use of chiropractic in the context of complementary and alternative medicine (Hewitt, et al., 2003; Mertens, et al., 2008). However this study did not examine what factors influence the use of chiropractic by childhood cancer survivors or how use of chiropractic may improve HRQOL.

**Late Effects**

*Musculoskeletal Late Effects*

Impairment of the musculoskeletal system is a common late effect experienced by childhood cancer survivors. Compared to siblings, survivors are 8.5 times (CI, 6.5 to 11.2 times) more likely to report any musculoskeletal problem (Ness, Mertens, et al., 2005). These problems can include impaired bone maturation and osteonecrosis (Crofton, et al., 2000; Henderson, Madsen, Davis, & Gold, 1996; Karimova, et al., 2007; Kaste, et al., 2006), decreased bone mineral density (Arikoski et al., 1998; Brennan, Rahim, Adams, Eden, & Shalet, 1999; Kaste et al., 2001; Nysom et al., 2001; Nysom et al., 1998), decreased peripheral muscle strength and ankle dorsiflexion (Hartman, et al., 2008), hypoextensibility of calf musculature (Wright, Halton, Martin, & Barr, 1998), muscle atrophy (Hovi, et al., 1993), and pain (Hudson, et al., 2003), among other conditions.
A recent report from the Childhood Cancer Survivor Study reported on the health outcomes of long-term survivors of childhood acute lymphoblastic leukemia (ALL) (Mody et al., 2008). One or more medical conditions were reported in 50% of survivors, compared to 37.8% of siblings. Highest late effect risk were seen for musculoskeletal (OR, 7.7), cardiac (OR, 6.9) and neurologic (OR, 5.3) conditions. Most of the grade 3 to 4 musculoskeletal morbidity reported was related to major joint replacement. Survivors who did not receive radiation as part of their treatment and had not relapsed were 22.8 times as likely to report musculoskeletal conditions compared to siblings.

Similarly, another recent report from the CCSS reported on the long-term outcomes of survivors of childhood acute myeloid leukemia (AML) (Mulrooney et al., 2008). Half of AML survivors reported a chronic medical condition, including more than 16% with a severe or life-threatening (grade 3 or 4) condition, compared with 5.8% of siblings. Grade 3 or 4 musculoskeletal conditions were reported in 2.5% of AML survivors, compared to 22.8% of non-AML CCSS survivors.

The foundations of bone health are determined primarily in childhood when the majority of an individual’s bone is laid down in the first two decades of life (Specker & Schoenau, 2005). Adolescence is also an important time because bone formation is significantly influenced by diet, sex hormones, and growth hormones (Alvarez, et al., 2007). Children who undergo cancer treatment during the normal period of bone mass accrual may be at risk for future deficits in bone mineral density (BMD) and its sequelae of fractures, kyphosis, and pain (Kaste, 2008). Disabilities involving bone, teeth, and muscle and other soft tissues are reported in up to a third of survivors of various pediatric cancers (Bhatia & Landier, 2005). Bony abnormalities reported in survivors include
scoliosis, atrophy or hypoplasia, avascular necrosis (AVN), and osteoporosis (Bhatia & Landier, 2005).

Childhood cancer treatments such as, hormone therapy, chemotherapy, radiation therapy and surgery can all directly or indirectly damage bone and lead to loss of bone mass (Aksnes & Bruland, 2007). Bone loss in normal aging is usually associated with hypogonadism (Aksnes & Bruland, 2007); therefore, studies of bone loss in survivors of adult cancers have mainly focused on therapies that induce hypogonadism (Bae & Stein, 2004; Fontanges, Fontana, & Delmas, 2004; Hawkins, 2006; Hoff & Gagel, 2005; Holmes-Walker, Woo, Gurney, Do, & Chipps, 2006; Michaud & Goodin, 2006; Pfeilschifter & Diel, 2000; Smith, 2003). However, studies of bone loss in childhood cancer survivors have focused on how specific treatments and diagnoses have impacted bone loss. Therefore, the results are diverse thus making it difficult to draw any strict conclusions (Barr et al., 1998; Haddy, Mosher, & Reaman, 2001; Holzer et al., 2003; Kaste, 2004; Kaste et al., 1999; Mandel, Atkinson, Barr, & Pencharz, 2004; Odame et al., 2006; Othman, Guo, Webber, Atkinson, & Barr, 2002; Vassilopoulou-Sellin et al., 1999).

Factors that contribute to deficient bone mineral density (BMD) in long-term survivors of childhood cancer include catabolic hormone therapy (steroids) (Mandel, et al., 2004); chemotherapy (Arikoski et al., 1998; Brennan, Rahim, Adams, Eden, & Shalet, 1999; Kaste et al., 2001; Mandel, Atkinson, Barr, & Pencharz, 2004; Nysom et al., 1998; Strauss et al., 2001; Swiatkiewicz et al., 2003); direct radiation to skeletal regions such as the spine; cranial radiation that affects hormonal regulation (Alvarez, et al., 2007); genetic predisposition (Arikoski, et al., 1998; Howard, et al., 1995; Krall, Parry, Lichter, & Dawson-Hughes, 1995); inactivity (Afghani et al., 2003; Cooper et al.,
Osteopenia in survivors of childhood acute lymphoblastic leukemia has been found to be related to cranial irradiation, methotrexate, and corticosteroid use (Gilsanz, Carlson, Roe, & Ortega, 1990). A study by Mandel and colleagues (2004) examined BMD in 106 survivors of ALL. Those survivors who suffered from reduced bone mineral density received an accumulated Methotrexate dose greater than 40 g/m² or a total corticosteroid dose of greater than 9 g/m². Studies have shown that children treated for brain tumors and bone sarcomas may also have low BMD years after therapy (Barr, et al., 1998; Holzer, et al., 2003; Odame, et al., 2006).

Some chemotherapeutic agents are known to induce bone loss. Methotrexate increases bone resorption and reduces bone formation (Aksnes & Bruland, 2007). In addition, it inhibits matrix mineralization and thereby further reduces bone formation (Michaud & Goodin, 2006; Pfeilschifter & Diel, 2000; Theriault, 2004; van Leeuwen, Kamps, Jansen, & Hoekstra, 2000). Cyclophosphamide inhibits bone formation and bone resorption by directly arresting the cell division of preosteoblasts and osteoclasts which leads to decreased numbers of osteoblasts and osteoclasts on bone surfaces (Michaud & Goodin, 2006; Pfeilschifter & Diel, 2000). In vitro studies of doxorubicin have shown that the drug inhibits proliferation and differentiation of osteoblasts and selectively reduces the rate of bone formation by altering the interaction of parathyroid hormone with the osteoblast receptor (Michaud & Goodin, 2006; Pfeilschifter & Diel, 2000).
It is also known from previous studies that children treated with vincristine for ALL demonstrate decreased motor performance, which may last a number of years following completion of chemotherapy (Harten, et al., 1984; Reinders-Messelink, et al., 1996; Vainionpaa, 1993; Wright, et al., 1998). However, children with other malignancies have also demonstrated impaired motor performance after chemotherapy containing vincristine (Hartman, et al., 2006). Reduced muscle strength and reduced passive ankle dorsiflexion, both of which have been reported in survivors of ALL (Gocha Marchese, et al., 2003; Hovi, et al., 1993; Wright, Halton, & Barr, 1999; Wright, et al., 1998), may impair motor performance.

Radiotherapy in children with cancer can cause muscle atrophy, fibrosis, fractures, and limb length discrepancies (Butler, Robertson, Rate, D'Angio, & Drummond, 1990; Fletcher, 1997; Parisi, Fahmy, Kaminsky, & Malogolowkin, 1999). Limb atrophy or hypoplasia has been reported to follow radiation of the long bones at doses exceeding 20 Gy when there is involvement of epiphyses in the radiation field (Larson, Kroll, Jaffe, Serure, & Goepfert, 1990). Patients who receive radiotherapy to the trunk may develop scoliosis or kyphosis. This is most commonly seen in survivors of childhood Wilm’s tumor or neuroblastoma (Aksnes & Bruland, 2007). In a study of late effects after treatment for Wilm’s tumor, children treated with radiation doses below 24 Gy had a lower incidence of scoliosis compared to those who received more than 24 Gy (Paulino, 2004). The incidence was further reduced in patients who received 10-12 Gy, and the incidence progressed with time from treatment.

Surgical procedures, which include amputation and limb-sparing surgery, often result in skeletal and soft tissue deformities, especially if these treatments were done
before the adolescent growth spurt (Castellino & Hudson, 2002). Amputation and limb-sparing surgery each has advantages and disadvantages with regard to late functional outcomes (Nagarajan, Neglia, Clohisy, & Robison, 2002). More frequent complications have been observed in childhood cancer survivors who had limb-sparing surgery procedures (Oeffinger & Hudson, 2004). Late complications unique to amputation include stump-prosthetic problems, chronic stump pain, phantom limb pain, and bone overgrowth (Nagarajan, et al., 2002). Survivors who have undergone limb-sparing surgery may experience non-union, pathologic fracture, aseptic loosening, limb-length discrepancy, endoprosthetic fracture, poor joint movement, and stump-prosthesis problems (Nagarajan, et al., 2002). Scoliosis has also been found to be a complication of treatment with surgical laminectomy for intraspinal tumors (Paulino & Fowler, 2005). Survivors of bone cancer and soft-tissue sarcoma are vulnerable to musculoskeletal problems because surgical procedures can result in damage to, or loss of, structures required to execute movement (Ness, Mertens, et al., 2005).

Mansky and colleagues (2007) examined the treatment late effects in long-term survivors of pediatric sarcoma who received locoregional therapy (i.e., surgery, radiation, or both). The study included a sample of 32 sarcoma survivors, of which 28 did not have any amputation. Participants demonstrated reduced musculoskeletal functioning related to treatment. Range of motion (ROM) of the affected extremity was reduced by 40% in 12 of 13 (92%) non-amputated participants with lower extremity and pelvic sarcoma. All 28 non-amputated participants completed a 6-minute walk test, and velocity was abnormal (<90% predicted) in 9 (32%), all of which had trunk/pelvic or lower extremity sarcoma. Study participants also demonstrated a diminished capacity to perform ADL’s,
with both motor (P<0.0001) and process (P<0.0001) scores significantly lower than matched controls. Though not statistically significant, participants in this study rated themselves lower than controls on the Physical Component Summary subscale of the SF-36 (P=0.065), which could have clinical significance.

Pain is another musculoskeletal complication often experienced by survivors. Some survivors report more general pain compared to people with no history of cancer (Lyne, Coyne, & Watson, 2002; Polomano & Farrar, 2006). Sensory pain, pain in the radiated area, and muscular pain have been reported (Aksnes & Bruland, 2007). Studies often do not report the cause and extent of pain in childhood cancer survivors. However, Hudson and colleagues (2003) found that survivors of bone tumors were more likely to have more pain as a result of their cancer and its treatment than other survivors of childhood tumors.

Treatments associated with pain in survivors include radiation and surgery. Some of the most pronounced effects seen in young children treated with high-dose radiation therapy are muscle wasting and bone atrophy (Castellino & Hudson, 2002). Cosmetic and functional problems may result from the subsequent reduced or asymmetric growth and may be associated with chronic pain (Castellino & Hudson, 2002). Some studies indicate that higher radiation doses (above 60 Gy) result in more pain, and larger dose per fraction may lead to damage to the muscle and soft tissue that can lead to long-term pain (Aksnes & Bruland, 2007). Surgery may also cause pain either from nerve damage or physical impairment (Aksnes & Bruland, 2007). Children with cancer treated for extremity localized sarcomas are likely to experience physical impairment after treatment because
this group is generally treated with either amputation or limb salvage as well as massive chemotherapy (Aksnes & Bruland, 2007).

Bone tumor childhood cancer survivors with multiple late effects more frequently experience severe musculoskeletal problems (Oeffinger, et al., 2006). Even with modern limb-sparing procedures, the life-altering musculoskeletal morbidity faced by bone tumor survivors is clinically significant and will increase as weight-bearing joints age more rapidly due to asymmetric stress and altered function (Eiser, Darlington, Stride, & Grimer, 2001; Nagarajan, et al., 2002; Ness, Mertens, et al., 2005).

**Neurological Late Effects**

Childhood cancer survivors are particularly vulnerable to neurological sequelae and poor physical outcomes (Ness & Gurney, 2007). Results of a previous study indicated that late effects of the neurologic system were highly prevalent, with 42.6% of survivors reporting at least 1 problem in this category (Ness, Mertens, et al., 2005). Prolonged pain or an abnormal sensation in the trunk or extremities was the most commonly reported neurologic impairment among survivors (31.1%) and siblings (14.4%). Weakness in the arms or legs was reported by 9.2% of survivors. The risk for any neurologic impairment among survivors was 2.4 times (CI, 2.2 to 2.5 times) that of siblings. Sensory problems were 4.3 times (CI, 3.5 to 5.3 times) more common among survivors than in siblings.

Therapy directed at the central nervous system in the form of cranial/craniospinal irradiation, intrathecal treatment, or high-dose systemic methotrexate therapy may affect neurological function (Castellino & Hudson, 2002). With contemporary treatment
protocols, peripheral neuropathy or motor neuropathy typically develops acutely during therapy with vinca alkaloids (vincristine, vinblastine) or cisplatin (Castellino & Hudson, 2002). Paralytic syndromes (e.g., hemiparesis) or cranial neuropathies are more likely the residual sequelae of the primary tumor presentation (Castellino & Hudson, 2002).

Previous reports indicate that survivors of brain cancer are particularly vulnerable to neurologic sequelae and poor physical outcomes (Foreman, et al., 1999; Lannering, Marky, Lundberg, & Olsson, 1990; Macedoni-Luksic, Jereb, & Todorovski, 2003; Packer, et al., 2003). Balance deficits, ataxia, paralysis, and difficulty walking have been reported in studies of survivors of brain cancer that have used various study designs (Foreman, et al., 1999; Lannering, et al., 1990; Macedoni-Luksic, et al., 2003; Packer, et al., 2003).

A recent study examined long-term neurologic and neurosensory sequelae in 1,607 adult survivors of childhood brain tumors (Packer, et al., 2003). Seventeen percent of survivors developed neurosensory impairment. Coordination and motor control problems were reported in 49% and 26%, respectively, of survivors. Children who received at least 50 Gy radiation to the frontal brain regions had a moderately elevated risk for motor problems after treatment ended (RR, 2.0; P<0.05).

Chemotherapy-induced peripheral neuropathy is a significant, debilitating symptom directly related to the administration of neurotoxic chemotherapy for the treatment of cancer (Visovsky, Collins, Abbott, Aschenbrenner, & Hart, 2007). Peripheral neuropathy usually affects the hands and feet and may cause muscle weakness and pain (Aksnes & Bruland, 2007). Chemotherapeutic agents such as cisplatin, oxaliplatin, taxanes, and vinca alkaloids are known to cause neuropathy (Hausheer,
Schilsky, Bain, Berghorn, & Lieberman, 2006; Polomano & Farrar, 2006; Quasthoff & Hartung, 2006). Direct damage to nerve cells either by pressure or trauma (tumor or surgery) can also cause neuropathy (Aksnes & Bruland, 2007). Peripheral neuropathy may resolve once treatment has stopped or it may persist for years in some patients. The incidence and prevalence of long-term peripheral neuropathy is not known in childhood cancer survivors (Polomano & Farrar, 2006).

Studies suggest that long-term gross and fine motor performance measures are significantly compromised in childhood cancer survivors of ALL compared with age and sex-matched controls (Galea, et al., 2004; Reinders-Messelink, et al., 1999; Wright, Galea, & Barr, 2005; Wright, et al., 1998). These deficits continue to be evident 5 years after completing therapy (Lehtinen, et al., 2002). In a group of 32 childhood leukemia survivors, 31% had fine motor difficulties (Lehtinen, et al., 2002). Fine motor problems continued to be present 2 years after completion of therapy in a group of 18 childhood leukemia survivors (Reinders-Messelink, et al., 1999). In addition to children with ALL, decreased motor performance has been found in survivors of Wilm’s tumor, B-cell non-Hodgkin lymphoma, and malignant mesenchymal tumors, independent of cumulative Vincristine dose (Hartman, et al., 2006).

As mentioned previously, a recent analysis of the CCSS demonstrated that ALL survivors were at high risk for neurologic late effects (Mody et al., 2008). The grade 3 or 4 neurologic late effects that were reported included cranial nerve paralysis, monoquadriplegia, and other paralysis syndromes. Relapsed childhood cancer survivors were more likely to report neurologic late effects than nonrelapsed survivors. A similar analysis was conducted examining the long-term outcomes of AML survivors.
(Mulrooney, et al., 2008) which found that 15% of AML survivors reported a grade 3 or 4 neurologic late effect, compared to 9.2% of non-AML CCSS survivors.

Problems with balance as well as limitation in running speed and strength have also been identified in survivors of ALL using standardized gross motor assessment (Wright, et al., 1998). Effective maintenance of balance requires the coordination of three sensory systems with motor output (Galea, et al., 2004), and postural control is ascribed to complex interaction between the neural and musculoskeletal systems (Shumway-Cook & Woollacott, 2001). In a healthy central nervous system (CNS) postural control depends on a number of factors. First, the musculoskeletal system must be able to enact messages from the CNS (Galea, et al., 2004). As previously mentioned, survivors of ALL may be compromised in this area due to muscle weakness, lack of adequate muscle extensibility, unstable joints/bones, and pain. Secondly, individual sensory elements must be able to encode visual, vestibular, and somatosensory information (Galea, et al., 2004). Intrathecal methotrexate therapy and cranial irradiation could compromise central pathways (Harila-Saari, et al., 1998), and vincristine-induced neuropathy (Legha, 1986) can compromise the functioning of proprioceptive feedback from skin, muscles, and joints, thereby interfering with somatosensory functioning. Finally, important structures of the CNS are organized to relay feed forward and feedback information to the musculoskeletal system (Galea, et al., 2004). This depends on accurate transmission and reception via the spinal cord and various cortical areas, and this coordination by the CNS may be disrupted by chemotherapy (Harila-Saari, Vainionpaa, Kovala, Tolonen, & Lanning, 1998).

