

CCSS Analysis Concept Proposal
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1. Title: Physical Therapy and Chiropractic Use in Adult Survivors of Childhood Cancer: Impact on Health-Related Quality of Life

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3. Background and rationale:

Due to improved treatment modalities, the overall 5-year survival rate for children diagnosed with cancer is now almost 80% [1]. These improvements in survival have not come without a cost, however. Treatment with chemotherapy, radiation, and/or surgery can have detrimental effects to developing organ systems. Childhood cancer survivors are at increased risk for musculoskeletal [2-5], neurological [4, 6-8], and cardiovascular late effects [4, 9-11]. Some late effects of therapy are identified early in follow-up and resolve before they become chronic conditions. However, others may persist, become chronic problems, and influence the progression of other diseases associated with aging [4].

Because the population of children who are diagnosed with cancer is increasing in number and progressing in age, medical late-effects that interfere with optimal physical function are particularly important. Reduced mobility and inability to perform basic and or complex activities necessary for daily life have the potential to interfere with the ability of an individual to live independently and fully participate in family and societal roles. In turn, poor performance and the inability to participate may impact the cancer survivor's perception of their own well-being and eventually result in a reduction in health-related quality of life (HRQOL). [12-14] Musculoskeletal conditions are common among children with cancer, both during and after therapy, and include impaired bone maturation and osteonecrosis [2, 5, 15, 16], decreased bone mineral density [17-21], decreased peripheral muscle strength and ankle dorsiflexion [3], hypoextensibility of calf musculature [22], muscle atrophy [6], and pain [23, 24]. Neurological impairments are also possible and can be very debilitating [4]. Some long-term childhood cancer survivors have permanent neurological deficits such as motor impairment [6], coordination and motor control problems [8], and fine motor problems [7]. Cardiac abnormalities may also interfere with physical function among childhood cancer survivors. Those with a history of exposure to certain chemotherapeutic agents (i.e., anthracyclines) or thoracic radiotherapy are at an increased risk for late onset cardiac toxicity [4]. Chemotherapy related cardiomyopathy [25, 26] or vessel disease [27], and radiation related valvular disease [28], pericardial thickening, and ischemic heart disease have been observed [4].

Physical therapists (PTs) provide rehabilitative services to individuals in circumstances where movement and function are impaired. Services are appropriate for functional loss related to injury, disease, or the aging process. Often, the goals of Physical Therapy (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, neurological, and cardiovascular systems [29-32]. There is little documentation that describes PT utilization among childhood cancer survivors. One study indicates that 13% of survivors report using the services of a physical therapist, occupational therapist, or other therapist in the past year [4]. It is likely that PT services are used more frequently among survivors reporting who have one or more functional limitation.

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 model. It is often characterized as one category of “complementary and alternative medicine” [33]. Chiropractors address disorders of the musculoskeletal system, with a particular emphasis on spinal health. Intervention is designed to correct spinal alignment and to relieve nervous system impingements [34]. Surveys indicate that patients frequently utilize chiropractors for the treatment of musculoskeletal complaints. In a recent report from the Childhood Cancer Survivor Study, 12.1% of survivors reported seeing a chiropractor compared to 14% of their siblings [35]. The specific factors that predicted chiropractic use were not examined in their global report.

Both physical therapy and chiropractic improve musculoskeletal complications in the healthy population [36-41], and in survivors of adult cancers [42-44]. These interventions may have the potential to ameliorate some of the physical performance limitations experienced by childhood cancer survivors, and subsequently, may also improve HRQOL.

It is estimated that by 2010 one in every 250 to 400 adults between the ages of 21 and 44 will be a survivor of a childhood or an adolescent cancer [45]. 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 physical performance limitations becomes more important. Understanding the associations between chronic late effects, physical therapy and/or chiropractic utilization, and health-related quality of life is important for members of the medical community who may be in the position to recommend such services. Irreversible organ system deficits as the result of childhood cancer and its treatment may not be amenable to medical intervention; however, physical performance limitations can be remediated or ameliorated with compensatory and adaptive strategies provided by physical therapists and chiropractors [46], thus improving health-related quality of life.

