Title: Peripheral motor and sensory neuropathy and associated outcomes in long-term survivors of childhood cancer – Last updated 1/10/2019

Working Group and Investigators: Chronic Disease (primary), Psychology, Cancer Control

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Background and Rationale:

Peripheral neuropathy can be a debilitating toxicity of selected chemotherapeutic agents, particularly in children with cancer treated with vinca alkaloids or platinums.[1] Additional agents that have been associated with peripheral neuropathy in this population include topoisomerase inhibitors and intrathecal chemotherapy.[2,3] Neuropathy can cause both sensory and motor deficits including pain and impaired sensation as well as weakness, diminished reflexes and muscle atrophy which can present as impairment in critical gross and fine motor skills.[4-7]

More studies are needed to evaluate the long-term effect of peripheral neuropathy across all pediatric malignancies. Most literature focuses on peripheral neuropathy in the acute setting, and largely focuses on Acute Lymphoblastic Leukemia (ALL). The rates in ALL patients range from approximately 25%-100%.[3,8-12] However, solid tumor patients are also frequently exposed to vincristine and platinum agents at high doses, and long-term prevalence of peripheral neuropathy warrant further investigation. Studies with small sample sizes suggest that peripheral neuropathy may be more prevalent in solid tumor survivors than in ALL survivors, with one study of 67 survivors six months off therapy reporting prevalence of peripheral neuropathy as high as 60%.[2] A study of 531 survivors in the St. Jude Lifetime Cohort also suggests that solid tumor survivors experience peripheral neuropathy as a long-term effect with a prevalence of motor and sensory neuropathy of 20% and 18%, respectively.[13] The CCSS is an informative cohort to assess the prevalence of peripheral neuropathy on a larger scale and across disease groups.

Another important gap in our knowledge regarding peripheral neuropathy is its impact on comorbid conditions, as well as financial and educational outcomes among childhood cancer survivors. It has been observed that peripheral neuropathy is associated with a lower level of physical functioning and diminished quality of life among childhood cancer survivors, though activity levels and rates of obesity have not been evaluated.[12,14] This population may also be at risk for adverse emotional outcomes, as peripheral neuropathy has been associated with anxiety and depression in survivors of adult cancers.[15] Survivors of childhood cancer have been shown to have higher rates of special education in school, as well as lower rates of some college education.[16] Peirpheral neuropathy may be one factor related to this lower educational attainment as it has been shown to be associated with impairment in handwriting and slower writing time in children being treated for ALL.[17] Childhood cancer

survivors are also known to have higher rates of unemployment, lower incomes and less skilled jobs compared to their siblings.[18] Survivors with persistent neuropathy may be particularly at risk for missed work and lower income given the known impact of neuropathy on physical function.[12] We aim to better elucidate conditions associated with peripheral neuropathy so that we can target interventions to help survivors with peripheral neuropathy.

The Childhood Cancer Survivor Study presents a unique opportunity to study the long-term prevalence of motor and sensory peripheral neuropathy across disease groups over time, and to identify other outcomes which may be associated with the presence of peripheral neuropathy, but have not been previously well described. We anticipate that this study will provide a more comprehensive understanding of the burden of peripheral neuropathy in long-term childhood cancer survivors.

Specific Aims:

Aim 1: Estimate the prevalence of peripheral motor and sensory neuropathy overall and by diagnosis in CCSS survivors at five years from diagnosis in comparison to the sibling group.

Hypotheses:

- The prevalence ratios for any peripheral neuropathy will be elevated in five-year survivors in comparison to the sibling group.
- Prevalence ratios for motor neuropathy will be elevated in five-year survivors of ALL, lymphoma, soft tissue sarcoma, Ewing sarcoma, Wilms tumor, and CNS tumors in comparison to the sibling group.
- Prevalence ratios of sensory neuropathy will be elevated in five-year survivors of neuroblastoma, osteosarcoma and CNS tumors in comparison to the sibling group.