Childhood cancer survivors who received hematopoietic stem cell transplantation (HSCT) as part of their cancer treatments are also at risk for neurological late effects.
Because patients who receive HSCT from an allogeneic source may develop acute or chronic graft-versus-host disease, they are treated with cyclosporine A. Neurotoxicity is a recognized complication of cyclosporine A and may include generalized seizures, occipital blindness, and hemiparesis (Gurney et al., 2006). An analysis of the Bone Marrow Transplant Survivor Study, a collaborative study between City of Hope Cancer Center and the University of Minnesota evaluated the incidence of neuromotor and neurosensory outcomes among 235 childhood cancer survivors who were treated with hematopoietic stem cell transplantations and compares outcomes to 705 siblings of childhood cancer survivors (Gurney et al., 2006). Persistent pain was the most common sensory impairment reported by survivors (21%). In addition, survivors were 4.3 times (95% CI: 3.2-18.5) more likely to report coordination problems and 3.5 times (95% CI: 1.6-7.9) more likely to report muscle weakness than those in the comparison group. Persistent dizziness was reported by 3.4% (RR:4.0; 95% CI, 1.4-11.5) of survivors versus 0.8% in the comparison group.

Late Effect Severity

Oeffinger and colleagues graded chronic conditions in a sample of 96 childhood cancer survivors seen in a follow-up clinic (Oeffinger, et al., 2000). Approximately 69% of the patients (n=66) had at least one late effect. Thirty-three percent of patients had a single chronic condition, and 36% and two or more conditions. Twenty patients (24%) were diagnosed with an asymptomatic late effect of grade 2-4. Thirty percent of childhood cancer survivors had a grade 3 or 4 condition. Twenty-four percent of these survivors had musculoskeletal chronic conditions, and the majority (n=13) were grade 3
or 4. Neurological chronic conditions were reported in 6% (n=6) of this sample, and they were evenly disbursed between grades 1, 2, and 3/4.

In a second study conducted by Oeffinger and colleagues (2006), prevalence and severity of chronic conditions was also ascertained using the Childhood Cancer Survivor Study. Of the 10,397 survivors included in the study 62.3% had at least one chronic condition; 27.5% had a severe or life-threatening condition (grade 3 or 4). Groups at highest risk for having a condition of grade 3 or 4 were survivors of bone tumors (RR, 38.9; 95% CI, 31.2-48.5), CNS tumors (RR, 12.6; 95% CI, 10.3-15.5), and Hodgkin’s disease (RR, 10.2; 95% CI, 8.3-12.5).

Various treatments contributed to severity of late effects as well. Exposure to one of five specific combinations of treatments was associated with a risk of having a condition of grade 3 or 4 that was at least 10 times the expected risk: chest radiation plus bleomycin (RR, 13.6; 95% CI, 9.8-18.7), chest radiation plus anthracycline (RR, 13.0; 95% CI, 10.4-16.3), chest radiation plus abdominal or pelvic radiation (RR=10.9; 95% CI, 8.9-13.2), anthracycline plus an alkylating agent (RR, 10.9; 95% CI, 9.0-13.1), and abdominal or pelvic radiation plus an alkylating agent (RR, 10.0; 95% CI, 8.2-12.1).

Prevalence and severity of late effects was evaluated in a sample of 241 childhood cancer survivors recruited from a long-term follow-up clinic in South Korea (Han, et al., 2009). Late effects were identified in 59.8% of survivors, and 23.2% had two or more conditions. Sixty-one survivors (25.3%) had grade 1 (mild) late effects and 83 (34.4%) had grade 2 (moderate) late effects. Grade 3 or 4 late effects were found in 10.8% of survivors.
Survivors treated with radiotherapy had a much higher grade of chronic conditions than did survivors who did not receive radiotherapy (1.5 ± 0.1 vs. 0.8 ± 0.1, p<0.001). A history of chemotherapy or HSCT was associated with more severe chronic conditions when compared with the grade of late effects in survivors who did not receive chemotherapy or HSCT (1.1 ± 0.1 vs. 0.1 ± 0.1, p<0.001; 1.4 ± 0.1 vs. 1.0 ± 1.0 ± 0.1, p=0.025). Fifty-two percent of all brain tumor survivors had grade 3 or higher chronic conditions, compared with only 4.2% of leukemia survivors.

Geenen and colleagues (2007) assessed the burden of late effects in a cohort of 1362 five-year survivors of childhood cancer. To evaluate total burden of late effects, the authors classified survivors into four different groups based on the total number of events and the grade of each. Survivors with one or more grade 1 late effects were classified as having low burden; those with one or more grade 2 and/or one grade 3 late effects, a medium burden; those with two or more grade 3 late effects, or one grade 4 condition and at most one grade 3 late effect, a high burden; and those with more grade 3 or 4 events or a grade 5 event, a severe burden.

In this sample, 1015 (74.5%) had one or more late effects. Approximately 37% of survivors had at least one severe or life-threatening late effect, and 23.4% had a high or severe burden of late effects. Survivors of bone tumors most often had a high or severe burden of events (64%), while survivors of leukemia or Wilm’s tumor were less likely to have a high or severe burden (12% each). Treatment-specific risk factors were also examined.

Survivors who received radiation as part of their treatment had a significantly increased risk of an event of at least moderate severity, compared with survivors treated
with surgery only. Survivors who received radiation only had the highest risk for late effects of moderate severity (RR, 1.49; 95% CI, 1.27-1.74). Survivors who received radiation only were also most likely to develop a high or severe late effect burden.

**Physical Therapy and Chiropractic Use in Survivors**

As previously mentioned, cancer or its treatment in childhood can result in late effects involving the musculoskeletal system, the neurological system, or both that may diminish functioning (performance limitations). Performance limitations can restrict the childhood cancer survivor’s ability to participate fully in daily activities necessary for self-care, home management, or work (Ness, Mertens, et al., 2005). Performance limitations and participation restrictions have been reported in as many as 69% of childhood cancer survivors (Crom, Chathaway, Tolley, Mulhern, & Hudson, 1999; Garre et al., 1994; Hudson et al., 2003).

Survivors with musculoskeletal late effects versus those without musculoskeletal late effects (RR, 1.9; CI, 1.7 to 2.0) and survivors with neurologic late effects versus those without neurologic late effects (RR, 2.0; CI, 1.9 to 2.2) had the highest risk for reporting a performance limitation (Ness, Mertens, et al., 2005). Survivors with neurologic or sensory impairments versus those without such impairments had the highest risk for reporting restrictions in their ability to perform personal care skills, to participate in routine activities, and to work or school (Ness, Mertens, et al., 2005).

Although not all musculoskeletal and neurological late effects can be avoided or eliminated, their impact on physical performance limitations, participation in routine
activities, and HRQOL can be influenced by rehabilitation measures designed to restore function or remediate loss in function (Ness, Mertens, et al., 2005). Two such rehabilitation measures include physical therapy (PT) and chiropractic.

**Physical Therapy**

Rehabilitation too often remains clinically underutilized in the care of children with cancer and childhood cancer survivors (Cheville, Khemka, & O'Mahony, 2007). There may be a perception that only those survivors who are capable of full community and vocational pursuits and who have unrestricted life spans will benefit from rehabilitation services, though this perception is inaccurate. Although rehabilitation was initially focused on transitioning individuals with anatomically devastating injuries back to productive lives, the physical therapy treatment area has broadened considerably (Cheville, et al., 2007). Although rehabilitation services are part of standard care for patients with pulmonary and cardiac disease, comparable services are rarely offered to children with cancer and childhood cancer survivors.

Because the continually improving survival rates in childhood cancer is resulting in a growing population of survivors, the psychological well-being and physical functioning of survivors is important from a public health standpoint (Doyle, et al., 2006). Impairments faced by childhood cancer survivors are associated with abrupt functional decline in the absence of rehabilitation (Cheville, et al., 2007). Cancer of the bone and surgical procedures used to treat these malignancies can undermine the essential supporting structures of the musculoskeletal system, often resulting in abnormal and ultimately dysfunctional biomechanical movements (Cheville, et al., 2007).
Rehabilitation services, such as PT, focus on reducing the level of disability and handicap associated with particular impairments. Impairments most commonly remediated are those due to neurological or musculoskeletal injuries (Cheville, et al., 2007). Studies provide support for the effectiveness of PT intervention in improving function in patients affected with neurological and musculoskeletal dysfunction. However, little of the rehabilitation literature pertains specifically to cancer patients or survivors.

Cancer patients and survivors are keenly interested in receiving rehabilitation services (Cheville, et al., 2007), but often are not receiving the necessary PT referrals. Physical activity is one therapy that is gaining credibility in enhancing quality of life and reducing the burden of disease (Keats, Culos-Reed, & Courneya, 2007). Keats and colleagues (2007) examined the beliefs, attitudes and counseling practices of a group of pediatric oncologists toward physical activity in childhood cancer survivors. All responding physicians (n=12) regarded both personal exercise and physical activity for childhood cancer survivors as moderately to extremely important and indicated that they provided verbal counseling for physical activity. However, only one physician indicated that they would refer the patient to a specialist if specific program details were sought or required and none of the remaining respondents indicated that they had made use of any type of referral mechanism (e.g., exercise physiologist, physical therapist or certified fitness instructor/program).

Because most oncologist physicians do not have the expertise to develop individualized exercise programs for cancer survivors, it is important that survivors are referred to physical therapists. Furthermore, supervised exercise programs may have
advantages over home-based programs in that cancer survivors can be directly observed, which may decrease the risk of injury and also improve exercise adherence (Irwin, 2009).

The Oncology Nursing Society recommends physical therapy as an intervention for chemotherapy-induced peripheral neuropathy that is likely to be effective, though effectiveness has not been established (Visovsky, Collins, Abbott, Aschenbrenner, & Hart, 2007). Though few studies address the value of PT for individuals with peripheral neuropathy, performing passive range of motion exercises enhances reinervation in denervated muscle and appears to have therapeutic value (Visovsky, 2005). Some evidence suggests that resistance exercises may be of benefit in increasing strength for individuals weakened by neuropathy (Aksnes & Bruland, 2007; Visovsky, 2005) and that PT may improve balance and coordination (Aksnes & Bruland, 2007).

The majority of studies pertaining to the use of PT in cancer survivors has been conducted in survivors of adult cancers and has shown that physical therapy can be an effective intervention for improving function and health-related quality of life in cancer survivors. Several investigators have conducted systematic reviews of the evidence and reported that exercise rehabilitation in cancer survivors improves quality of life, cardiorespiratory fitness, physical functioning, and fatigue (Galvao & Newton, 2005; Knols, Aaronson, Uebelhart, Fransen, & Aufdemkampe, 2005; McNeely, et al., 2006; Stevinson, Lawlor, & Fox, 2004).

In a study examining the efficacy of PT in improving shoulder function, pain, and quality of life in breast cancer survivors, functional shoulder impairments and pain in the shoulder/arm were reduced significantly after PT (both p<0.001) at three months compared to the control group (Beurskens, van Uden, Strobbe, Oostendorp, & Wobbes,
In addition, pain decreased on the Visual Analogue Scale (VAS) by 3.4 points in the treatment group compared to a 0.5 point decrease in the control group. Shoulder flexion increased in the treatment group by 45 degrees ($p=0.003$) and abduction by 70 degrees ($p=0.005$) versus 11 and 13 degrees respectively in the control group.

A systematic review conducted by Cheema and colleagues (2008) located 10 trials that used progressive resistance training in breast cancer patients as part of their rehabilitation programs. These studies indicated that resistance training has a great potential to improve some of the negative effects of cancer, such as muscle atrophy, reduced bone mineral density, and fatigue (Galvao & Newton, 2005; Ohira, Schmitz, Ahmed, & Yee, 2006; Oldervoll, Kaasa, Hjermstad, Lund, & Loge, 2004; Ott, et al., 2004; Segal, et al., 2003; Twiss, et al., 2001).

De Backer and colleagues (2008) investigated the long-term effects of high-intensity resistance training in a sample of 49 survivors of adult cancers. Survivors who completed an 18-week resistance training program were followed for one year and compared to a group of 22 patients treated with chemotherapy in the same period who did not receive any exercise rehabilitation. Outcome measures were muscle strength, cardiopulmonary function, fatigue, and health-related quality of life. Results indicated that all outcome measures were improved in the intervention group and remained at the same level one year after the completion of rehabilitation. Muscle strength at one year was significantly higher in patients who completed the resistance training program than in the comparison group.

In order to overcome cancer-related problems and to improve quality of life, an intensive multi-focus rehabilitation program was implemented in a sample of 34 adult
cancer patients (van Weert, et al., 2004). The six-week intensive multi-focus rehabilitation program consisted of four components: individual exercise, sports, psycho-education, and information. Statistically significant improvements were found in all physical outcome variables, including oxygen pulse, muscle force, and muscle fatigue. After six weeks of rehabilitation, patients showed a statistically significant improvement in physical functioning, role limitation due to emotional problems and vitality in the RAND-36 domains, as compared with baseline values. Furthermore, the score on the change of health domain, which reflects a comparison between the present situation and the situation a year ago, was increased and reached a value which was greater than the mean score of the general population.

As previously mentioned, one of the main musculoskeletal effects experienced by survivors of childhood cancer is decreased bone mineral density. Treatment of BMD deficits in children includes increasing weight-bearing exercise as tolerated (Wasilewski-Masker, et al., 2008). The results of a study that examined which factors affected BMD in survivors of ALL provided evidence that increased weight-bearing exercise at a younger age favorably affected BMD (Kaste, et al., 2006).

The clinical manifestations of peripheral neuropathy include distal symmetrically distributed burning, numbness, tingling, decreased or altered sensation, or increased sensitivity that may be painful (Hausheer, et al., 2006). Though less commonly reported, motor weakness due to peripheral neuropathy may also occur. There is currently no treatment that can reverse nerve damage. Therefore, treatment is directed toward symptom management. Physical therapy may be helpful in providing improved strength, balance, and coordination (Aksnes & Bruland, 2007). In addition, the current standard of
care for soft tissue sarcoma (STS) is limb salvage surgery and adjuvant radiotherapy (Parsons & Davis, 2004). However, the extensive surgical resection and subsequent reconstruction result in chronic disability. Rehabilitation aims to optimize functional independence and quality of life and is routinely offered to patients undergoing surgical treatment (Parsons & Davis, 2004).

Chiropractic

Complementary and alternative medicine (CAM), which includes chiropractic, refers to the health care practices that are not an integral part of conventional medicine (National Institute of Health, 2000). CAM therapies are administered for the purpose of disease diagnosis, treatment, or health promotion (Ni, Simile, & Hardy, 2002). There is an increasing trend in the use of CAM not only in patients with specific conditions, but also in the general population (Eisenberg, et al., 1998). An estimated 29% of U.S. adults used at least one CAM therapy in the past year, and the three most commonly used therapies were spiritual healing or prayer (13.7%), herbal medicine (9.6%), and chiropractic therapies (7.6%) (Ni, et al., 2002). However, a recent report of CAM use in 567 patients in an outpatient clinic found that 85% acknowledged using one or more CAM therapies (Boutin, Buchwald, Robinson, & Collier, 2000). Of these patients, 14% used chiropractic and 28% thought chiropractic therapy should be offered. Fifteen percent of physicians sampled in this study recommended chiropractic care to their patients.

The widespread use of complementary and alternative medicine has been well categorized by researchers in terms of demographics and use of CAM treatment modalities (Boutin, et al., 2000; Eisenberg, et al., 1998; Paramore, 1997). Individuals
who use CAM tend to be Caucasian women (Boutin, Buchwald, Robinson, & Collier, 2000; Ni, Simile, & Hardy, 2002; Secor, Markow, Mackenzie, & Thrall, 2004) who are older (Ni, et al., 2002; Secor, et al., 2004). CAM users also tend to have a higher income, higher levels of education (Ni, et al., 2002), and health insurance (Ni, et al., 2002) than those who do not utilize CAM. Compared to nonusers, CAM users are also more likely to have a usual place to go for medical care, to have a customary health provider for medical care, to have visited a medical specialist or general medical doctor in the past year, and to have entered the emergency room in the past 12 months (Ni, et al., 2002). Reasons for seeking CAM services include a decrease in quality of life, increased pain, and general discomfort (Secor, et al., 2004).

The proportion of the population using chiropractic services has doubled in the last two decades, with chiropractors accounting for 31% of the total estimated number of alternative health care visits (Coulter, et al., 2002). The focus of chiropractic therapy is the detection and correction of spinal subluxations (Redwood, 2006), and many chiropractors view themselves as primary care providers (Baer, 2006; Barnett, McLachlan, Hulbert, & Kassak, 1997) or general practitioners with “an important role in health promotion and injury or disease prevention” (Killinger, 2004, p.232).

Chiropractors predominantly treat patients with musculoskeletal problems, about 60% of whom suffer from low back pain (Ernst, 2008). In the United States, 13% of all back pain sufferers consult a chiropractor (Carey et al., 1996). Neck pain is also a common problem for which patients seek chiropractic care (Ernst, 2008). A survey of chiropractic patients reported that more than 70% of patients specified back and neck problems as their health problem for which they sought chiropractic care (Coulter, et al.,
Though physical therapists also practice spinal manipulation, chiropractors deliver more than 90% of all spinal manipulations (Meeker & Haldeman, 2002).

Eisenberg and colleagues (1993) conducted a survey of 1539 adults to determine the prevalence and patterns of use of unconventional medicine in the United States. One in three respondents (34%) reported using at least one unconventional therapy in the past year. Ten percent reported using chiropractic in the past 12 months. Reasons for using chiropractic therapy included back problems, arthritis, and headache.