4. Specific Aims/Objectives/Research hypotheses:

The purpose of the proposed manuscript is to describe utilization patterns of physical therapy and chiropractic care in the CCSS cohort at the 2003 follow-up questionnaire. We also propose to describe the diagnosis, treatment, demographic and chronic disease characteristics of those who are receiving PT or chiropractic. Finally, we propose to evaluate the impact of PT or chiropractic on HRQOL among individuals with musculoskeletal, neurological, and cardiovascular chronic conditions.

| The specific aims of this study are as follows:

- (1) Determine the frequency of utilization of physical therapy and chiropractic care in a sample of childhood cancer survivors and compare utilization rates between survivors and siblings.
- (2) Describe the relationship between chronic disease status and physical therapy and/or chiropractic utilization.
- (3) Describe the relationship between demographic/personal and diagnosis/treatment-related variables and chronic disease status and physical therapy and/or chiropractic utilization.
- (4) Determine whether or not individuals with chronic musculoskeletal, neurological chronic or cardiovascular conditions who report physical therapy and/or chiropractic use report better health related quality of life than those with musculoskeletal, neurological or cardiovascular chronic conditions who do not report physical therapy or chiropractic use in the two years prior to the 2003 follow-up survey.

Hypothesis #1: Adult survivors of childhood cancer will report an increased frequency of physical therapy and chiropractic services at the 2003 follow-up questionnaire when compared to siblings.

Hypothesis #2: Those with any musculoskeletal, neurological, or cardiovascular chronic condition (measured at baseline) will report increased use of PT, chiropractic, or both at the 2003 follow-up questionnaire when compared to those with no musculoskeletal, neurological, or cardiovascular condition.

Hypothesis #3: Demographic, diagnosis/treatment-related, and personal variables associated with the highest utilization of either physical therapy and/or chiropractic will include white race, female gender, survivors of bone tumors or CNS malignancies, older age at diagnosis, higher educational attainment, current health insurance, and higher household income.

Hypothesis #4: Among individuals with musculoskeletal, neurological, or cardiovascular chronic conditions, those receiving physical therapy and/or chiropractic will report higher mean values on the physical component summary and the mental component summary of the SF-36 when compared to those not receiving PT or chiropractic.

5. Analysis Framework:

Sample

Survivor and sibling participants who completed the baseline and the second follow-up CCSS questionnaires are eligible for these analyses. For the analyses of treatment effects, those who consented to and had a medical record abstraction will be included.

Outcome of Interest: The primary outcome of interest for these analyses is utilization of physical therapy and/or chiropractic (questions A1 from the second follow-up2 questionnaire) and health-related quality of life (questions E1-22 and F1-14 from the follow-up2 questionnaire).

Independent (Exploratory) Variables

A. Diagnosis and treatment variables

1. Cancer Diagnosis and diagnosis group (8 category and detailed diagnosis variable from the case status database).

2. Age at Diagnosis (date of diagnosis and date of birth from Baseline A)
3. Years of Survival (date of diagnosis and date at questionnaire completion from Follow-up 2 Main)
4. Radiation – radiation, cranial; radiation, neck; radiation, chest; radiation, abdomen; radiation, pelvis; radiation, lower extremity; radiation, upper extremity; no radiation (Medical Records Abstraction Form).
5. Chemotherapy – alkylating agent, anthracycline, both alkylating agent and anthracycline, other chemotherapy agent, no chemotherapy (Medical Records Abstraction Form, Chemotherapy Section II).
6. Surgery – amputation, lower extremity; amputation, upper extremity; limb sparing, lower extremity; limb sparing, upper extremity; scoliosis surgery; other surgery of the spinal cord or spine; joint replacement; other surgery; no surgery (Medical Records Abstraction Form, Surgical Procedures Section).
7. Musculoskeletal^a, neurological^b, or cardiovascular^c chronic disease at baseline (severity determined using the scoring rubric used by Oeffinger, et al [47] based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3 and the scoring system developed by the National Cancer Institute [48]).