Aim 2: Examine temporal trend of peripheral neuropathy by estimating the cumulative incidence of peripheral neuropathy in childhood cancer survivors more than five years from diagnosis, and comparing rates between diagnosis groups and similar age siblings.

Hypothesis: Cumulative incidence will remain elevated in childhood cancer survivors in comparison to the age-adjusted sibling group, but cumulative incidence will plateau with time since diagnosis.

Aim 3: Identify socio-demographic factors and treatment exposures associated with peripheral motor and sensory neuropathy within the CCSS survivor group.

Hypotheses:

- Peripheral motor neuropathy will be associated with any exposure to intrathecal methotrexate, and with exposure to vinca alkaloids and topoisomerase inhibitors with a dose response relationship.
- Peripheral sensory neuropathy will be associated with exposure to platinums with a dose response relationship.
- Overall peripheral neuropathy will be associated with older age at time of diagnosis.

Aim 4: To determine if peripheral motor and sensory neuropathy is associated with other adverse outcomes within the survivor group, including reduced levels of activity, being obese, having adverse emotional and neurocognitive outcomes, lower levels of educational attainment and unemployment.

Hypothesis: The presence of peripheral motor and sensory neuropathy will be associated with inactivity, obesity, anxiety and depression, neurocognitive impairment, lower educational attainment and higher rates of unemployment.

Analysis Framework:

<u>Study population</u>

Inclusion Criteria

- The study population will consist of all CCSS survivors diagnosed between 1970 and 1999 who completed a baseline survey (N=24,363).
- The comparison group will consist of siblings who completed a baseline survey (N=5,059).
- There will be a subset analysis of participants who completed FU2 (original cohort) or FU5 (expansion) to determine neurocognitive outcomes.

Exclusion criteria:

- Survivors or siblings with a history of known congenital neuromuscular disease (J.1 original and expanded baseline) will be excluded, as they may have neuropathy unrelated to their cancer treatment.
- Survivors who develop a subsequent malignant neoplasm (SMN) except non-melanoma skin cancer will be excluded from the analysis as of the time at which they develop their SMN since they may have been treated with additional therapies that can cause or exacerbate neuropathy (Question 17 FU1, P1 FU4, S1 FU5).

Data to be analyzed:

Motor and Sensory Neuropathy (Primary outcome, aim 1, 2 and 3):

The presence of motor and sensory peripheral neuropathy will be the primary outcome. It will be graded based on the methods used by Oeffinger et al. and will use Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 to score peripheral neuropathy grades 1-4.[19] The data sources will be the baseline survey J.8-J.13 and expanded baseline J.5-J.6, J.8-J.11, and K.6-K.13 in FU4 and FU5. We will create a binomial variable with age of onset for peripheral motor neuropathy (impaired balance, upper or lower extremity strength or tremor), sensory neuropathy, and any motor or sensory peripheral neuropathy, with any CTCAE grade $\geq$1 indicating presence of neuropathy (see chronic disease matrix below).[20] Given that peripheral neuropathy is graded as 1 in the setting of uncertainty (i.e., lowest grade assigned in settings of uncertainty), CTCAE grade $\geq$1 will be used as a cutoff for peripheral neuropathy instead of a higher value. Please note that presence of peripheral motor and sensory neuropathy will also be predictor variables for aim 4.

CCSS Chronic Disease Matrix

Peripheral Motor Neuropathy Criteria					
Chronic Condition	**Definition/Grade**	**Original Baseline**	**Expansion Baseline**	**Follow-up 4**	**Follow-up 5**
Balance	**Grade 1:** Problems with balance or ability to manipulate objects (mild)	Balance (J.8), Dizzy (C.5)	Balance severity [1] (J.5)	Balance severity [1] (K.5))	Balance severity [1] (K.5)
	Grade 2: Problems with balance or ability to manipulate		Balance severity [2] (J.5)	Balance severity [2] (K.5))	Balance severity [2] (K.5)