About 90% of chiropractic patients are self-referred (Menke, 2003) and are more likely than medical patients to be obese, have few chronic conditions, and take few drugs (Hurwitz & Chiang, 2006). In contrast to what was reported for CAM users as a whole, chiropractic patients also are more likely to lack a regular doctor, be uninsured, and to be dissatisfied with health care (Hurwitz & Chiang, 2006). Reasons for patients not to seek chiropractic care include the fear of adverse effects and lack of scientific proof (Menke, 2003).

Many national guidelines recommend chiropractic for acute and chronic low back pain (Bigos et al., 1994; Bogduk, 1999; Royal College of General Practitioners, 1999; van Tulder, Goossens, Waddell, & Nachemson, 2000). Though there is not a comprehensive scientific body of evidence demonstrating the effectiveness of chiropractic care, no other therapy has been shown to make a real difference for back pain sufferers (Ernst, 2008). Recent studies suggest that a prospectively identifiable subgroup of patients with back pain may benefit from spinal manipulation, whereas others do not (Brennan, et al., 2006; Childs, et al., 2004; Fritz, Brennan, & Leaman, 2006; Fritz, Childs, & Flynn, 2005).
Contraindications for chiropractic have been established by current literature relative to techniques specific for articular derangements, bone weakening and destruction disorders, circulatory and cardiovascular disorders, or neurological disorders (Reid, Desimone, & Eubank, 2002). These contraindications include osteoporosis, local malignancies, bone fractures, bone infections, and bleeding disorders (Dagenais & Haldeman, 2002), as well as active inflammatory arthropathy, ligamentous laxity, hypermobility, local metastases, dislocations, myelopathy, and cauda equine syndrome (Gay, 2006). Other contraindications include severe spondylosis, distant malignancies/metastases, local benign tumors, spinal trauma, chronic spondylarthropathy, history of spinal surgery, acute soft tissue or disc injuries, history of vertebrobasilar insufficiency, and osteopenia (Gay, 2006). Knowledge of these contraindications would be critical for nurses caring for childhood cancer survivors considering they may experience these disorders as a result of their disease or treatment.

A recent study of CAM use among children in primary care settings found that 33% of parents surveyed reported using CAM for their child within the past year and 49% reported ever using it (Loman, 2003). Of the 191 parents surveyed, 8 (4%) reported their child had ever used chiropractic care and 4 (2%) had used chiropractic within the past year. Twenty-seven (14.1%) of the parents had ever used chiropractic themselves. White parents with children school-age or older and who used CAM for themselves were significantly more likely to provide CAM for their child.

Patients are showing an increasing interest in the use of CAM in the treatment of acute and chronic diseases (Ernst, 2000), both in adults (Cottencin, Mullet, & Sorum, 2006; Widmer, Herren, Donges, Marian, & Busato, 2006) and in children (Fletcher &
Clarke, 2004; McCann & Newell, 2006; Shaw, Thompson, & Sharp, 2006). In adult oncology CAM is used to a significant extent (Ernst, 2000b; Ernst & Cassileth, 1998). However, few studies have been conducted on the prevalence of use of complementary and alternative medicine, and in particular chiropractic, in pediatric oncology.

The use of CAM in children ranges from 9% to 73% (Ernst, 1999; Ernst & Cassileth, 1998). Studies in Canada and the United Kingdom report prevalence of CAM use in pediatric cancer patients between 33% (Molassiotis & Cubbin, 2004) and 42% (Bold & Leis, 2001). In the United States, 46% to 84% of children with cancer use CAM (Friedman et al., 1997; Gagnon & Recklitis, 2003; Kelly et al., 2000; McCurdy, Spangler, Wofford, Chauvenet, & McLean, 2003; Neuhouser et al., 2001).

In a recent study of CAM use in general and specialty pediatric clinics 52.3% (147/281) of children used one or more types of CAM therapies in the past year (Post-White, Fitzgerald, Hageness, & Sencer, 2009). Children with epilepsy (61.9%) and cancer (59%) reported the highest use of CAM. Chiropractic care was one of the most frequently used CAM therapies, with 25.9% of the total sample of children having used this type of therapy. In oncology patients, 18.1% reported using chiropractic care. The top three reasons why children with cancer used CAM were to manage side effects, cope with the emotional effects, and feel more hopeful.

In a survey of parents of children with cancer in Germany, 35% (367/1063) stated that they had used CAM in the course of their child’s illness (Laengler, et al., 2008). The most frequent reasons for the use of CAM were “physical stabilization,” “to strengthen the immune system,” “to improve the chance of cure,” “to help cope with side-effects of the conventional medicine,” and “to feel we have done everything possible.” The reasons
for non-use were lack of information (29%), so as not to additionally burden the child (18%), too little known about interactions (15%), doctor advised against it (13%), and CAM is ineffective (8%).

An exploratory multivariate analysis showed that the following factors had a significant influence on the probability of CAM use in children with cancer: earlier experience of CAM, diagnosis with poor prognosis, and higher social status. Age at diagnosis and sex of the child were not relevant for the decision to use CAM. However, there was a higher probability of CAM use among those who were privately insured, had more education, and had higher income.

In a qualitative study, Fletcher and Clarke (2004) interviewed parents of children with cancer to determine their views on CAM. For those who used CAM, chiropractors were one of the more frequently used CAM therapies.

Only one study to date has examined the use CAM in childhood cancer survivors (Mertens, et al., 2008). The authors reported that 12.1% of survivors reported the use of chiropractic care in the previous 12 months. Females were more likely to use chiropractic than males, but other factors influencing use (i.e., diagnosis, treatment, chronic conditions) were not examined.

**Health-Related Quality of Life in Childhood Cancer Survivors**

The terms “quality of life” (QOL) and “health-related quality of life” (HRQOL) are important concepts for health care providers as well as social policy makers. The terms are multidimensional and no clear definitions have been agreed upon by those who use these phrases (Ferrans & Powers, 1992; Kimmel, 2000), and they are often used
interchangeably in the literature. The lack of a universally accepted definition and consistent use of terms has created a significant shortcoming in the literature when QOL or HRQOL studies are compared and synthesized.

Quality of life typically denotes satisfaction or happiness with one’s life (Ferrans & Powers, 1992) and can include such dimensions as life satisfaction, socioeconomic status, physical health, affect, perceived stress, friendship, family, marriage, life goals, housing and neighborhood, city and nation, self-esteem, depression, psychological defense mechanisms, and coping (Ferrans & Powers, 1985). However, since health has such a large impact on perceived quality of life, the phrase has taken on more meanings, including well-being, psychosocial adjustment, physical functioning, symptoms, and health status (Ferrans, Zerwic, Wilbur, & Larson, 2005). The term “health-related quality of life” refers to the person’s appraisal of their current health status, regarding physical and mental health (Hemmett, Holmes, Barnes, & Russell, 2004; McCabe & McKern, 2002). In health care, health-related quality of life measurement has served to legitimize the idea that the patient’s perspective has equal validity to that of the health-care provider when it comes to monitoring the effects and outcomes of disease and treatment (Leplege & Hunt, 1997).

As mentioned, the number of childhood cancer survivors is steadily growing. However, the transition from diagnosis and treatment to long-term survivorship is often marked with physical, emotional, and psychosocial concerns (Hewitt, et al., 2006), and survivors face many challenges related to their cancer history (Beckjord, et al., 2008).

The need for HRQOL research among childhood cancer survivors as an outcome measure of the cancer experience is critical because of they are at a high risk for medical
and psychosocial sequelae that can adversely affect their health (Hewitt, et al., 2003; Hudson, et al., 2003; Robison, et al., 2002). The increase in survival rates in pediatric oncology requires researchers and clinicians who provide care for these individuals to attend to the late effects that develop as a consequence of successful treatment and quality of life for these survivors (Zebrack & Zeltzer, 2003). HRQOL assessment in cancer research has become critical to fully evaluate overall treatment effectiveness by also formally including the patient’s perspective as an important objective (Efficace, et al., 2008). Major cancer societies have been supporting the use of HRQOL as a key outcome for more than two decades (American Society of Clinical Oncology, 1996). In particular, large-scale studies of longer-term survivors that examine HRQOL are important for advancing research and informing clinical practice (Ayanian & Jacobsen, 2006; Grunfeld, 2006; Hewitt, Greenfield, & Stovall, 2006).

The need for HRQOL research among survivors of childhood cancer is compounded by the estimation that most survivors will live several decades after being cured, during which they will have little or no contact with a cancer specialist or other specialist (Aziz, Oeffinger, Brooks, & Turoff, 2006; Cox, et al., 2009; Oeffinger & McCabe, 2006). As a result, evidence-based interventions to screen, treat, and promote physical and psychosocial functioning and HRQOL among childhood cancer survivors are being developed and tested (Nelson & Meeske, 2005; Prouty, Ward-Smith, & Hutto, 2006; Reckltis, O'Leary, & Diller, 2003; Sherman, Cooke, & Grant, 2005; Smith & Hare, 2004). However, in order for successful interventions to be developed and implemented research studies investigating the major determinants and factors of HRQOL for survivors is needed (Cantrell & Lupinacci, 2008).
Though research is limited, the literature on HRQOL among childhood cancer survivors, particularly survivors in the CCSS, is emerging (Cantrell, 2007). Though findings of these studies have varied, some of the most recently published studies report high perceptions of HRQOL among survivors (Boman & Bodegard, 2000; De Clercq, De Fruyt, Koot, & Benoit, 2004; Punyko, et al., 2007; Shankar, et al., 2005). Among 417 survivors of rhabdomyosarcoma enrolled in the CCSS, most were successful in attaining life goals despite an increased number of physical impairments as compared to their siblings (Punyko, et al., 2007). In a study comparing quality of life among survivors of childhood cancer and healthy controls, childhood cancer survivors reported higher levels of QOL than did healthy children (De Clercq, et al., 2004).

In a sample of 176 childhood cancer survivors between the age of 16 and 28 years, the majority of survivors experienced positive quality of life in which they rated themselves high on happiness, feeling useful and satisfied with life, and their ability to cope as a result of having had cancer (Zebrack & Chesler, 2002). Psychological well-being was influenced most strongly by physical health status and living arrangements, whereas social QOL was related to physical health status and age at which cancer was diagnosed. Conditions other than cancer that required a doctor’s care and late effects of treatment had a significant impact on quality of life scores in this sample. Reporting a condition requiring a doctor’s care sometime during the previous 10 years is significantly associated with lower overall quality of life and lower quality of life in the physical, psychological and social domains. Late effects were also associated with lower quality of life in the social dimension. In addition, a notable difference is that CNS/brain tumor survivors score significantly lower overall quality of life (standardized beta
coefficient=0.158, p50:05) and lower quality of life in the social dimension (standardized beta coefficient=0.365, p50:001) than do all other survivors combined. The lingering physical effects (i.e., fatigue, pain) of these survivors’ cancer and its treatment seemed to have a significant influence on their HRQOL.

HRQOL was evaluated in 86 childhood cancer survivors attending a long-term follow-up clinic (Meeske, Patel, Palmer, Nelson, & Parow, 2007). Survivors’ total, physical, and psychosocial functioning mean scores were not significantly different than those reported for healthy children. Scores were significantly lower (poorer HRQOL) for patients diagnosed with a brain tumor and for those patients reporting fatigue, pain, or for those with more severe late effects.

Physical performance limitation, restricted participation in life-roles, and reports of reduced scores on QOL instruments are prevalent in some bone tumor survivors, but not in others (Nagarajan, Mogil, Neglia, Robison, & Ness, 2009). In a report from the Childhood Cancer Survivor Study, survivors were asked about physical limitations and participation restrictions (Ness, Mertens, et al., 2005). After adjustment for age and sex, survivors (19.6%) were nearly twice as likely to report performance limitations when compared with siblings (11.8%) (RR, 1.8 [CI, 1.7 to 2.0]). In an age- and sex-adjusted model, compared with siblings, survivors of bone cancer were 2.9 times (CI, 2.6 to 3.3 times) as likely and survivors of brain cancer were 2.5 times (CI, 2.2 to 2.8 times) as likely to report a performance limitation. Cancer type also affected the prevalence of childhood cancer survivor’s participation restrictions. Survivors of brain cancer were most likely to report restrictions in personal care activities (10.5%) or routine activities.
(20.9%) and were most likely to report that poor health prevented them from attending school or work (20.0%).

In the same cohort, bone tumor survivors scored lower than an age and gender referenced population comparison group on the physical component summary (PCS) of the SF-36 but higher than an age and gender referenced population comparison group when asked about their current life satisfaction (Zeltzer, et al., 2008).

A recent study examined the long-term neurologic and musculoskeletal complications and their impact on health-related quality of life in 20 survivors of intraspinal tumors (Poretti, et al., 2008). Ten (50%) of subjects had neurological complications, including paraparesis and monoparesis, and of these ten, 80% reported these complications limited HRQOL. Ten (50%) reported pain, 7 (35%) reported scoliosis, 10 (50%) reported impaired fitness, and 2 (10%) reported clumsiness. All of survivors who had musculoskeletal chronic conditions reported lower HRQOL. Compared with healthy controls, the intraspinal tumor survivors rated their HRQOL as being slightly lower (patient median on the PedsQL: 79.35; control mean: 83.00).

Direct and indirect determinants of HRQOL for children with cancer include physical health, perceived level of self-esteem, coping abilities, personality characteristics, hopefulness, social support, and overall experiences during treatment (Cantrell, 2007). Skeletal toxicities in childhood cancer survivors are frequent and may contribute to chronic and significant compromise of physical function and quality of life (Kaste, 2008). Adolescents who have experienced radical amputation or limb salvage surgery for treatment of osteogenic sarcoma of the lower leg have a decreased perceived level of QOL (Postma, et al., 1992). In addition, female survivors are at a higher risk of
long-term negative physical effects from their cancer experience (Armstrong, Sklar, Hudson, & Robison, 2007; Hudson, et al., 2003) and report decreased HRQOL compared to male survivors (Barr, et al., 2003; Langeveld, et al., 2004; Shankar, et al., 2005; Wu, et al., 2007; Zebrack & Chesler, 2002; Zeltzer, et al., 1997; Zevon, Neubauer, & Green, 1990). Shankar and colleagues (2005) also reported that survivors of non-neurologic solid tumors and survivors who had been diagnosed with cancer more than six years before the study reported higher overall HRQOL scores when compared to healthy controls.

Blaauwbroek and colleagues (2007) investigated the association between chronic condition severity and HRQOL measured with the RAND-36. In a sample of 123 childhood cancer survivors, 54% had grade 1-2 chronic conditions, 39% had grade 3-4, and 70% had two or more chronic conditions. Survivors scored lower than the control group on the subscales Physical Functioning (p=0.033), Social Functioning (p=0.009), Vitality (p=0.003) and General Health (p=0.000). Survivors who had no chronic condition, or only mild chronic conditions, scored significantly better than survivors who had severe chronic conditions on the subscales Physical Functioning (p=0.023, p=0.011), Role Physical (p=0.030, p=0.044), Vitality (p=0.009), and General Health (p=0.003).

Physical Therapy and HRQOL

Structural or physiologic impairments of the body’s organ systems as a consequence of either the cancer or treatment intervention may alter normal organ system functioning of childhood cancer survivors. In turn, impaired functioning may limit the physical performance, executive function, or emotional health of the childhood cancer
survivor, and thus interfere with educational attainment, marriage opportunities, employability (social roles), and health-related quality of life (HRQOL) (American Physical Therapy Association, 2001; Nagi, 1976; World Health Organization, 2002). Therefore, PT intervention may potentially improve the HRQOL of childhood cancer survivors suffering from musculoskeletal and neurological late effects that impairs their function. However, the body of literature pertaining to the effect of PT on quality of life in cancer survivors is limited, and most work has been conducted in survivors of adult cancers. These studies suggest that physical training is primarily associated with improved physical and functional aspects of quality of life, rather than the social and emotional domains (Courneya, Friedenreich, et al., 2003; Courneya, Mackey, et al., 2003; De Backer, et al., 2008; Karvinen, Courneya, North, & Venner, 2007; van Weert, et al., 2004).

A recent study implemented a 12-week group-based multidisciplinary self-management rehabilitation program which combined physical training (PT) and cognitive-behavioral therapy (CBT) in a group of survivors of adult cancers (May, et al., 2008) to determine its effects on quality of life. This group was compared with a group of survivors who received PT only. Significant improvements (p<0.001) in global quality of life and in the other domains of quality of life (e.g., physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, and fatigue) were found in the PT group and in the PT+CBT group immediately following the intervention and at 3- and 9-months post-intervention compared to pre-intervention. These results are consistent with studies that have implemented rehabilitation programs in prostate cancer survivors (Segal et al., 2003; Segal et al., 2009).
Another study estimated self-reported HRQOL associated with two rehabilitation interventions for breast cancer survivors compared to a non-intervention group (Gordon, et al., 2005). Women either received an early home-based physiotherapy intervention (DAART, n=36) or a group-based exercise and psychosocial intervention (STRETCH, n=31). Assessments were conducted pre-, post-intervention, 6-, and 12-months post-diagnosis. Comparing pre/post-intervention measures, benefits were apparent for functional well-being, including reductions in arm morbidity and upper-body disability for participants completing the DAART intervention at one-to-two months following diagnosis. In contrast, minimal changes were noted for the STRETCH group. Overall, mean HRQOL scores improved gradually across all groups from 6- to 12-months post-diagnosis. The authors concluded that early physiotherapy after surgery for breast cancer has the potential for short-term functional, physical, and overall HRQOL benefits.

The use of PT has also been shown to improve quality of life in patients with rheumatoid arthritis (Mustur & Vujasinovic-Stupar, 2007), in patients with frozen shoulder (Ma, et al., 2006), in children and adolescents with cerebral palsy (Verschuren, et al., 2007), and in patients with cardiovascular conditions (Choo, et al., 2007; van Tol, Huijsmans, Kroon, Schothorst, & Kwakkel, 2006).