B. Demographic and personal factors

1. Age at second follow-up (completion date of second follow-up and date of birth)
- ~~1.~~2. Gender (Question A2 – baseline)
- ~~2.~~3. Race/ethnicity (Five race categories used in methodology manuscript)
4. Household income at follow-up 2003 (S1)
5. Education at follow-up 2003 (1)
6. Employment status at second follow-up (Question 4-6)
7. Physician visit within past two years at follow-up 2003 (A1)
- ~~3.~~8. Health insurance at second follow-up (M1)

Analysis Plan

The analysis plan for each specific aim is as follows:

1. The frequencies and percents of the three different outcomes, chiropractor, PT, or both, will be calculated at follow-up 2 and compared between siblings and survivors, adjusting for education, employment status, and household annual income using generalized estimating equations. Results will be reported as odds ratios with 95% confidence intervals (Table 2).
2. The association between chronic disease status and physical therapist visits will be evaluated among survivors in a multiple variable logistic regression model. Similarly, the association between chronic disease status and chiropractic visits will be evaluated among survivors in a multiple variable logistic regression model. We will consider age at diagnosis, age at follow-up, gender, race, education, household annual income, health insurance status, and physician visit within the past 2 years. Independent variables that contribute to the fit of the model or alter the association between chronic disease status and PT or chiropractic visit will be retained. Results will be reported as odds ratios with 95% confidence intervals (Table 3).

3. The association between diagnosis and physical therapist visits will be evaluated among survivors in a logistic regression model. We will adjust for years of survival, education, household annual income, and health insurance status. Similarly, the association between diagnosis and chiropractic visits will be evaluated among survivors in a logistic regression model. Again, we will adjust for years of survival, education, household annual income, and health insurance status. Results will be reported as odds ratios with 95% confidence intervals (Table 4).
4. The association between treatment and physical therapist visits will be evaluated among survivors in a logistic regression model. We will adjust for years of survival, education, household annual income, and health insurance status. Similarly, the association between treatment and chiropractic visits will be evaluated among survivors in a logistic regression model. Again, we will adjust for years of survival, education, household annual income, and health insurance status. Results will be reported as odds ratios with 95% confidence intervals (Table 5).
5. To evaluate the impact of the use of PT or chiropractic on HRQOL among those who report a particular chronic condition, we will compare scores on the summary scales of the SF-36 between those who report receiving services and those who do not. Mean differences will be evaluated in linear models adjusted for age at diagnosis, age at follow-up, gender, and race. Differences in proportions of those whose SF-36 summary scores are <40 will be compared in logistic regression models adjusting for age at diagnosis, age at follow-up, gender, and race. Results will be reported separately as both mean differences and odds ratios (classifying those with SF-36 scale and subscales score of < 40 as a poor outcome) with 95% confidence intervals (Tables 6).

If the prevalence of physical therapy, chiropractic, or both is >10%, we will use a generalized linear model with a binomial distribution and a log link and present results as a risk ratio with 95% confidence intervals.

6. Special consideration:

This analysis will be the focus of my dissertation for the doctoral program in the School of Nursing at the University of Alabama at Birmingham. I am required to do my own analysis for my dissertation, and I work at St. Jude. Therefore, it is requested that Dr. Kiri Ness be allowed to assist with the statistical analysis. All code and output will be sent to FHCRC for review and approval.

^aMusculoskeletal chronic disease conditions: Amputation of a digit; Amputation, not specified; Amputation of hand (part or whole); Amputation foot (part or whole); Amputation of arm above elbow; Amputation of upper arm; Amputation of arm at shoulder, disarticulation; Forequarter amputation, shoulder; Amputation of arm; Amputation below knee; Amputation, above knee; Removal of ball & socket of femur; Hip disarticulation; Amputation of leg; Hemipelvectomy, modified; Reattachment of lower leg; Major joint replacement