	objects (moderate)				
	Grade 3: Problems with balance or ability to manipulate objects (severe)		Balance severity [3] (J.5)	Balance severity [3] (K.5)	Balance severity [3] (K.5)
	Grade 4: Problems with balance or ability to manipulate objects (disabling)		Balance severity [4] (J.5)	Balance severity [4] (K.5)	Balance severity [4] (K.5)
Tremors	**Grade 1:** Tremors or problems with movement	Tremor (J.9)	Tremor(J.6)	Tremor (K.6)	Tremor (K.6)
Weakness in leg	**Grade 1:** weakness in leg(s), mild limitation	Move leg(J.11) W1Block (N14E)[2]	Move leg(J.12) W1Block O20e)[2]	Move leg(K.12) W1Block O20e)[2]	Move leg(K.12) W1Block O20e)[2]
	Grade2: weakness in leg(s), moderate limitation	Move leg(J.11) W1Block (N14E)[1]	Move leg(J.12) W1Block O20e)[1]	Move leg(K.12) W1Block O20e)[1]	Move leg(K.12) W1Block O20e)[1]
Weakness in arm	**Grade 1: weakness in arm(s)**	Move arm (J10)	Move arm (J11)	Move arm (K11)	Move arm (K11)

Peripheral Sensory Neuropathy					
Chronic Condition	**Definition/Grade**	**Original Baseline**	**Expansion Baseline**	**Follow-up 4**	**Follow-up 5**
Sensory Neuropathy	**Grade 1: sensory neuropathy**	Touch (J12) Absent (J13)	Touch (J8) Absent (J10)	Touch(K8) Absent (K10)	Touch(K8) Absent (K10)

Patient and treatment characteristics (Predictor Variables, Aim 3)

We will analyze demographic, disease and treatment related predictor variables for association with any peripheral neuropathy, and motor and sensory neuropathy (as defined above, based on responses from baseline survey, FU 4 and FU5).

1. **Demographic** predictor variables will include: sex (A2 baseline), age (A1 baseline), and race/ethnicity (A4 original baseline, A5 expanded baseline).
2. **Disease related** predictor variables will be evaluated from medical record abstraction and will include primary cancer diagnosis, age at diagnosis, time since diagnosis.

3. **Treatment related** predictor variables will include:
    a. Chemotherapy: Any chemotherapy (Y/N), vinca alkaloids (Y/N/Cumulative from expansion cohort), etoposide (Y/N/Cumulative), platinums (Y/N/Cumulative) or intrathecal chemotherapy (Y/N)
    b. Radiation Therapy:
        i. Cranial radiation, we will use the following thresholds of maximum tumor dose (maxTD) to the brain for high, moderate and low dose [21]
            1. High dose (>50Gy)
            2. Moderate dose (30Gy-50Gy)
            3. Low dose (<30Gy)
        ii. Non-cranial radiation (Y/N, and by tertile of exposure)
        iii. Spinal radiation (Y/N, and by tertile of exposure)
        iv. Total body irradiation (TBI) (Y/N)

Potential physical, psychological and social outcomes associated with peripheral neuropathy (Outcome variables, Aim 4):

We will perform univariate analysis and multivariable analysis within the survivor group to determine association between prior motor neuropathy, sensory neuropathy, any peripheral neuropathy and the following cross sectional outcomes. We will only include peripheral neuropathy as an existing condition if its onset is prior to or simultaneous to the report of the outcomes below.

1. **Activity level** as measured by**:**
    a. Limitation in activity in past 2 years. We will sum the number of activities limited for more than 3 months in the survivor and sibling groups and compare the distributions. We will then create a binomial vs. an ordinal variable for physical impairment with impairment defined as < 10^{th} percent of the sibling group. (N14 a-f baseline original, N10 a-f baseline <18, O20 a-f baseline expanded, FU4 N26 a-f).