**Chiropractic and HRQOL**

Chiropractic patients report significantly worse health status on all SF-36 scales than an age- and gender-matched general population sample (Coulter et al., 2002). Though the literature is limited, studies indicate that the use of chiropractic can improve the health-related quality of life of patients. Secor and colleagues (2004) examined pain
and HRQOL in a complementary and alternative medicine clinic. Study participants (n=352) were seen in the clinic for acupuncture, chiropractic, and naturopathy. Chiropractic subjects were treated most for back pain and muscle spasms. Patients receiving chiropractic had a starting mean pain level of 4.2, which was significantly (p<0.0001) reduced by 52% to a mean value of 2.0. In addition, scores on the SF-12, which is the shorter version of the SF-36 and was used to measure HRQOL, improved as well. Specifically, those patients receiving chiropractic demonstrated significant improvements in Bodily Pain (p<0.02), General Health (p<0.001), and Vitality (p<0.005).

In a patient with chronic low pain, chiropractic was found to improve health-related quality of life (Wenban & Nielsen, 2005). This patient had low SF-36 scores before chiropractic care began, but scores approached those of the normal population on 3 subscales and exceeded normal population values on 5 subscales after 9 months of treatment. The SF-36 physical and mental composite scores improved from mean baseline scores of 23.4 and 25.3 to 43.7 and 62.8, respectively.

When examining the use of CAM therapies and its correlates to HRQOL in breast cancer survivors, Buettner and colleagues (2006) reported that of 1,928 participants, 12% used chiropractic therapy. However, users of chiropractic care also scored worse on all subscales of the SF-36 than non-users.
Gaps in Literature

As mentioned above, there is literature to support the association between certain individual and diagnosis/treatment-related factors and musculoskeletal and neurological late effects in childhood cancer survivors. In addition, there is literature supporting that these factors may also impact the health-related quality of life of survivors. No studies to date have examined PT use in childhood cancer survivors, and only one study (Mertens, et al., 2008) examined chiropractic use in the context of complementary and alternative medicine use. However, specific factors associated with use were not examined. Though there is literature to support that these services has improved HRQOL in other patient populations, the health-related quality of life in survivors who have musculoskeletal or neurological late effects and use physical therapy or chiropractic has not been described. Furthermore, the mediating role that the use of PT and/or chiropractic may play in the relationship between late effect severity and HRQOL has not been studied. Therefore, future research looking at these relationships in this high-risk population needs to be conducted.
CHAPTER 3

METHODOLOGY

This study, a secondary analysis, utilized existing data from the Childhood Cancer Survivor Study. The methods used in the study are described in this chapter and include study design, data collection instruments, procedure for collection of data, and methods of data analysis.

Design

A non-experimental, correlational design was utilized to explore relationships among the variables. Independent variables in this study included: demographic/personal factors (e.g., gender, age at follow-up, race, health insurance), diagnosis/treatment factors (e.g., cancer diagnosis, age at diagnosis, treatment type), and late effect severity (i.e., severity of musculoskeletal and neurological late effects). These variables were tested for associations with PT and chiropractic use. A second outcome of interest was HRQOL. The HRQOL of survivors with grade 3 or 4 late effects who reported using PT and/or chiropractic was compared to those survivors with the same grade late effects who did not use either service. In addition, the mediating effect of PT and chiropractic use on the relationship between late effect severity and HRQOL (i.e., physical health and mental health) was also examined.

A non-experimental, correlational design was appropriate for this study because
of the need to examine patterns of relationships among individual factors, musculoskeletal and neurological late effects, PT and chiropractic use, and HRQOL. Correlational designs are appropriate to understand the relationships among variables in the research questions (Polit & Beck, 2004).

This study was a secondary analysis of data previously collected from childhood cancer survivors who participated in the Childhood Cancer Survivor Study. The Childhood Cancer Survivor Study (CCSS) is a multi-institutional collaborative project designed to assess the long-term morbidity and mortality associated with childhood cancer and its treatment. The design for the original study and data collection procedures were described in detail in a previous publication (Robison, et al., 2009; Robison, et al., 2002) and are also discussed below.

*Childhood Cancer Survivor Study (CCSS)*

The CCSS was designed as a multicenter hospital-based retrospective cohort study with longitudinal follow-up (Leisenring, et al., 2009; Robison, et al., 2009; Robison, et al., 2002). The CCSS has been estimated to have captured approximately 40% to 45% of 5-year survivors diagnosed between 1970 and 1986 in the United States and Canada and, in doing so, has established a cohort of sufficient size and heterogeneity to overcome many of the previous limitations of studies of childhood cancer survivors (Leisenring, et al., 2009). The CCSS is an epidemiologic follow-up study that began in 1994, and was initiated to overcome many of the limitations of single-institution studies and to establish a resource for assessing late adverse effects following treatment for childhood and adolescent cancer. The study was funding by a shared resource grant
(U21-CA-55727) from the National Cancer Institute, the University of Minnesota Children’s Cancer Research Fund, and American Lebanese Syrian Associated Charities (ALSAC).

Sample and Setting

The CCSS database includes over 14,000 children diagnosed with a selected group of cancer diagnoses prior to age 21 years between 1970 and 1986 who survived at least 5 years from diagnosis. Cases were drawn from 26 participating institutions in the United States and Canada, and each institution identified participants who fulfilled the following criteria: (a) diagnosis and initial treatment of leukemia, central nervous system (CNS) malignancy, Hodgkin disease, non-Hodgkin lymphoma, neuroblastoma, soft tissue sarcoma, kidney cancer, or bone cancer; (b) diagnosis date between January 1, 1970 and December 31, 1986; (c) age less than 21 years at diagnosis; (d) alive five years from the date of diagnosis, regardless of disease or treatment status; (e) English or Spanish speaking (due to logistics of questionnaires and interviews); and (f) resident of the United States or Canada at the time of initial follow-up contact. The institutional review board at each participating center reviewed and approved the CCSS protocol, and all study participants provided informed consent (Robison, et al., 2009).

Study Procedures

The CCSS project team identified and recruited all survivors meeting eligibility criteria at 26 institutions in the United States (n=25) and Canada (n=1). Ascertainment and registration of participants occurred at each center using a comprehensive unified
protocol to achieve complete ascertainment of eligible participants. Of the 22,124 participants initially registered with the CCSS Coordinating Center, 94% (N=20,691) were confirmed to be eligible. Since the original establishment of the CCSS, the project Coordinating Center has been relocated to St. Jude Children's Research Hospital.

Study participant contact began in 1992, and after an initial letter from the treating institution, a letter from the CCSS Coordinating Center containing the baseline survey, informed consent, and a request for medical record release was sent to each eligible patient (or parent if the patient was younger than 18 years at the time of contact). Next of kin, typically parents or a spouse, was contacted for those eligible subjects who were known to have died after achieving 5-year survivorship (Robison, et al., 2002). If no response was received, a postal reminder was sent, ultimately followed by telephone call from the Coordinating Center by a trained telephone interviewer who provided the option of completing the baseline survey by telephone. Completed questionnaires received by the coordinating center were reviewed, edited, and computerized according to a structured protocol.

Medical records were abstracted to document chemotherapy, radiation therapy and surgical procedures. Data management staff from each participating institution received training for procedures in medical record abstraction according to a structured protocol. Information was abstracted regarding exposure to 49 specific chemotherapy agents and routes of administration. Additionally, cumulative dose information was abstracted for 26 of these agents/routes of administration. To assess possible errors in medical records abstraction, each institution was asked to perform an independent (i.e.,
different abstractor) re-abstraction of records of five subjects every 3 months for the first 15 months of the project.

Measures

The CCSS Baseline questionnaire, which was sent in 1995-1996, contains questions on demographics (i.e., marital status, level of education, household income, employment, and health insurance), medical care practices during the past two years, and prescription medications taken during the past two years. Medical conditions diagnosed by a doctor (plus the age at diagnosis) for conditions related to hearing, speech, vision, hormonal systems, heart and circulatory systems, respiratory system, digestive system, brain and nervous systems, mood/depression, and pain, as well as surgical procedures, cancer recurrence, development of subsequent neoplasms are also included in the baseline questionnaire. Although the specific content of the follow-up surveys has varied, each typically updates major health events in addition to collecting information on focused topics such as, health care utilization, health-related quality of life, health behaviors, medical outcomes, mental health, psychosocial outcomes, and use of complementary and alternative therapies (Robison, et al., 2009). The majority of the items in the baseline and the 2003 follow-up questionnaires came from the National Health Interview Survey and were validated in a study of childhood cancer survivors (Louie, et al., 2000).
Overall at the initial CCSS contact, 3,058 participants (15%) could not be located and were lost to follow-up, 3,205 (15%) declined participation, and 65 participants were unable to participate due to language difficulties (Leisenring, et al., 2009). Ultimately, 14,357 eligible participants completed the baseline questionnaire, representing 69% of the total eligible population. All 14,054 participants who completed the baseline questionnaire were asked to sign a separate consent form to allow access to all medical records since their cancer diagnosis. Ninety-one percent returned a signed consent. The CCSS has completed three additional follow-up surveys of this cohort. The 2003 follow-up questionnaire was sent to 11,581 participants. Of this number, 9,308 (80%) completed the survey (Leisenring, et al., 2009).

The demographic-, disease-, and treatment-related characteristics of participants, contacted non-participants, and those lost to follow-up were compared to determine the potential for bias (Mertens, et al., 2004; Robison, et al., 2002). It was determined that while differences were moderate in size (<10% increase), the study retains more female, white race, college-educated, higher-income, and older participants (Leisenring, et al., 2009).

Survivors eligible for the CCSS cohort included a higher proportion of males (55%) (Childhood Cancer Survivor Study, n.d.). Of those subjects who returned a baseline questionnaire, 87% reported their race as Caucasian, 2% Black, 5% Hispanic, 1% Asian, and 5% other. Diagnoses include leukemia (33%), lymphoma (21%), neuroblastoma (7%), CNS tumor (13%), bone tumor (8%), kidney tumor (9%), and soft tissue sarcoma (9%). Sixty-five percent of the eligible cohort was 10 years of age or
younger at the time of their initial diagnosis, and only 18% were 15-20 years of age. At time of initial contact, the study participants were an average of 23 years of age. Overall, 79% were treated with chemotherapy, 68% with radiation, and 82% had a surgical procedure. Follow-up questionnaires have been sent at intervals to continue to document medical, educational, psychosocial, and healthcare utilization outcomes.

**Strengths and Limitations of the CCSS**

The main strength of the CCSS study is that it provides access to a large, diverse, and well-characterized survivor population, and the large sample size of the CCSS enhances external validity. However, there are limitations of the database that restrict the possible scope and detail of the research.

First, the CCSS population was restricted to specific diagnoses (i.e., ALL, AML, other leukemias NOS, Astrocytomas, other CNS tumors, Hodgkin’s disease, non-Hodgkin’s lymphoma, kidney tumors, neuroblastoma, soft tissue sarcoma, Ewing’s sarcoma, osteosarcoma, and other bone tumors). Therefore, it would not be possible to examine outcomes in survivors of less common childhood malignancies. Secondly, the CCSS study relies on self-reported, questionnaire-based information, which was necessary given the large size of the cohort. Also, many of the survivors no longer return to the treatment facility where they were diagnosed and received their treatment. Therefore, access could only be obtained through mailed questionnaires. The many logistical and financial issues related to detailed clinical evaluations in a multi-institutional setting are also a limitation (Robison, et al., 2002). Third, the cohort includes a relatively small number of minority survivors, which limits the ability to adequately
investigate the potential influence of race/ethnicity on risk outcomes or adequately
describe the occurrence of late effects within a given racial or ethnic population. Finally,
the CCSS currently represents a static cohort including patients diagnosed only as
recently as 1986. This limits the utility of the cohort for studying newer treatment
approaches.

**Protection of Human Subjects**

To ensure the protection of human subjects, the research plan was submitted to
and approved by the University of Alabama at Birmingham’s Institutional Review Board
(IRB). St. Jude Children's Research Hospital’s IRB granted approval for all analyses of
the CCSS. A full IRB review was not necessary since this study was a secondary data
analysis of previously collected data and no personal health information (PHI) was
available, no new data was collected, and no contact was made with subjects to obtain
missing data.

**Subjects and Setting**

For the purposes of this study, only childhood cancer survivors who completed
both the baseline and 2003 follow-up CCSS questionnaires, who were 18 years old or
older at the 2003 follow-up, and who consented to and had a medical record abstraction
were included. The sample consisted of data from a sample of approximately 9289. The
CCSS database is housed at St. Jude Children’s Research hospital (St. Jude Children's
Research Hospital, 2008).
Instruments (Measurement)

The data that were analyzed for this study were collected using two separate instruments. These instruments were the 1995/1996 baseline and 2003 follow-up questionnaires in the CCSS (Robison et al., 2002). Copies of these instruments can be found on the St. Jude Childhood Cancer Survivor Study website at http://www.stjude.org/epidemiology/0,2081,864_5705_21764,00.html.

Physical therapy or chiropractic use in the two years prior to the 2003 follow-up was the primary outcomes of this study and was measured by question A1 from the 2003 follow-up questionnaire (http://www.stjude.org/SJFile/ccss_fu2.pdf). The question read, “During this two year period, which of the following health care providers (excluding dentists) did you see or talk to for medical care? This includes routine and sick care.” Possible responses included: none, physician (including osteopath), nurse, chiropractor, physical therapist, and other.

The secondary outcome, HRQOL, was measured with the Medical Outcome Study Short-Form 36 (SF-36) (Ware & Sherbourne, 1992), which is embedded in the 2003 Follow-up questionnaire. The measure consists of 36 items with two summary measures, physical & mental health, based on a total of eight health domains, four for physical health and four for mental health. For physical health, the four domains include physical function, physical role, bodily pain, and general health. For mental health, the four domains consist of vitality, social functioning, emotional role, and mental health. A variety of three, five, and six point scales comprise each of the 8 domains with multiple choices for each. All correlations between items and their hypothesized scales exceeded the suggested standard of 0.40 for satisfactory item-consistency.
Per domain, SF-36 raw scores will be transformed to standardized scores on a scale from 0 to 100, with a higher score reflecting a better HRQOL. The SF-36 can also be scored as two summary scales, the Physical Component Summary scale (PCS) and the Mental Component Summary scale (MCS). General population norms are available for the subscales and summary scales (McHorney, Kosinski, & Ware, 1994). The general population norm scores for the PCS and MCS are normalized and presented as t-scores with a normal population mean score set at 50 with a standard deviation of 10. Reliability estimates for physical and mental summary scores usually exceed 0.90 (Jenkinson, Coulter, & Wright, 1993; Revicki, Sorensen, & Wu, 1998; Ware, Kosinski, & Dewey, 2000). It has good construct validity based on factor analysis and good criterion validity when compared to other health rating scales (Ware, Kosinski, & Dewey, 2000).

Reulen and colleagues (2006) recommended the SF-36 for use in studies in long-term survivors of childhood cancer. Across all scales, the Cronbach's alpha coefficient of reliability was found to be higher than the suggested value of 0.70. Consistent across all cancer groups, the physical health related scale scores correlated strongly with the Physical Component Summary (PCS) scale scores and weakly with the Mental Component Summary (MCS) scale scores. Also, the mental health and role limitation-emotional scales correlated strongly with the MCS scale score and weakly with the PCS scale score. Moderate to strong correlations with both summary scores were found for the general health perception, energy/vitality, and social functioning scales.

In order to assess if there is a sound basis for using the SF-36 for measuring HRQOL, Ware and colleagues (Ware, Kosinski, & Gandek, 2000) correlated SF-36 scales with the general health scale and with a general measure of quality of life. All
correlations were significant and positive as hypothesized. Most were substantial in magnitude. All correlations between the general health scale and the other SF-36 scales were substantial, ranging from 0.43 for the role-emotional scale to a high of 0.69 for the physical functioning and role-physical scales.

**Individual Domain**

The variables under the individual domain construct of the model were individual variables and diagnosis/treatment variables. The individual variables include: age at follow-up, gender, race, household income, education at follow-up, employment status, health insurance, and physician visit in the past two years. The diagnosis/treatment variables include: cancer diagnosis, age at diagnosis, time since diagnosis, radiation treatment, chemotherapy treatment, and surgery. These variables were determined from the Baseline and the 2003 Follow-up questionnaires used in the Childhood Cancer Survivor Study (CCSS). These questionnaires were described above.

**Biological Domain**

*Musculoskeletal Late Effect Severity.* Musculoskeletal late effect severity is defined as the presence and severity of musculoskeletal late effects as reported by survivors in the baseline questionnaire. Musculoskeletal late effects include: bone, spine scoliosis; cervical spine, range of motion; extremity, lower (gait/walking); extremity, upper (function); fracture; joint, function; local complication, device/prosthesis-related; lumbar spine, range of motion; muscle weakness; muscular/skeletal, hypoplasia; osteonecrosis; osteoporosis; amputation; and soft tissue necrosis.
The musculoskeletal late effects will be operationalized as the grade of severity according to the Common Toxicity Criteria, Version 3 (CTCvs3) developed by the National Cancer Institute (National Cancer Institute, 2006). The system grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), and life-threatening or disabling (grade 4). Only musculoskeletal late effects that occurred subsequent to the cancer diagnosis or its treatment were included.

Neurological Late Effect Severity. The presence and severity of neurological late effects as reported by survivors in the baseline questionnaire and verified through medical record abstraction. Neurological late effects include: decreased fine motor coordination; seizure; tremor; neuropathy, motor; neuropathy, sensory; dizziness; involuntary movement; and ataxia (incoordination).