^bNeurological chronic disease conditions: Neurological Seizure disorder, not on medication; Problems with balance/vertigo; Disturbance in coordination; Tremors; Weakness in legs, mild limitation; Weakness in arms, mild limitations; Facial nerve palsy; Decreased sense of touch or feeling in hands, fingers, arms, or legs/prolonged pain or abnormal sensation in arms, legs, or back; Other disturbance of skin sensation; Phantom limb pain; Other conditions of brain; Other nervous system disorders; Seizure disorder, on medication; Weakness in legs, moderate limitation; Monoplegia, unspecified; Developmental coordination disorder; Obstructive hydrocephalus; Other disorders of central nervous system; Facial/cranial nerve paralysis; Paralysis of vocal cords; Neurogenic bowel; Cognitive deficit, severe; Intracranial abscess; Symptomatic torsion dystonia; Monoplegia of lower limb; Diplegia of upper limbs; Hemiplegia; Paraplegia; Quadriplegia; Other specified paralytic syndromes; Paralysis, unspecified; Guillain-Barre syndrome; Neurological; Endocrine Hypothyroidism, not on medication

^cCardiovascular chronic disease conditions: Cardiovascular Dysthythmia, not on medication; Hypertension, not on medication; Lipid disorder; Valvular disease, unspecified; Heart disease, unspecified; Other disorders of circulatory system; Cardiomyopathy, not on medication; Dysrhythmia, on medication; Hypertension, on medication; Aortic valve disorder; Mitral valve disorder; Raynaud's syndrome; Lymphedema, other; Coronary artery disease, on medication; Congestive heart failure, on medication; Atrial fibrillation or flutter; Supraventricular dysrhythmia; Hypotension; Myocardial infarction; Heart transplant for cardiomyopathy; Cerebrovascular accident Endocarditis; Cardiac arrest; Arterial embolism; Myocardial infarction, death; Congestive heart failure, death

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Table 1: Characteristics of Study Population

<i>Characteristic</i>	<i>Survivors: N (%)</i>	<i>Siblings: N (%)</i>	<i>p-value</i>
	Years (SD)	Years (SD)	
Age at Follow-up			
Age at Diagnosis			
Years of Survival			
Gender			
Male			
Female			
Race			
White			
Black			
Hispanic			
Asian			
Other			
Primary Diagnosis			
ALL			
AML			
Other or unspecified leukemia			
Astrocytomas			
Medulloblastoma, PNET			
Other CNS tumors			
Hodgkin's disease			
Non-Hodgkin's lymphoma			
Soft tissue sarcoma			
Wilm's tumor			
Neuroblastoma			
Ewing's sarcoma			
Osteosarcoma			
Other bone			
Chronic Disease Status			
≤ Grade 2			
Grade 3 or 4			
Surgery			
Amputation, lower extremity			
Amputation, upper extremity			
Limb Sparing, lower extremity			
Limb Sparing, upper extremity			
Joint Replacement			
Scoliosis Surgery			
Other Spinal Cord or Spine Surgery			
Other Surgery			
No Surgery			
Chemotherapy			
Alkylating Agent			
Anthracycline			
Both Alkylating Agent and Anthracycline			

Other Chemotherapy Agent

No Chemotherapy

Radiation

Cranial

Neck

Chest

Abdomen

Pelvis

Lower Extremity

Upper Extremity

None

Education

1-12 years

Completed High School/GED

Non-College Training after High School /Some College

College Graduate/Post-graduate work

Employment Status

Working/caring for home or family

Student

Unemployed/looking for work

Unable to work

Household Annual Income (\$U.S.)

None

20,000 – 39,000

40,000 - 59,000

60,000 – 79,000

80,000 – 99,000

≥ 100,000

Health Insurance

Yes

No

Canadian

Physician Visit Within Past 2 Years

Yes

No

Table 2: Predictors for the Utilization of PT, Chiropractic, or Both in Survivors Compared to Siblings^{ab}

Variables	<i>PT</i>		<i>Chiropractic</i>		<i>Both</i>	
	OR	95% CI	OR	95% CI	OR	95% CI
Case						
Survivors						
Survivors with <grade 2 chronic illness						
Siblings						
Gender						
Male						
Female						
Race						
White						
Black						
Hispanic						
Asian						
Other						
Age at Follow-up						
18-24 years						
25-29 years						
30-34 years						
35-39 years						
≥ 40 years						
Health Insurance						
Yes						
No						
Canadian						

^aAdjusted for Education, Employment Status, and Household Annual Income

^bEach row represents a separate model fit

Table 3: Association of Chronic Disease and Utilization of PT, Chiropractic, or Both in Survivors