The neurological late effects will be operationalized as the grade of severity according to the Common Toxicity Criteria, Version 3 (CTCvs3) developed by the National Cancer Institute (National Cancer Institute, 2006). The system grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), and life-threatening or disabling (grade 4). Only neurological conditions that occurred subsequent to the cancer diagnosis or its treatment were included.

Behavioral Domain

Physical Therapy Use. Physical therapy is the provision of services in circumstances where movement and function are threatened by injury, disease or the process of aging with the goal is to develop, maintain, and restore maximum movement and functional ability throughout the lifespan (American Physical Therapy Association,
PT use is defined as any self-reported physical therapy visit in the two years prior to the 2003 follow-up questionnaire. A self-reported visit to a physical therapist was measured by question A1 from the 2003 follow-up questionnaire.

Chiropractic Use. Chiropractic care addresses disorders of the musculoskeletal system and how these aberrations may impinge upon the nervous system, subsequently affecting general health (Evans & Rupert, 2006). Chiropractic use is defined as any self-reported visit to a chiropractor in the two years prior to the 2003 follow-up questionnaire. A self-reported visit to a chiropractor was measured by question A1 from the 2003 follow-up questionnaire.

Question A1 in the 2003 follow-up questionnaire asks, “During this two year period, which of the following health care providers (excluding dentists) did you see or talk to for medical care? This includes routine and sick care.” Responses included: none, physician (including osteopath), nurse, chiropractor, physical therapist, and other-specify.

Health Outcomes Domain

Health-related quality of life. HRQOL is a personal appraisal and satisfaction with the domains of life as they affect the person’s health (McCabe & McKern, 2002). Health-related quality of life was measured by questions E1-22 and F1-14 from the 2003 follow-up questionnaire. These questions came directly from the SF-36.

The SF-36 was selected because it is one of the most often used measures to assess health status in the research literature, having been documented in approximately 4,000 publications and has demonstrated high validity and reliability in a wide variety of groups, including the intended sample (Ware, Kosinski, & Dewey, 2000). It is a generic
measure, not targeted to a specific group, and has proved to be useful for a variety purposes (Ware, Kosinski, & Dewey, 2000). In this study, HRQOL was represented by the Physical Component Summary (PCS) score and the Mental Component Summary (MCS) score. The sum of the four physical health domains comprised the PCS score, and the MCS was computed using the summary score of each of the four mental health domains.

Medical Outcomes Study (MOS) projects led to the development of the PCS and MCS measures for the SF-36 (Ware & Kosinski, 2001). These summary measures are based on the physical and mental components (factors) shown to account for about 82% of the reliable variance in scale scores. Further, factor loadings for the eight subscales in relation to these two components go hand-in-hand with their validity as evaluated using clinical criteria (McHorney, Ware, & Raczek, 1993). In addition to supporting the construct validity of the eight subscales, these results suggested that the physical and mental component scores would serve as useful summary health measures.

Data Extraction

Data collection for the CCSS was discussed previously. A CCSS Analysis Concept Proposal was submitted to Dr. Greg Armstrong and Dr. Kiri Ness in the Department of Epidemiology, Cancer Control, and Cancer Survivorship at St. Jude Children’s Research Hospital and to the members of the Chronic Disease Working Group in order to gain access to the entire CCSS database. After initial approval, it was forwarded to Publications Committee for final approval. Approval was granted September, 2008, and the concept analysis proposal was forwarded to the statistical
coordinating center for the CCSS located at the Fred Hutchinson Cancer Research Center in Seattle, Washington.

A statistician and data analyst were assigned by CCSS to create a dataset which only include those variables necessary for this secondary analysis. These variables were based on those listed in the concept analysis proposal. A code book was created and sent with the dataset.

**Statistical Analyses**

SAS version 9.1 (SAS Institute Inc., 2004) was used for all statistical analyses. The level of significance was set at alpha = .05. Descriptive statistics were calculated to summarize the demographic and diagnosis characteristics of the sample. Frequencies and percents of PT use, chiropractic use, or both were also calculated.

For the second aim, multiple variable logistic regressions models were used to evaluate the associations between late effect severity (grade ≤ 2 and grade 3 or 4) and PT use, chiropractic use, or both. Separate logistic regression models were employed to evaluate the associations between diagnosis and use of PT, chiropractic, or both, as well as the associations between treatment and use of PT, chiropractic, or both.

To evaluate the impact of use of physical therapy or chiropractic on HRQOL among those who report grade 3 or 4 musculoskeletal or neurological late effect, scores on the summary scales of the SF-36 were compared between those who report use of PT or chiropractic and those who do not use PT or chiropractic. Mean differences were evaluated in linear models. Differences in proportions of those whose SF-36 summary scores are ≤40 were compared in logistic regression models.
For the following tests, standard multiple regression statistical analyses were completed with the variables to be controlled entered first as the independent variables, followed by the variable to be tested, with the outcome variable entered as the dependent variable (See Figure 3). To determine the mediating effect of physical therapy and chiropractic use the criteria established by Baron and Kenny (1986) were followed:

1. the independent variable (musculoskeletal and neurological late effects) must affect the dependent variable (physical and mental health);

2. the independent variable must affect the mediator (PT and chiropractic use) and;

3. the mediator must affect the dependent variable while reducing the effect of the independent variable on the dependent variable.

If the conditions were met, then the effect of the independent variable (musculoskeletal and neurological chronic conditions) on the dependent variable (HRQOL) must be less than the effect of PT and chiropractic use. Perfect mediation was considered to have occurred if the independent variable had no effect when controlling for the mediator. If any of the steps did not meet the expected conditions, no further testing was warranted and testing was not completed. The following steps were undertaken to test for mediation (Baron & Kenny, 1986). For the first mediation model:

1. Physical health (1: ≤40, 2: >40) was regressed on musculoskeletal late effects (1: grade 3 or 4, 2: grade 2 or less).

2. In step two, physical therapy and chiropractic use (1: yes, 2: no) was regressed on musculoskeletal late effects.

3. In step three, physical health was regressed on PT and chiropractic use, controlling for musculoskeletal late effects.
For the second mediation model:

1. Physical health (1: \( \leq 40 \), 2: >40) was regressed on neurological late effects (1: grade 3 or 4, 2: grade 2 or less).

2. In step two, physical therapy and chiropractic use (1: yes, 2: no) was regressed on neurological late effects.

3. In step three, physical health was regressed on PT and chiropractic use, controlling for neurological late effects.

These steps were repeated using mental health as the dependent variable.

Figure 3

*Mediation Model for Physical Therapy and Chiropractic Use in the Relationship Between Musculoskeletal and Neurological Late Effects and Health-Related Quality of Life*
Limitations of Study

When interpreting the results of this study, there were some limitations that were considered. The study population reflects a subset of the entire CCSS population. Therefore, those survivors included in the current analysis may not be fully representative of the population from which they were derived. The known characteristics of participants and non-participants were compared and it was determined that they did differ with regard to some sociodemographic factors including gender, race/ethnicity, and education. The information utilized to classify the health-related quality of life, as well as the independent measures, was based upon self-reported data. The self-report nature of the instrumentation is a limitation in that the accuracy of those reports cannot be validated. This can lead to decreased reliability of the data by both overestimating and underestimating the incidence and severity of various chronic health conditions (Oeffinger, et al., 2006). Lastly, while the CCSS population represents a large and heterogeneous cohort of five year survivors, results may not generalize to all childhood cancer survivors. As a group, CCSS participants may be more informed regarding risks and health promotion because of newsletters received as part of participation in the study. Also, the majority of the sample was Caucasian, which means the results are not generalizable to minority populations.

Finally, there are limitations associated with secondary analyses, namely threats to internal and external validity. Internal validity refers to the extent to which it is possible to make an inference that the independent variable is truly causing or influencing the dependent variable and that the relationship between the two is not the spurious effect
of an extraneous variable (Polit & Beck, 2004). One threat to internal validity would be history, which refers to the occurrence of external events that take place concurrently with the independent variable that can affect the dependent variable (Polit & Beck, 2004). Because the data for this study will be obtained through secondary analysis of the CCSS data, there is a lack of control over external variables (i.e., health care provider referral, PT and chiropractic supply, knowledge of services). Therefore, it is possible that there may be other confounding variables that may affect the use of PT and chiropractic services by survivors that were not available in the data set and analyzed.

There were 20,276 eligible subjects for the Childhood Cancer Survivor Study. However, 69% (14,054) completed and returned the questionnaire. The subjects who returned the questionnaires may have been different in some important way than the people who elected not to participate. Whatever variable or variables were different in this later group may affect the outcomes of the study. Also, the incomplete follow-up may result in an overestimation of survivors with more severe musculoskeletal or neurological late effects, since healthy survivors may be less likely to be traced and to participate. On the other hand, survivors with severe musculoskeletal or neurological late effects may have declined to participate because of their poor health status, which would lead to an underestimation of survivors with more severe late effects.

External validity refers to the generalizability of the research findings to other settings or samples (Polit & Beck, 2004). One threat to the external validity of the CCSS data may be expectancy effects. Because they were aware that they were participating in a follow-up study, subjects in the CCSS may have provided answers they felt the researchers were seeking. This is called a Hawthorne effect (Polit & Beck, 2004).
Therefore, subjects may have reported more or less PT and chiropractic use or better or worse HRQOL, thus skewing results.
CHAPTER 4
RESULTS

This chapter will describe the results of the statistical analyses. A description of the final sample size is followed by demographic data and an analysis of each separate specific aim.

Sample

Childhood cancer survivors who completed the baseline and the 2003 follow-up CCSS questionnaires and were 18 year old or older at the 2003 follow-up were eligible for these analyses. For the analyses of treatment effects, those who consented to and had a medical record abstraction were included. The total sample for this study was 9289 survivors. Univariate P-values were generated by the chi-square test. These significant P-values should be interpreted with caution due to the large sample size of the study because as sample size increases, the P-value will approach zero even though the difference is of no clinical importance (du Prel, Hommel, Rohrig, & Blettner, 2009).

Characteristics of the Individual and Environment

The sample of survivors was comprised of slightly more males than females (50.7% vs 49.3%). The majority of the participants were White (89%), had at least a high school education (52%), were employed (80%), and had an annual household income
over $20,000 (74%). The majority of respondents had health insurance (87%) and had seen a physician within the past 2 years (87%). The mean age at the 2003 follow-up was 31 years (SD = 7.5), mean age at diagnosis was 8 years (SD=5.8), and mean years of cancer survival was 24 years (SD=4.5). With regards to childhood cancer diagnosis and treatment, the majority of the study participants had been diagnosed with leukemia (34%) and were treated with an alkylating and/or anthracycline agent (55%) and radiation (61%). Seventy-three percent of the sample had some form of surgery. At the 2003 follow-up the majority of the sample had late effects that were grade 2 or less (89.7%). Demographic data are displayed in Table 1.

Table 1

*Characteristics of Study Population*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survivors:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
</tr>
<tr>
<td><strong>Mean Years (SD)</strong></td>
<td></td>
</tr>
<tr>
<td>Age at Follow-up</td>
<td>31.3 (7.5)</td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td>7.7 (5.8)</td>
</tr>
<tr>
<td>Years of Survival</td>
<td>23.6 (4.5)</td>
</tr>
<tr>
<td><strong>n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4708 (50.7)</td>
</tr>
<tr>
<td>Female</td>
<td>4581 (49.3)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>8267 (89.0)</td>
</tr>
<tr>
<td>Black</td>
<td>332 (3.6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>394 (4.2)</td>
</tr>
<tr>
<td>Other</td>
<td>261 (2.8)</td>
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<tr>
<td>Not reported</td>
<td>35 (0.4)</td>
</tr>
<tr>
<td>Primary Diagnosis</td>
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</tr>
<tr>
<td>Leukemia</td>
<td>3163 (34.1)</td>
</tr>
<tr>
<td>CNS tumors</td>
<td>1175 (12.7)</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>1187 (12.8)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>701 (7.6)</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>817 (8.8)</td>
</tr>
<tr>
<td>Wiím’s tumor</td>
<td>868 (9.3)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>618 (6.7)</td>
</tr>
<tr>
<td>Bone Cancer</td>
<td>760 (8.2)</td>
</tr>
<tr>
<td>Late Effect Severity</td>
<td></td>
</tr>
<tr>
<td>≤ Grade 2</td>
<td>8333 (89.7)</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>956 (10.3)</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Amputation, lower extremity</td>
<td>360 (3.9)</td>
</tr>
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</table>
### Specific Aims

**Aim1**

The frequencies and percents of the three different outcomes, chiropractor, PT, or both, were calculated at the 2003 follow-up (Table2.1). Household annual income was
not a significant predictor for any of the three outcomes, thus was excluded from the final models. Results were reported as odds ratios with 95% confidence intervals (Table 2.2).

Slightly more survivors reported use of chiropractic (12.3%) compared to PT (9.3%), while 2.4% of survivors used both PT and chiropractic. Female gender was a significant predictor of PT (OR=1.3; 95% CI, 1.1-1.5) and chiropractic (OR=1.2; 95% CI, 1.1-1.4) use. While race was not predictive of which survivors were more likely to use PT, chiropractic, or both, Black survivors were significantly less likely to use chiropractic (OR=0.3; 95% CI, 0.2-0.6). Survivors who were older (OR=1.5; 95% CI, 1.2-1.9), had health insurance (OR=1.8; 95% CI, 1.4-2.5), and were unable to work (OR=3.3; 95% CI, 2.7-4.1) were also more likely to report use of PT. Similarly, chiropractic use was also predicted by older age (OR=1.4; 95% CI, 1.1-1.7) and having health insurance (OR=1.3; 95% CI, 1.1-1.7).

Table 2.1

<table>
<thead>
<tr>
<th></th>
<th>PT N (%)</th>
<th>Chiropractic N (%)</th>
<th>Both N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>859 (9.3)</td>
<td>1139 (12.3)</td>
<td>219 (2.4)</td>
</tr>
</tbody>
</table>
Table 2.2

Predictors for the Use of PT, Chiropractic, or Both in Survivors at the 2003 Follow-up

<table>
<thead>
<tr>
<th>Variables</th>
<th>PT</th>
<th></th>
<th>Chiropractic</th>
<th></th>
<th>Both</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.3</td>
<td>(1.1-1.5)</td>
<td>1.2</td>
<td>(1.1-1.4)</td>
<td>1.1</td>
<td>(0.8-1.4)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
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<td>1.0</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.8</td>
<td>(0.5-1.2)</td>
<td><strong>0.3</strong></td>
<td>(0.2-0.6)</td>
<td>0.6</td>
<td>(0.2-1.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.2</td>
<td>(0.8-1.6)</td>
<td>0.8</td>
<td>(0.6-1.2)</td>
<td>1.1</td>
<td>(0.5-2.2)</td>
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<tr>
<td>Other</td>
<td>0.9</td>
<td>(0.6-1.5)</td>
<td>0.9</td>
<td>(0.6-1.4)</td>
<td>1.5</td>
<td>(0.7-3.3)</td>
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<tr>
<td><strong>Age at Follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt; 25 years</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>≥ 25 years</td>
<td><strong>1.5</strong></td>
<td>(1.2-1.9)</td>
<td><strong>1.4</strong></td>
<td>(1.1-1.7)</td>
<td><strong>1.3</strong></td>
<td>(0.9-2.1)</td>
</tr>
<tr>
<td><strong>Health Insurance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
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<td>1.0</td>
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<tr>
<td>Yes</td>
<td><strong>1.8</strong></td>
<td>(1.4-2.5)</td>
<td><strong>1.3</strong></td>
<td>(1.1-1.7)</td>
<td><strong>1.2</strong></td>
<td>(0.7-2.0)</td>
</tr>
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<td><strong>Employment Status</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Working/caring for home</td>
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<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>family</td>
<td>Student</td>
<td>1.4</td>
<td>(1.0-2.0)</td>
<td>0.7</td>
<td>(0.5-1.1)</td>
<td>0.8</td>
</tr>
<tr>
<td>Unemployed/looking for</td>
<td>1.5</td>
<td>(1.0-2.1)</td>
<td>1.2</td>
<td>(0.9-1.7)</td>
<td>1.7</td>
<td>(0.9-3.1)</td>
</tr>
<tr>
<td>work</td>
<td><strong>3.3</strong></td>
<td>(2.7-4.1)</td>
<td>0.9</td>
<td>(0.6-1.1)</td>
<td>1.3</td>
<td>(0.8-2.1)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-12 years</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>High school graduate</td>
<td>1.1</td>
<td>(0.8-1.6)</td>
<td>1.0</td>
<td>(0.7-1.4)</td>
<td>0.7</td>
<td>(0.3-1.3)</td>
</tr>
<tr>
<td>College Graduate</td>
<td>1.3</td>
<td>(0.9-1.8)</td>
<td>0.9</td>
<td>(0.6-1.3)</td>
<td>0.6</td>
<td>(0.3-1.3)</td>
</tr>
</tbody>
</table>

*Bold indicates significant at p<.05

Aim 2

The association between late effect severity and PT use was evaluated among survivors using a multiple variable logistic regression model. Similarly, the association between late effect severity and chiropractic use or both PT and chiropractic use were evaluated among survivors using two multiple variable logistic regression models. Ages at diagnosis, age at follow-up, gender, race, education, household annual income, health insurance status, and physician visit within the past 2 years were initially included in the
models for all three outcomes. Education and household annual income were not significant predictors for any of the three outcomes, thus were excluded from the final models. Results were reported as odds ratios with 95% confidence intervals (Table 3).

Survivors who had grade 3 or 4 musculoskeletal or neurological late effects were 70% more likely to use physical therapy, but chronic condition was not significantly associated with chiropractic use or use of both services. Age at diagnosis was a significant predictor of chiropractic use (OR=1.3; 95% CI, 1.1-1.5), with those survivors who were diagnosed between the age of 10 and 14 years being more likely to use chiropractic. Those survivors who were 25 years old or older were also more likely to use PT (OR=1.5; 95% CI, 1.2-1.8) or chiropractic (OR=1.3; 95% CI, 1.1-1.6). Female survivors were more likely than male survivors to report having used PT (OR=1.3; 95% CI, 1.1-1.5) or chiropractic (OR=1.2; 95% CI, 1.1-1.3). Again, Black survivors were less likely to use chiropractic (OR=0.2; 95% CI, 0.1-0.4). In this model, health insurance was a significant predictor for PT use only (OR=1.5; 95% CI, 1.1-2.0). Those survivors who reported having seen a physician within the past 2 years were significantly more likely to report PT use (OR=2.7; 95% CI, 1.9-3.7), chiropractic use (OR=2.0; 95% CI, 1.6-2.5), or both (OR=6.2; 95% CI, 2.5-15.3).

Table 3

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivors</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PT</td>
<td>Chiropractic</td>
<td>Both</td>
<td></td>
</tr>
<tr>
<td>Late Effect Severity</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>≤ Grade 2</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>1.7 (1.4-2.0)</td>
<td>1.0 (0.8-1.2)</td>
<td>1.4 (0.9-2.1)</td>
<td></td>
</tr>
</tbody>
</table>
The association between diagnosis and PT use was evaluated among survivors using a logistic regression model. Similarly, the associations between diagnosis and chiropractic use or both PT and chiropractic use were evaluated among survivors in using two logistic regression models. Age at diagnosis, age at follow-up two, gender, race, education, household income, and health insurance status were initially included in the models as covariates. Age at diagnosis, education and household income were not significant predictors of any of the three outcomes, thus were not included in the final models. Results were reported as odds ratios with 95% confidence intervals (Table 4).

Childhood cancer survivors of central nervous system (CNS) tumors were 70% more likely to report use of PT but were 20% less likely to use chiropractic. Soft tissue sarcoma survivors were significantly more likely to use PT (OR=1.6; 95% CI, 1.2-2.1) or
both PT and chiropractic (OR=1.7; 95% CI, 1.1-2.8). In addition, bone cancer survivors were more likely to report use of PT (OR=1.7; 95% CI, 1.3-2.2). Female survivors who were 25 years or older and had health insurance were also more likely to use PT or chiropractic. Again, Black survivors were 80% less likely to use chiropractic (OR=0.3; 95% CI, 0.2-0.6). Health insurance was a significant predictor of PT and chiropractic use only (OR=1.7; 95% CI, 1.3-2.3).

Table 4

Association of Cancer Diagnosis and Use of PT, Chiropractic, or Both in Survivors

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivors</th>
<th>PT</th>
<th>OR</th>
<th>95% CI</th>
<th>Chiropractic</th>
<th>OR</th>
<th>95% CI</th>
<th>Both</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td></td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>CNS tumors</td>
<td></td>
<td>1.7 (1.3-2.1)</td>
<td>0.8 (0.6-0.9)</td>
<td>0.9 (0.6-1.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td></td>
<td>1.3 (1.0-1.6)</td>
<td>1.1 (0.9-1.4)</td>
<td>1.1 (0.7-1.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td></td>
<td>1.2 (0.9-1.6)</td>
<td>1.1 (0.9-1.5)</td>
<td>0.8 (0.4-1.5)</td>
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<td>Soft tissue sarcoma</td>
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<td>1.7 (1.1-2.7)</td>
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<td>Wilm’s tumor</td>
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<td>0.9 (0.5-1.6)</td>
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<tr>
<td>Age at Follow-up</td>
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<td>1.4 (1.1-1.7)</td>
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<td>Female</td>
<td></td>
<td>1.4 (1.2-1.6)</td>
<td>1.2 (1.1-1.4)</td>
<td>1.2 (0.9-1.6)</td>
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<tr>
<td>Black</td>
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<td>0.9 (0.6-1.3)</td>
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<td>Hispanic</td>
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<td>1.2 (0.4-2.2)</td>
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<td>1.5 (0.8-3.0)</td>
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<td>Health Insurance</td>
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<td></td>
<td>1.7 (1.3-2.3)</td>
<td>1.3 (1.1-1.6)</td>
<td>1.2 (0.7-1.8)</td>
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</tbody>
</table>

*A Bold indicates significant at p ≤ 0.05

Aim 4

The association between treatments and PT use was evaluated among survivors using a logistic regression model. Age at diagnosis, age at follow-up, gender, race,
education level, household income and health insurance status were included in the model as covariates. Similarly, the associations between treatments and chiropractic use or both PT and chiropractic use were evaluated among survivors in using two logistic regression models. Age at diagnosis, age at follow-up, gender, race, education level, household income and health insurance status were initially included in the model as covariates. Education and household income were not significant predictors for all three outcomes, thus were excluded from the final models. Survivors for whom medical records were abstracted were included in these analyses. Results were reported as odds ratios with 95% confidence intervals (Table 5).

Type of cancer treatment was a significant predictor of PT use only. Survivors who had an amputation of a lower extremity (OR=1.7; 95% CI, 1.2-2.5), had a joint replacement (OR=3.0; 95% CI, 1.5-6.2), had spine surgery (OR=2.1; 95% CI, 1.4-3.4), or had other surgery (OR=1.3; 95% CI, 1.1-1.6) reported use of PT. Those survivors who had cranial radiation were 30% less likely to use chiropractic. Survivors who had been diagnosed between 10 and 14 years of age were 1.3 times more likely to use chiropractic, and those who were older at follow-up were more likely to use PT (OR=1.4; 95% CI, 1.1-1.8). Female survivors were more 40% more likely than males to use PT and 20% more likely to use chiropractic. In addition, Black survivors were less likely to use chiropractic (OR=0.3; 95% CI, 0.2-0.7). Those survivors who had health insurance were significantly more likely to use PT only (OR=1.7; 95% CI, 1.3-2.3).
Table 5

Association of Cancer Treatment and Use of PT, Chiropractic, or Both in Survivors

<table>
<thead>
<tr>
<th>Variables</th>
<th>PT OR (95% CI)</th>
<th>Chiropractic OR (95% CI)</th>
<th>Both OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amputation, lower extremity</td>
<td>1.7 (1.2-2.5)</td>
<td>0.9 (0.6-1.2)</td>
<td>1.0 (0.5-2.0)</td>
</tr>
<tr>
<td>Amputation, upper extremity</td>
<td>2.3 (1.0-5.4)</td>
<td>0.9 (0.4-2.2)</td>
<td>2.0 (0.6-7.1)</td>
</tr>
<tr>
<td>Limb Sparing</td>
<td>1.1 (0.5-2.4)</td>
<td>0.6 (0.3-1.2)</td>
<td>0.7 (0.2-2.9)</td>
</tr>
<tr>
<td>Joint Replacement</td>
<td>3.0 (1.5-6.2)</td>
<td>0.7 (0.3-1.7)</td>
<td>1.7 (0.5-6.0)</td>
</tr>
<tr>
<td>Spine Surgery</td>
<td>2.1 (1.4-3.4)</td>
<td>0.8 (0.5-1.2)</td>
<td>1.0 (0.4-2.4)</td>
</tr>
<tr>
<td>Other Surgery</td>
<td>1.3 (1.1-1.6)</td>
<td>0.9 (0.7-1.0)</td>
<td>0.7 (0.5-1.1)</td>
</tr>
<tr>
<td>No Surgery</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkylating Agent and/or Anthracycline</td>
<td>1.0 (0.8-1.2)</td>
<td>1.0 (0.8-1.2)</td>
<td>0.8 (0.5-1.1)</td>
</tr>
<tr>
<td>Other Chemotherapy Agent</td>
<td>0.8 (0.6-1.1)</td>
<td>1.1 (0.9-1.4)</td>
<td>0.8 (0.5-1.3)</td>
</tr>
<tr>
<td>No Chemotherapy</td>
<td>1.0</td>
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</tr>
<tr>
<td>Radiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial Radiation</td>
<td>1.1 (0.9-1.3)</td>
<td><strong>0.7 (0.6-0.9)</strong></td>
<td>0.8 (0.5-1.1)</td>
</tr>
<tr>
<td>Other Radiation</td>
<td>1.0 (0.8-1.2)</td>
<td>0.9 (0.8-1.1)</td>
<td>0.9 (0.6-1.3)</td>
</tr>
<tr>
<td>No Radiation</td>
<td>1.0</td>
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</tr>
<tr>
<td>Age at Diagnosis</td>
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<td></td>
<td></td>
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<tr>
<td>0-4 years</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
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<tr>
<td>5-9 years</td>
<td>1.0 (0.8-1.2)</td>
<td>1.2 (1.0-1.5)</td>
<td>0.9 (0.6-1.4)</td>
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<tr>
<td>10-14 years</td>
<td>1.0 (0.8-1.2)</td>
<td><strong>1.3 (1.1-1.6)</strong></td>
<td>0.9 (0.6-1.5)</td>
</tr>
<tr>
<td>15-21 years</td>
<td>1.1 (0.8-1.4)</td>
<td><strong>1.3 (1.1-1.6)</strong></td>
<td>1.2 (0.7-1.8)</td>
</tr>
<tr>
<td>Age at Follow-up</td>
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<td></td>
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<tr>
<td>&lt; 25 years</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>≥ 25 years</td>
<td><strong>1.4 (1.1-1.8)</strong></td>
<td><strong>1.3 (1.1-1.6)</strong></td>
<td><strong>1.6 (1.1-2.5)</strong></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td><strong>1.4 (1.2-1.7)</strong></td>
<td><strong>1.2 (1.1-1.4)</strong></td>
<td>1.2 (0.9-1.6)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Black</td>
<td>1.0 (0.6-1.5)</td>
<td><strong>0.3 (0.2-0.5)</strong></td>
<td>0.7 (0.3-2.0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.2 (0.9-1.8)</td>
<td>0.8 (0.6-1.1)</td>
<td>1.2 (0.6-2.3)</td>
</tr>
<tr>
<td>Other</td>
<td>1.0 (0.6-1.6)</td>
<td>0.8 (0.5-1.3)</td>
<td>1.4 (0.6-3.0)</td>
</tr>
<tr>
<td>Health Insurance</td>
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<tr>
<td>Yes</td>
<td><strong>1.7 (1.3-2.3)</strong></td>
<td>1.3 (1.0-1.6)</td>
<td>1.2 (0.7-1.8)</td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
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</table>

*Bold indicates significant at p < .05

Aim 5

The HRQOL of childhood cancer survivors with grade 3 or 4 musculoskeletal or neurological late effects who report use of PT or chiropractic was evaluated and
compared to survivors with those same grade late effects who did not report use of those services. Scores on the summary scales of the SF-36 were compared between those survivors with grade 3 or 4 musculoskeletal and neurological late effects who report use of these services and those who do not. Mean differences were evaluated in linear models adjusted for age at diagnosis, age at follow-up, gender, and race. Differences in proportions of those whose SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores are \( \leq 40 \) were compared using logistic regression models adjusting for age at diagnosis, age at follow-up, gender, and race. Results were reported separately as both adjusted means and odds ratios (classifying those with SF-36 scale and subscales score of \( \leq 40 \) as a poor outcome) with 95% confidence intervals (Table 6.1).

Among those 7416 survivors who completed the SF-36 questionnaire, 6% of them had musculoskeletal late effects and 3% of them had neurological late effects. The mean SF-36 scores were shown in Table 6.2. The evaluations of HRQOL were focused on these survivors only. Race was excluded from the model predicting mental health on those who had neurological late effects because all survivors who had neurological late effects and an SF-36 MCS score \( \leq 40 \) were single race (white).

Survivors who had musculoskeletal late effects who reported using PT or chiropractic were 80% more likely to report poorer physical health-related quality of life than those who did not use these services. The mean score for the physical component summary for survivors with musculoskeletal late effects was 40.1, which is lower than the population norm of 50 (Ware, Kosinski, & Gandek, 2000).
Survivors who had neurological late effects who reported using PT or chiropractic were significantly more likely to report poorer physical health-related quality of life (OR=3.4, 95% CI, 1.6-6.9) than those survivors who did not use these services. The mean score for the physical component summary for survivors with neurological late effects was 34.7, which is lower than the population norm of 50 (Ware, Kosinski, & Gandek, 2000). In addition, survivors with musculoskeletal or neurological late effects who used either PT or chiropractic scored lower on all subscales of the SF-36 than those who did not use either service and lower than population norms (Ware, Kosinski, & Gandek, 2000) (Table 6.2).
Table 6.1

*Frequency and Percentage of Those Scoring 40 or Less on the Summary Scales of the SF-36 by Late Effect Severity and Physical Therapy and/or Chiropractic Use with OR and 95%CI Comparing Those Using and Not Using Services*

<table>
<thead>
<tr>
<th>Late Effect Severity</th>
<th>Physical Component Summary</th>
<th>Mental Component Summary</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Service</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT and/or Chiropractic</td>
<td>43</td>
<td>44.3</td>
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<tr>
<td>Neither</td>
<td>97</td>
<td>31.1</td>
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<tr>
<td><strong>Neurological</strong></td>
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<td></td>
</tr>
<tr>
<td>Health Service</td>
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<tr>
<td>PT and/or Chiropractic</td>
<td>23</td>
<td>52.3</td>
</tr>
<tr>
<td>Neither</td>
<td>37</td>
<td>25.0</td>
</tr>
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</table>

*Adjusted for Age at Diagnosis, Age at Follow-up, Gender, and Race

*Bold indicates significant at p≤.05*
Table 6.2

*SF-36 Scores in Survivors With Musculoskeletal or Neurological Late Effects*

<table>
<thead>
<tr>
<th>Mean SF-36 Scale Scores</th>
<th>N</th>
<th>Physical Functioning</th>
<th>Role physical</th>
<th>Bodily pain</th>
<th>General health</th>
<th>Vitality</th>
<th>Social functioning</th>
<th>Role emotional</th>
<th>Mental health</th>
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<td><strong>Population Norms</strong></td>
<td>2,474</td>
<td>84.15</td>
<td>80.96</td>
<td>75.15</td>
<td>71.95</td>
<td>60.86</td>
<td>83.28</td>
<td>81.26</td>
<td>74.74</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT and/or Chiropractic</td>
<td>97</td>
<td>40.0</td>
<td>42.6</td>
<td>44.5</td>
<td>46.2</td>
<td>40.9</td>
<td>46.1</td>
<td>43.2</td>
<td>53.3</td>
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<tr>
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<td>312</td>
<td>43.4</td>
<td>46.6</td>
<td>48.3</td>
<td>48.5</td>
<td>44.1</td>
<td>48.9</td>
<td>47.1</td>
<td>55.0</td>
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<td><strong>Neurological Late Effects</strong></td>
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<tr>
<td>PT and/or Chiropractic</td>
<td>44</td>
<td>39.2</td>
<td>38.2</td>
<td>44.4</td>
<td>42.0</td>
<td>37.8</td>
<td>41.6</td>
<td>44.9</td>
<td>52.8</td>
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<tr>
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<td>45.6</td>
<td>47.0</td>
<td>52.3</td>
<td>48.2</td>
<td>44.4</td>
<td>47.9</td>
<td>47.3</td>
<td>55.6</td>
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Aim 6

Determine whether or not PT or chiropractic use mediates the relationship between musculoskeletal and neurological late effects and HRQOL. In order to evaluate this, mediation analyses of the relationship of late effects (musculoskeletal and neurological only), health service use (PT and chiropractic) and HRQOL (PCS and MCS) were done based on those 601 survivors with musculoskeletal or neurological late effects who completed the SF-36 questionnaire. Since the mediators and outcomes were dichotomous variables, the analyses were conducted using logistic regressions using the steps outlined by Baron and Kenny (1986) and the Sobel Test. The Sobel Test (Sobel, 1982) was conducted using appropriate transformations (Herr, 2006) to assess if the relationship between musculoskeletal and neurological late effects and HRQOL significantly decreased after PT and chiropractic were added to the regression models.

The method of standardization that brings logistic regression coefficients estimated using different regression models into the same scale are based on the paper by Mackinnon and Dwyer (1993).

Table 7.1 shows a list of outcomes and initial variables for each mediation model, and test results are shown in Table 7.2. Results of the Sobel Test indicate that PT and/or chiropractic use mediated the relationship between musculoskeletal late effects and physical health. The use of these services did not mediate the relationship between neurological late effects and physical health or either condition and mental health.
### Table 7.1

**Mediation Models**

<table>
<thead>
<tr>
<th>Model</th>
<th>Y (HRQOL)</th>
<th>X (Late Effects)</th>
<th>M (Health Service)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td><strong>SF-36 Physical summary score (1: ≤40 2: &gt;40)</strong></td>
<td><strong>Musculoskeletal Late Effects (1: Yes 2: No)</strong></td>
<td><strong>PT and/or Chiropractic Use (1: Yes 2: No)</strong></td>
</tr>
<tr>
<td>Model 2</td>
<td><strong>SF-36 Physical summary score (1: ≤40 2: &gt;40)</strong></td>
<td><strong>Neurological Late Effects (1: Yes 2: No)</strong></td>
<td><strong>PT and/or Chiropractic Use (1: Yes 2: No)</strong></td>
</tr>
<tr>
<td>Model 3</td>
<td><strong>SF-36 Mental summary score (1: ≤40 2: &gt;40)</strong></td>
<td><strong>Musculoskeletal Late Effects (1: Yes 2: No)</strong></td>
<td><strong>PT and/or Chiropractic Use (1: Yes 2: No)</strong></td>
</tr>
<tr>
<td>Model 4</td>
<td><strong>SF-36 Mental summary score (1: ≤40 2: &gt;40)</strong></td>
<td><strong>Neurological Late Effects (1: Yes 2: No)</strong></td>
<td><strong>PT and/or Chiropractic Use (1: Yes 2: No)</strong></td>
</tr>
</tbody>
</table>

### Table 7.2

**Mediation Analyses**

<table>
<thead>
<tr>
<th>Model</th>
<th>Sobel test statistics</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>-2.0909</td>
<td>0.0365</td>
</tr>
<tr>
<td>Model 2</td>
<td>-1.1485</td>
<td>0.2507</td>
</tr>
<tr>
<td>Model 3</td>
<td>-1.9411</td>
<td>0.0523</td>
</tr>
<tr>
<td>Model 4</td>
<td>-1.1215</td>
<td>0.2620</td>
</tr>
</tbody>
</table>
Hypotheses

Hypothesis 1

Survivors of bone tumors or CNS malignancies who are white race, female gender, older age at follow-up, higher educational attainment, current health insurance, and higher household income will be more likely to report use of either physical therapy and/or chiropractic as compared to non-white, male survivors of other childhood cancers who were younger at the 2003 follow-up, have lower educational attainment, do not have health insurance, and have lower household income.