Variables	Survivors					
	<i>PT</i>		<i>Chiropractic</i>		<i>Both</i>	
	OR	95% CI	OR	95% CI	OR	95% CI
Chronic Disease Status						
≤ Grade 2						
Grade 3 or 4						
Age at Diagnosis						
0-4 years						
5-9 years						
10-14 years						
15-21 years						
Age at Follow-up						
18-24 years						
25-29 years						
30-34 years						
35-39 years						
≥ 40 years						
Gender						
Male						
Female						
Race						
White						
Black						
Hispanic						
Asian						
Other						
Education						
<High School						
Completed High School/GED						
Non-College Training after High School /Some College						
College Graduate/Post-graduate work						
Household Annual Income (\$U.S.)						
None						
20,000 – 39,000						
40,000 - 59,000						
60,000 – 79,000						
80,000 – 99,000						
≥ 100,000						
Health Insurance						
Yes						
No						
Canadian						
Saw Physician Within Past 2 Years						
Yes						
No						

Table 4: Association of Cancer Diagnosis and Utilization of PT, Chiropractic, or Both in Survivors^a

Variables	Survivors					
	<i>PT</i>		<i>Chiropractic</i>		<i>Both</i>	
	OR	95% CI	OR	95% CI	OR	95% CI
Primary Diagnosis						
ALL						
AML						
Other or unspecified leukemia						
Astrocytomas						
Medulloblastoma, PNET						
Other CNS tumors						
Hodgkin's disease						
Non-Hodgkin's lymphoma						
Soft tissue sarcoma						
Wilm's tumor						
Neuroblastoma						
Ewing's sarcoma						
Osteosarcoma						
Other bone						
Age at Diagnosis						
0-4 years						
5-9 years						
10-14 years						
15-21 years						
Age at Follow-up						
18-24 years						
25-29 years						
30-34 years						
35-39 years						
≥ 40 years						
Gender						
Male						
Female						
Race						
White						
Black						
Hispanic						
Asian						
Other						

^aAdjusted for Years of Survival, Education, Household Annual Income, and Health Insurance Status

Table 5: Association of Cancer Treatment and Utilization of PT, Chiropractic, or Both in Survivors

Variables	Survivors					
	<i>PT</i>		<i>Chiropractic</i>		<i>Both</i>	
	OR	95% CI	OR	95% CI	OR	95% CI
Surgery						
Amputation, lower extremity						
Amputation, upper extremity						
Limb Sparing, lower extremity						
Limb Sparing, upper extremity						
Joint Replacement						
Scoliosis Surgery						
Other Spinal Cord or Spine Surgery						
Other Surgery						
No Surgery						
Chemotherapy						
Alkylating Agent						
Anthracycline						
Both Alkylating Agent and Anthracycline						
Other Chemotherapy Agent						
No Chemotherapy						
Radiation						
Cranial						
Neck						
Chest						
Abdomen						
Pelvis						
Lower Extremity						
Upper Extremity						
None						
Age at Diagnosis						
0-4 years						
5-9 years						
10-14 years						
15-21 years						
Age at Follow-up						
18-24 years						
25-29 years						
30-34 years						
35-39 years						
≥ 40 years						
Gender						
Male						
Female						
Race						
White						
Black						
Hispanic						
Asian						
Other						

^aAdjusted for Years of Survival, Education, Household Annual Income, and Health Insurance Status

Table 6: Frequency and Percentage of Those Scoring 40 or Less on the Summary Scales of the SF-36 by Chronic Disease Status and Physical Therapy and/or Chiropractic Utilization with OR and 95%CI Comparing Those With and Without a Chronic Disease^a

Chronic Disease	Physical Component Summary (n=)					Mental Component Summary (n=)				
	n	%	Mean	OR	95% CI	n	%	Mean	OR	95% CI
Musculoskeletal Impairment										
Health Service										
PT										
Chiropractic										
Both										
Neither										
Neurological Impairment										
Health Service										
PT										
Chiropractic										
Both										
Neither										
Cardiovascular Impairment										
Health Service										
PT										
Chiropractic										
Both										
Neither										

^aAdjusted for Age at Diagnosis, Age at Follow-up, Gender, and Race