This hypothesis was partially supported by the data. Survivors of bone tumors were more likely to use physical therapy but not chiropractic. Survivors of CNS malignancies were more likely to use chiropractic (see Table 4). Those survivors who were female, older at follow-up, and had health insurance were more likely to use physical therapy or chiropractic, though only older age at follow-up predicted using both services. Education and income were not predictive of use of physical therapy, chiropractic, or both.

Hypothesis 2

Survivors with grade 3 or 4 musculoskeletal or neurological late effects (measured at baseline) will report greater use of PT, chiropractic, or both at the 2003 follow-up questionnaire when compared to those with grade 2 or less musculoskeletal or neurological late effects.

Again, this hypothesis was partially supported by the data. Those survivors who had grade 3 or 4 late effects were more likely to report use of physical therapy (OR=1.7,
95% CI, 1.4-2.0) compared to survivors with grade 2 or less late effects, but late effect severity was not associated with use of chiropractic or both PT and chiropractic (Table 3).

Hypothesis 3

Among childhood cancer survivors with musculoskeletal or neurological late effects, those who report use of PT and/or chiropractic will report higher mean values on the Physical Component Summary score and the Mental Component Summary score, as well as the physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health subscales of the SF-36 when compared to those not receiving PT or chiropractic.

This hypothesis was not supported by the data. Results indicated that those survivors who had grade 3 or 4 musculoskeletal late effects late effects and used either PT or chiropractic had had 1.8 times the odds of reporting lower SF-36 physical component summary scores (PCS) compared those survivors with the same conditions who did not use either service (see Table 6.1). Survivors with grade 3 or 4 neurological late effects who used PT or chiropractic had 3.4 times the odds of reporting lower SF-36 PCS scores compared to those survivors with the same conditions who did not use either service (Table 6.1).

In addition, survivors with musculoskeletal or neurological late effects who reported use of PT and/or chiropractic scored lower on all subscales of the SF-36 compared to those survivors with the same conditions who did not report use of these services (see Table 6.2). Survivors with musculoskeletal and neurological late effects
scored lower than population norms (Ware, Kosinski, & Gandek, 2000) regardless of service use (Table 6.2).

**Hypothesis 4**

PT and/or chiropractic use will mediate the relationship between musculoskeletal and neurological late effects and HRQOL in survivors who use these services.

This hypothesis was only partially supported. Results of the Sobel Test indicate that PT and/or chiropractic mediated the relationship between musculoskeletal late effects and physical health only (see Table 7.2). Use of PT and/or chiropractic did not mediate the relationship between neurological late effects and physical health, nor did they mediate the relationship between musculoskeletal and neurological late effects and mental health.

**Summary**

In this study, descriptive statistics determined that 9.3% of childhood cancer survivors reported using PT in the two years prior to the 2003 follow-up and 12.3% used chiropractic care. Logistic regression analyses determined that significant predictors of PT use in survivors include female gender, older age at follow-up, having health insurance, and being unable to work. Survivors with grade three or four late effects who had been diagnosed with CNS tumors, soft tissue sarcoma, or bone cancer and treated with a lower extremity amputation, joint replacement, spine surgery, or other surgery also were more likely to use PT.
Analyses determined that female gender, older age at follow-up, and having health insurance was associated with use of chiropractic, while Black race was predictive of being less likely to use chiropractic. Late effect severity and treatment type were not associated with chiropractic use, and survivors of CNS tumors were 20% less likely to use chiropractic. Soft tissue sarcoma survivors were more likely to use both PT and chiropractic.

Childhood cancer survivors with musculoskeletal or neurological late effects who used either PT or chiropractic reported poorer HRQOL than those survivors with the same conditions who did not use either service. The mediation effect was significant for PT and/or chiropractic use on the relationship between musculoskeletal late effects and physical health. Further discussion and implications of these findings will follow in Chapter 5.
CHAPTER 5

DISCUSSION

In this study, a secondary analysis, the use of PT and chiropractic and predictors of use were examined in a sample of childhood cancer survivors. In addition, the HRQOL of survivors with musculoskeletal or neurological late effects who use PT or chiropractic was compared to those survivors with the same late effects who did not use either service. The main findings from this cross-sectional, descriptive study indicated that more survivors reported using chiropractic than PT, and those survivors who had musculoskeletal or neurological late effects and used PT or chiropractic reported poorer HRQOL than those who did not use those services.

In this chapter, the following sections are included: discussion of findings, implications, limitations, recommendations for future research, and conclusions. The results of this study add to the small but emerging literature on musculoskeletal and neurological late effects in childhood cancer survivors and which health services are may potentially be associated with their HRQOL.

Findings

PT and chiropractic use.

The relatively low number of childhood cancer survivors (9.3%) who reported using a PT in the two years prior to the 2003 follow-up questionnaire is a somewhat surprising finding of this study. Childhood cancer survivors are at increased risk for developing musculoskeletal and neurological late effects that can potentially limit their physical
functioning. Therefore, it would have been expected that a higher percentage of survivors would report the use of PT to manage these late effects.

The findings in the present study may be attributable to the fact that most insurance plans in the United States will reimburse only for PT services prescribed by a physician (Freburger, Holmes, & Carey, 2002). Therefore, physicians play an important role in access to and appropriate use of PTs, and those providing care for childhood cancer survivors may not have the necessary knowledge of late effects to provide appropriate referral to PT. Physicians do not have the expertise to develop individualized exercise programs for childhood cancer survivors, so it is important that they make the necessary referrals to physical therapists. Furthermore, exercise programs should be supervised by physical therapists in order to decrease the risk of injury and to improve exercise adherence (Irwin, 2009).

In addition, physicians may be reluctant to refer survivors to PT because they may have the inaccurate perception that only those survivors who are capable of full community and vocational pursuits will benefit from PT services (Cheville, et al., 2007). Cheville and colleagues (2007) have noted that although rehabilitation is part of standard care for patients with pulmonary and cardiac disease, PT is rarely offered to children with cancer and childhood cancer survivors.

As previously mentioned, the care of childhood cancer survivors is increasingly being managed in nurse-run follow-up clinics. Challenges faced by these types of clinics include developing an educated and independent staff that collaborates well with other healthcare providers and knows when referral is appropriate (Buchsel & Yarbro, 2005). The Oncology Nursing Society recommends PT as an intervention that is likely to be
effective in improving chemotherapy-induced peripheral neuropathy (Visovsky, et al., 2007). The low number of childhood cancer survivors reporting PT use in this study may therefore reflect that nurses also lack the necessary knowledge to make PT referral. A recent study examined the exercise counseling and referral patterns of nurse practitioners and found that of 398 NP’s surveyed, only 27% (n=96) referred patients in need of tailored exercise counseling to a PT (Thompkins, Belza, & Brown, 2009). An earlier study found that only 5% of NP’s refer their patients to PT (Mackey, Cole, & Veeser, 1999).

Access to physical therapists may also be associated with the low number of childhood cancer survivors who reported using PT. Physical therapists practice in hospitals, clinics, and private offices that have specially equipped facilities (Bureau of Labor Statistics U.S. Department of Labor, 2009). Participants in the Childhood Cancer Survivor Study are scattered throughout the United States and Canada, and the use of PT has been shown to vary by geographic area (Carter & Rizzo, 2007). Area variations may be indicative of physical therapist supply (Carter & Rizzo, 2007); this notion is consistent with another study in which physical therapist supply was positively associated with use of PT in any setting (Freburger & Holmes, 2005). A decreased local availability of physical therapists may lead to longer waits and less flexibility in scheduling, which could potentially decrease the use of PT (Freburger & Holmes, 2005). A limitation of this study was that geographic region of residence was not examined as a predictor of PT use, and many survivors may live in areas with limited access to PT services.

The low number of survivors who use a PT may also be affected by physician referral and type of physician seen. Previous studies have shown that patients with
musculoskeletal disorders were more likely to be referred if they were seen by an orthopedic surgeon or an osteopathic surgeon than if they were seen by a primary care physician or an allopathic physician, respectively (Freburger, Holmes, & Carey, 2003). Because survivors are most likely to be followed by their oncologist, family physician, or nurse practitioner, these individuals may be more focused on the patient’s cancer history and may not recognize the need for referral to a PT.

Though chiropractic is increasingly being utilized for musculoskeletal complaints, it is still considered “complementary” or “alternative” medicine and is not part of long-term follow-up clinical guidelines for childhood cancer survivors. The finding that more survivors reported using a chiropractor (12.3%) than a PT (9.3%) is therefore surprising. Similar results were noted in a study examining musculoskeletal conditions in patients with long-standing acromegaly (Miller, Doll, David, & Wass, 2008). Of the 58 patients who participated in the study, 26 (45%) reported using PT. However, 31 (54%) reported use of complementary therapists, which included chiropractors, osteopaths, and acupuncturists. Often childhood cancer survivors must deal with late effects of treatment or may have concerns about their future health, which may motivate them to use complementary and alternative therapies such as chiropractic (Mertens, et al., 2008).

More childhood cancer survivors may use chiropractic over PT because they may have easier access to chiropractic care than PT. Chiropractic use is not dependent upon referral from a physician or nurse practitioner, and more insurance providers are now covering chiropractic services (Bureau of Labor Statistics U.S. Department of Labor, 2009). In addition, compared to physical therapy, chiropractic care may be a more cost-effective treatment option for childhood cancer survivors suffering from musculoskeletal
or neurological late effects (Cherkin, Deyo, Battie, Street, & Barlow, 1998; Korthals-de Bos, et al., 2003).

Chiropractors held about 53,000 jobs in 2006, and this number is expected to increase 14 percent between 2006 and 2016, faster than average for all occupations (Bureau of Labor Statistics U.S. Department of Labor, 2009). Fifty-two percent of chiropractors are self-employed and are located in small communities (Bureau of Labor Statistics U.S. Department of Labor, 2009). This may mean that chiropractors are more accessible to childhood cancer survivors than are physical therapists because PT’s tend to be employed in hospitals or clinics that are generally located in larger cities. However, the distribution of chiropractors is not geographically uniform (Bureau of Labor Statistics U.S. Department of Labor, 2009). Recent efforts by the National Health Service Corps and Veterans Administration to enhance chiropractor availability in underserved areas (Thaker & Pathman, 2004) may also account for the greater percentage of childhood cancer survivors using chiropractic than PT.

Schmitt (1978) proposed four major theories to explain why patients use chiropractic care. First, the inadequate socialization theory states people use chiropractors out of ignorance about modern medicine and because they have not been socialized into the legitimate health care system. This theory is not likely to apply to this population of childhood cancer survivors considering the majority have graduated from high school or college. Also, treatment and follow-up for childhood cancer is often a very lengthy process, so these survivors have likely spent a large portion of their life in the health care system.
The subculture theory proposes that individuals seek out treatment modes that are consistent with their belief systems. Belief systems of survivors were not evaluated in this study, so conclusions cannot be made regarding this theory. Future studies should examine the beliefs and attitudes survivors have with regards to the health care system. The psychological theory argues that chiropractic care has psychological appeal to “neurotics,” the “worried well,” or people who are depressed or anxious who cannot get medical physicians to legitimate their illness. The Mental Component Summary Score (MCS) scores for the sample of childhood cancer survivors in this study were comparable to population norms indicating their mental health has not suffered due to their illness. Therefore, this theory likely does not apply.

The final theory is the “strain and pain” theory. This theory posits that patients use chiropractic largely for chronic or recurrent musculoskeletal problems that the medical health care system has not dealt with adequately. Considering the largest differences between survivors and population norms occurred in the physical health subscales of the SF-36, this theory is likely most applicable. In addition, those survivors who have spent years in the health care system and taken numerous medications may feel frustration that they are still experiencing functional limitations. Therefore, they may seek care from alternative providers such as chiropractors.

*Hypothesis testing.*

In this sample, the hypothesis that childhood cancer survivors with grade 3 or higher musculoskeletal or neurological late effects would be more likely to report use of PT, chiropractic, or both at the 2003 follow-up questionnaire when compared to those with grade 2 or lower musculoskeletal or neurological late effects was partially
supported. Survivors with grade 3 or 4 late effects were 1.7 times more likely to report having used PT within the previous two years. However, there was no association with chiropractic use or the use of both services. This finding may be due in part to the fact that the Children’s Oncology Group includes referral to PT as part of their clinical guidelines for the treatment of childhood cancer survivors with musculoskeletal or neurological late effects but does not currently include chiropractic in their recommendations (Children's Oncology Group, 2008).

The second hypothesis was that survivors most likely to report use of PT and/or chiropractic will have been diagnosed with bone tumors or CNS malignancies, will be white race and female gender, have been older at follow-up, and have higher educational attainment, current health insurance, and higher household income. This hypothesis was partially supported. In this study, White, female survivors who were older at follow-up and had been diagnosed with CNS malignancies or bone cancer and had health insurance were more likely to use PT. However, educational attainment and household income were not significant predictors of PT use. Chiropractic use was also more common among White females who were older at follow-up and had health insurance. However, those survivors with CNS malignancies were 20% less likely to use chiropractic, and Black survivors were 70% less likely to use chiropractic than whites. As with PT, education and household income was not associated with chiropractic use.

These results are consistent with previous research that has shown that individuals most likely to use PT are White, females with health insurance (Carter & Rizzo, 2007; Castillo, MacKenzie, Webb, Bosse, & Avery, 2005; Freburger, Carey, & Holmes, 2005; Freburger & Holmes, 2005). It is understandable that survivors without health insurance
would be less likely to use PT. However, Carter and Rizzo (2007) reported that individuals with public insurance were also less likely to use PT services. This study did not examine the different types of insurance survivors had (i.e., public or private), and future research should investigate the relationship between type of health insurance and PT use.

In the present study, Black childhood cancer survivors were 70% less likely to use chiropractic than Whites. Similarly, Thaker and Pathman (2004) reported that chiropractic use is more common among Whites than Blacks (8% vs. 4%, p=0.001). These results are consistent with those of research in other areas of health care use by people with musculoskeletal conditions (Dunlop, Manheim, Song, & Chang, 2002; Dunlop, Song, Manheim, & Chang, 2003; Mikuls, Mudano, Pulley, & Saag, 2003). It is not known whether the disparity in use of chiropractic is attributable to minority survivors not seeking chiropractic care or not perceiving a need for care. The differences in use may be explained by social and cultural norms that relate to expectations that cause members of minority groups not to seek health care services (Haas, et al., 2004).

Childhood cancer survivors of CNS tumors, soft tissue sarcoma, or bone cancer were almost twice as likely to use PT. In addition, survivors of soft tissue sarcoma or bone cancer were also almost twice as likely to use both PT and chiropractic. Cancer treatments that were associated with use of PT included amputation of a lower extremity (OR=1.7; 95% CI, 1.2-2.5), joint replacement (OR=3.0; 95% CI, 1.5-6.2), spine surgery (OR=2.1; 95% CI, 1.4-3.4), and other surgery (OR=1.3; 95% CI, 1.1-1.6). No specific diagnoses or treatment types were associated with increased use of chiropractic. However, survivors of CNS tumors were less likely to use chiropractic (OR=0.8; 95% CI,
0.6-0.9), as were survivors who had received cranial radiation (OR=0.7; 95% CI, 0.6-0.9).

Childhood cancer survivors of CNS tumors and bone cancer are most likely to report performance limitations, restricted ability to do routine activities, restricted ability to attend work or school, and restricted ability to perform personal care (Ness, Mertens, et al., 2005). Survivors of bone tumors in childhood with multiple late effects more frequently experience severe musculoskeletal problems (Oeffinger, et al., 2006). Soft tissue sarcoma patients are likely to have experienced intensive therapy, especially local control therapy that can also have significant long-term effects with similar sequelae to that of CNS tumors. CNS tumor, bone cancer, and soft tissue sarcoma survivors are at increased risk for performance limitations due to their disease and treatment. Performance limitations can restrict the childhood cancer survivor’s ability to participate fully in daily activities necessary for self care, home management, or work (Ness, Mertens, et al., 2005). Therefore, these childhood cancer survivors are most likely to be referred to PT.

PT provides services to individuals and populations to develop, maintain and restore maximum movement and functional ability throughout the lifespan (The World Confederation for Physical Therapy, 2009). PT is a key component of clinical guidelines for patients undergoing lower limb amputations, spinal surgeries, and total joint replacements (Chen, Frame, & White, 1998; Miller, Speechley, & Deathe, 2002; North American Spine Society Task Force on Clinical Guidelines, 2000). Therefore, it is logical that childhood cancer survivors who had an amputation of a lower extremity, joint replacement, spine surgery, or other surgery were more likely to report use of PT.
Additionally, because these surgeries typically result in some level of short-term or long-term functional impairment, PT would be a recommended intervention.

The finding that survivors who were treated with radiation were less likely to report use of chiropractic may be attributed to the fact that radiation treatment is associated with an increased risk of osteoporosis (Aisenberg, et al., 1998; Muszynska-Roslan, Konstantynowicz, Panasiuk, & Krawczuk-Rybak, 2009; Vassilopoulou-Sellin, et al., 1999; Warner, Evans, Webb, Bell, & Gregory, 1999). Osteoporosis is a contraindication for chiropractic use (Haldeman, 2005). There is no clear explanation for this finding. It may be that survivors who received radiation treatment were told of their increased risk of osteoporosis and conveyed this risk during their initial consultation with a chiropractor. Alternately, their health care provider may have been familiar with the contraindications for chiropractic care and may have informed them not to use chiropractic services.

**HRQOL.** The findings of this study add to the literature on musculoskeletal and neurological health outcomes among long-term survivors of childhood cancer by evaluating HRQOL. It was hypothesized that childhood cancer survivors with musculoskeletal or neurological late effects who report use of PT and/or chiropractic would report higher mean values on the Physical Component Summary (PCS) score and the Mental Component Summary (MCS) score, as well as the physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health subscales of the SF-36 when compared to those not receiving PT or chiropractic. In this study, those survivors who had musculoskeletal or neurological late
effects and used either PT or chiropractic actually scored lower on the PCS score than those with the same conditions who did not use either service.

Survivors with musculoskeletal or neurological late effects who used PT and/or chiropractic also scored lower on all subscales of the SF-36 than those with the same conditions who did not use either PT or chiropractic. In addition, scores on these subscales were lower than population norms (Ware, Kosinski, & Gandek, 2000) for both those survivors who had musculoskeletal and neurological late effects who used PT and/or chiropractic and those with these same conditions who did not use either service. These findings indicate that these late effects negatively affect HRQOL of survivors whether or not they use PT or chiropractic.

Health-related factors, such as severity of condition, number of symptoms, and functional limitations, are associated with receiving physical therapy services (Carter & Rizzo, 2007). Therefore, the findings of this analysis may reflect the fact that those survivors with more severe late effects are the most likely to use either PT or chiropractic and, in turn, be more likely to report poorer HRQOL compared to survivors with less severe late effects. Studies have shown that significant predictors of PT use include the presence of more than one musculoskeletal condition (OR=2.10, 95% CI=1.84-2.39), at least some difficulty with physical function (OR=1.52, 95% CI=1.31-1.76), and having more than 7 ICD-9 codes (OR=1.33, 95% CI=1.11-1.49) (Carter & Rizzo, 2007). In addition, individuals who reported their health as fair or poor were more likely to report use of chiropractic compared to those who report their health as good, very good, or excellent (Thaker & Pathman, 2004). Coulter and colleagues (2002) reported that chiropractic patients scored significantly lower on all scales of the SF-36 compared to
population norms. The largest differences were seen on the physical health, role limitations due to physical problems, and pain scales, indicating that persons who seek chiropractic care are substantially physically impaired. These findings may indicate that those patients who perceive their health to be poor and have not found improvement from conventional treatments seek alternative therapy in an effort to improve their health.

In this study, significant predictors of PT included female gender, older age at follow-up, a diagnosis of CNS tumor, bone cancer or soft tissue sarcoma, having had surgery, and being unable to work. Similarly, female gender, older age at follow-up, and having been diagnosed with bone cancer predicted chiropractic use. Childhood cancer survivors of soft tissue sarcoma were also more likely to report using both PT and chiropractic. A recent systematic review of quality of life in childhood cancer survivors found that these same variables were associated with decreased quality of life in childhood cancer survivors (McDougall & Tsonis, 2009). Therefore, those survivors most likely to use PT or chiropractic are also most likely to report poorer HRQOL.

Secondly, some survivors with musculoskeletal and neurological late effects might have learned to live with their impairments and do not consider them as severe as others do. Because of this, they may not seek services such as PT or chiropractic, and they may be more likely to report improved HRQOL. Thus, the findings of this study may only apply to survivors with musculoskeletal and neurological late effects who seek specialty care and may not apply to survivors with less disabling late effects.

In addition to scoring lower than survivors who did not use either PT or chiropractic, survivors with either musculoskeletal or neurological late effects who reported using a PT or chiropractor scored considerably below population norms on the
PCS scale of the SF-36, a composite measure reflecting performance on the physical functioning, role-physical, bodily pain, and general health subscales. Importantly, both survivors with musculoskeletal or neurological late effects who used PT or chiropractic and survivors with those same conditions who did not use either service scored at or above the population norm on the MCS subscale. Thus, late effect severity and PT or chiropractic use is not predictive of poorer emotional health. Therefore, it may be that although survivors may suffer from physical limitation due to late effects, the main effect is a profound impact on survivors’ physical well-being and not on their emotional well-being. These findings may be important to primary health care providers who are most likely to have regular contact with this population and may be most able to screen for mental and physical health problems during routine care visits.

PCS Scores for survivors with neurological late effects who used PT or chiropractic were lower than survivors with musculoskeletal late effects who used either service. The two groups’ MCS Scores were similar. These findings were similar to other studies of survivors in which participants with a major medical condition were more likely than those without to report poor HRQOL across most domains, with the exception of mental health subscale and mental component summary scale (Zeltzer, et al., 2008).

Similar results have been seen in other populations affected by musculoskeletal conditions as well. In a study of hemophiliacs suffering from musculoskeletal complications scores for all subscales of the SF-36, except for role-emotional and mental health, were significantly lower than population norms (Aznar, Magallon, Querol, Gorina, & Tusell, 2000). Similarly when HRQOL was evaluated in patients with ankle osteoarthritis who suffered from other musculoskeletal comorbidities, the mean MCS
score for these patients (47 points) was slightly lower than that for the controls (P=0.018), and the mean PCS score (32 points) was substantially worse than those in the control group (p<0.0001). In addition, the number of musculoskeletal comorbidities significantly affected the PCS score (p=0.0002).

In a study of musculoskeletal conditions in patients with acromegaly, use of health services such as PT and chiropractic was evaluated, as was HRQOL (Miller, et al., 2008). In this group 45% reported using PT and 54% used complementary therapists, which included chiropractors. However, participants still reported significantly lower scores on all subscales of the SF-36 except the mental health and role-emotional subscales when compared to the general population norms.

Several conclusions regarding the interpretation of the results in the present study can be made. First, it is possible that the construct of physical health as measured in the SF-36 may not be a comprehensive conceptualization of the state of health of childhood cancer survivors with musculoskeletal and neurological late effects because it lacks information about other factors that often influence HRQOL such as current or prior medical conditions, medication use, health behaviors, and health care utilization. Second, it is also likely that the survivors in this sample were in poorer physical health compared to the general U.S. population.

Limitations

Although strengths of this study include the large sample size, several limitations need to be considered when interpreting the findings. First, incomplete participation in the CCSS by eligible patients may have biased our results if survivors with poorer HRQOL were less (or more) likely to join the CCSS cohort and to continue to contribute
information to the study. Although the response rate for the HRQOL questionnaire was good among those survivors enrolled in the CCSS (75.4%), non-respondents tended to be of lower socioeconomic status than participants and were somewhat more likely to have reported a major medical condition. These differences, not uncommon in health outcome studies, suggest caution be exercised when generalizing findings to low social and economic strata. Finally, all members of this cohort were treated in the period between 1970 and 1986 so caution must be taken in generalizing these results to patients treated on more contemporary protocols. Changes in the intensity of therapy may result in different HRQOL outcomes. Contemporary protocols often use lower doses of chemotherapy and radiation, and there have been improvements in the techniques and equipment used to deliver radiotherapy. Similarly, there have been improvements in surgical techniques. Thus, patients treated on more recent protocols warrant separate investigation.

The cross-sectional design of this study is also a limitation of this study. Because this was a cross-sectional design, conclusions about the direction of the relationships between musculoskeletal and neurological late effects, PT and chiropractic use, and HRQOL cannot be clearly established. A longitudinal design would allow greater understanding of whether improvements in baseline HRQOL are achieved after PT and chiropractic use. In addition, longitudinal designs could also answer questions about childhood cancer survivor factors that change over time such as severity of late effects, comorbidity of diseases associated with aging, behavioral problems, and functional decline and their effect on use of PT and chiropractic and HRQOL.

Another limitation is that number of visits to a PT or chiropractor could not be
confirmed and the content of those visits could not be characterized. Longitudinal design would allow for investigation of how number of visits and content of the visits to a PT or chiropractic affect HRQOL. In addition, this analysis did not allow for examination of what type of health provider (i.e., primary care physician, oncologist, nurse) made the referral to PT or chiropractic care or if it was self-referral. Gaining a better understanding of which providers are or are not making PT or chiropractic referrals is the first step in developing interventions that will ensure childhood cancer survivors are getting the appropriate services.

The study sample reflects a subset of the overall CCSS population, that is, those who responded to the baseline and 2003 follow-up questionnaires; therefore, survivors included in the current analysis may not be fully representative of the population from which they were derived. The information utilized to classify the independent measures, PT and chiropractic use, and HRQOL was based upon self-reported data. Lastly, while the CCSS population represents a large and heterogeneous cohort of five year survivors, results may not be generalizable to all childhood cancer survivors. As a group, CCSS participants may be more informed regarding risks and health promotion because of newsletters received as part of participation in the study.

Conclusions

The findings of the present study indicate that a higher percentage of survivors of childhood cancer who experience musculoskeletal or neurological late effects are more likely to use services from a chiropractor compared to a PT. Those survivors with more severe late effects (grade 3 or 4) were more likely to use a PT compared to those with less severe late effects (grade 2 or less), and severity was not associated with use of
chiropractic or both PT and chiropractic. In addition, those survivors with grade 3 or 4 musculoskeletal or neurological late effects who use PT and/or chiropractor report poorer HRQOL compared to those survivors with the same conditions who do not use these services, which may indicate that survivors’ perception of their health status influences their use of PT and/or chiropractic. Survivors' self-reported Mental Component Summary scores did not differ substantively from those of population norms, which is an encouraging finding that may reflect the resilience of these long-term childhood cancer survivors and their families.

**Implications**

Incidence and survival rates for childhood cancer are continuing to increase. Therefore, the population of childhood cancer survivors within the general population will continue to grow. These survivors will be at risk for developing late effects, such as musculoskeletal and neurological late effects. Health care providers need to be aware of the late effects experienced by childhood cancer survivors and knowledgeable of effective interventions and treatments for this vulnerable group.

Cancer survivors have considerable rehabilitation needs after treatment is finished (Mikkelsen, Sondergaard, Sokolowski, Jensen, & Olesen, 2009). Survivors of adult cancer have expressed feeling ‘left in limbo’ and not knowing where to seek help for their rehabilitation needs after discharge from the hospital (Kendall et al., 2006; Mikkelsen, Sondergaard, Jensen, & Olesen, 2008). Findings of this study indicate that childhood cancer survivors affected by musculoskeletal and neurological late effects may not be obtaining information about or getting appropriate referral to PT. Therefore, health
care providers may want to develop interventions or programs that specifically target this vulnerable population.

Mikkelson and colleagues (2009) reported that survivors of adult cancers wanted an ‘anchorperson’ assigned to them during their rehabilitation, and half would prefer this person be a nurse. Nurses involved in the follow-up of childhood cancer survivors need to not only be cognizant of the chronic conditions survivors may be experiencing, but also try to understand survivors’ need and desire for rehabilitation. Nursing represents the largest segment of the nation’s health care workforce and has a significant role in the front lines of cancer care (Ferrell, Virani, Smith, & Juarez, 2003; McCorkle, Frank-Stromborg, & Pasacreta, 1998); therefore, nurses may be the key health care provider for making PT referrals.

An ideal system of survivorship care would provide a range of direct services to survivors to identify, prevent, treat, and ameliorate late effects; bridge the realms of primary and specialty health care with education and outreach; coordinate medical care with educational and occupational services; and conduct research to better understand late effects and their prevention (Hewitt, et al., 2003). With only 9.3% of childhood cancer survivors reporting use of PT and 12.3% reporting use of chiropractic care, the health care system may be falling short of providing the ideal system of services. Nurses are well-suited to recommend these services given the emphasis in nursing education and training on patient assessment, symptom management, psychosocial care, and care planning (Hewitt, et al., 2006).

In addition to providing information regarding the factors associated with PT and chiropractic use in childhood cancer survivors, this study also adds to the literature
pertaining to HRQOL. Health care providers often rely on objective, physiologic measure of health such as blood pressure and heart rate. However, these data may not correlate with the functional capacity and well-being of the individual (Guyatt, Feeny, & Patrick, 1993). Childhood cancer survivors with the same or similar conditions may not respond to their situations in the same way.

Understanding the associations between musculoskeletal and neurological late effects in childhood cancer survivors and HRQOL is not only important for members of the rehabilitation community but for the entire nursing community as well. Irreversible deficits in these two systems may not be amenable to medical treatment. However, performance limitations can be remediated or eliminated with compensatory and adaptive strategies provided by rehabilitation and/or complementary health professionals, such as PT’s and chiropractors.

Studies show that nurse practitioner (NP) referral to CAM therapies ranges from 38% to 83% (Hayes & Alexander, 2000; Kayser, 1996; Sapp, 1997; Sohn & Loveland Cook, 2002), and that 47% to 74% of referrals were to a chiropractor (Hayes & Alexander, 2000; Sohn & Loveland Cook, 2002). A holistic perspective of health has traditionally been incorporated in nursing curricula with many nursing schools offering courses in alternative/complementary therapies (Dutta, et al., 2003). Nurses are in regular contact with patients and the public more frequently than medical doctor and often assist in making decisions about the type of care patients will receive. Therefore, it is important for nurses to be educated about complementary therapies, such as chiropractic, so that they can better inform the patients they encounter in practice. A recent survey of 1,000 nurses found that chiropractic ranked first in perceived effectiveness and was one of only
five therapies that more than half of the respondents believed to be effective (Brolinson, Price, Ditmyer, & Reis, 2001). Fifty-one percent of the nurses surveyed felt there was a “preponderance of evidence” or “conclusive evidence” supporting the effectiveness of chiropractic care. Chiropractic care ranked second in terms of perceived safety with 58% of nurses believing that chiropractic is “definitely” or “probably” safe. Also, nearly one-quarter (23%) of the nurses said they “periodically” or “regularly” recommend chiropractic care to their patients.

Future Research

As the result of this study, several areas for further research have been identified. Identification of survivors at risk for late effects and interventions to reduce risk and improve health outcomes should remain the focus of future research. A significant proportion of childhood cancer survivors develop musculoskeletal or neurological late effects that result in physical limitations that possibly increase their risk for falls. The present study reveals that few of these survivors (9%) are using PT services, thereby further increasing their risk for falls. Future research needs to examine the incidence of injuries in this population, the risk factors for injury, and potential prevention strategies.

Though this study revealed that only 9% of childhood cancer survivors report use of PT in the two years prior to the 2003 follow-up survey, the reasons that survivors use or do not use PT were not examined. Reasons for underuse may include the failure of health care providers to identify functional impairments, lack of appropriate referral for rehabilitation, lack of awareness of rehabilitation services, and lack of knowledge among family members (Kaplan, 2006). Which of these barriers, or what other barriers, exist needs to be clarified in order to effectively develop interventions and provide necessary

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services. In addition, research on the nurse’s role in access to or use of PT and chiropractic among childhood cancer survivors is needed.

Previous studies have demonstrated that use of PT and chiropractic is affected by geographic region (Carter & Rizzo, 2007; Freburger, et al., 2005; Freburger & Holmes, 2005; Thaker & Pathman, 2004). In this study, geographic location of the survivors was not evaluated, nor was whether they resided in a rural or urban setting. Future research should consider these variables when assessing the use of PT or chiropractic in this population. In addition, physical therapist supply is also positively associated with use of PT (Freburger & Holmes, 2005; Freburger, et al., 2003), and this could be affected by geographic location.

This study shed some light on the association between late effect severity, diagnosis, treatment and use of PT and/or chiropractic. In light of the fact that results of this study indicate that soft tissue sarcoma and bone cancer survivors are almost twice as likely to use both PT and chiropractic, future research needs to focus on specific complaints that are associated with the use of these services. Although survivors apparently value chiropractic care, they may not tell their health care provider when they seek care from an alternative health-care provider, perhaps out of concern that their provider would not approve (Eisenberg, et al., 1998; Rao, et al., 1999). In addition, survivors who are using both PT and chiropractic may not be disclosing use of chiropractic to their PT. It would be important to elicit information regarding whether or not survivors are disclosing of the use of chiropractic to their health care providers, and if they feel comfortable doing so.
Results of this study indicated that survivors who are Black, were diagnosed with CNS tumors, or who received cranial radiation were significantly less likely to use chiropractic, and there is no clear explanation for these findings. Future research should examine these subgroups of survivors to gain a better understanding of what factors facilitate or inhibit use of certain interventions such as chiropractic care. If future research were to show that use of chiropractic improved the HRQOL of childhood cancer survivors, a better understanding of these factors would be necessary in order to effectively intervene.

Focused quantitative studies using homogeneous samples should be conducted to provide insight into specific questions pertaining to PT and chiropractic use for certain subgroups of survivors (e.g., what factors are related to PT or chiropractic use in survivors with certain types of cancers or treatments?). Finally, biobehavioral studies need to be conducted that evaluate biological indicators of performance, whether or not these improve with PT or chiropractic use, and how these biological indicators correlate with HRQOL.
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APPENDIX A

IRB
DATE: 11/2/05

MEMORANDUM

TO: Michele Montgomery
Principal Investigator

FROM: Shanta Moore, CIP
Director, IRB

RE: Request for Determination—Exempt Research
IRB Protocol # N001172085 - Physical Therapy and Chiropractic Care in Adult Survivors of Childhood Cancer: Impact on Health-Related Quality of Life

The Office of the IRB has received the above referenced exemption application. The application has been reviewed according to the IRB Policies and Procedures and it has been determined that your project qualifies as Non Human Subjects Research. Should your research change you will need to resubmit to the IRB for further review and determination.

Sincerely,

Shanta Moore, CIP
Director, IRB