2. **Overweight or obese** as measured by:
    a. Obesity (BMI ≥30): Yes or No (Baseline A10-A11, Expanded A3-A4, FU2, FU4-5, BMI,=kg/m2)
    b. Overweight (BMI =25.0-29.9): Yes or No (Baseline A10-A11, Expanded A3-A4, FU2, FU4-5 BMI,=kg/m2)

3. **Emotional Outcomes** as measured by:
    a. BSI 18 (J16-37 baseline, K1-K20 expanded baseline)
    b. We will use method used by Zeltzer et al. and analyze global severity index, depression, anxiety, somatization and create T-scores compared to population normal values with a cutoff of ≥ 63 as a positive result.[22,23]

4. **Neurocognitive Outcomes** as measured by
    a. CCSS - NCQ (J1-25 for survivors who completed FU2, Q1-33 FU5)
    b. We will analyze neurocognitive impairment in four domains described by Krull et al.; task efficiency, emotional regulation, memory and organization.[24] The responses in survivors will be analyzed as continuous variables and compared to sibling scores, with the top 10^{th} percentile (greater than 1.28 standard deviation above sibling average) indicating impaired neurocognitive function.[25,26]

5. **Educational Attainment** as measured by
    a. Highest level of schooling completed (Categorical includes: grade school, part of high school, high school, training after high school other than college, some college, completed college, post-graduate level - O.1 baseline, R1 expanded baseline, In ≥18 cohort only 1 FU2, A3 FU4, use highest level reported):
    b. History of special education (Y/N/Not sure) (O.3 original baseline ≥18 and <18, R3 expanded baseline)
    c. History of AP program (Y/N/Not sure) (O.3 original baseline ≥18 and <18, R3 expanded baseline)

6. **Employment and financial status** (In ≥18 cohort only) as measured by
    a. Impairment or health problem prevents holding job/attending school "Y/N" (N.12 original baseline, O.18 expanded)
    b. Ever employed Y/N (Original baseline O.5, Expanded S.1)
    c. Currently unemployed Y/N (O.6 original baseline, S.2 expanded)
    d. Type of job (Open ended, O.8 original baseline, S.3 expanded baseline), will categorize response into professional, non-professional non-physical, and non-professional physical employment based on methods of Kirchhoff et al.[18]
    e. Household income (<9,999, 10,000-19,999, 20,000-39,999, 40,000-59,999, >60,000) (Q8 original baseline, T.1 expanded)
    f. Personal income (none, <9,999, 10,000-19,999, 20,000-39,999, 40,000-59,999, >60,000) (Q.8 original baseline, T.1 expanded baseline)

<u>Confounders/mediators/modifiers</u>

For aims 2 and 3 we will consider the following confounders as covariates in our analysis.

Aim 2: Demographic and treatment characteristics that predict neuropathy

1. Use of seizure medications (B8.11 original baseline, B.10 expanded baseline)
2. History of stroke (Based on chronic disease matrix)
3. History of diabetes (Based on chronic disease matrix)
4. Heavy alcohol use - Number of drinks per day (= 4 or more for women, =5 or more for men, >18 only, N7 baseline, O11 expanded)

Aim 3: Neuropathy as a predictor for other comorbid conditions (activity, obesity, emotional, neurocognitive and financial outcomes)

1. History of radiation therapy (medical record abstraction)
    a. Cranial radiation, we will use the following thresholds of maxTD to the brain for high, moderate and low dose [21]
        i. High dose (>50Gy)
        ii. Moderate dose (30Gy-50Gy)
        iii. Low dose (<30Gy)
    b. Non-cranial radiation (Y/N, and by tertile of exposure)
    c. Spinal radiation (Y/N, and by tertile of exposure)
    d. TBI (Y/N)
2. Surgical procedure of limb or spine (I2-I6 original and expanded baseline)

3. Amputation (I1 original and expanded baseline)
4. History of hemiplegia or paralysis (J.2 original and expanded baseline)
5. History of stroke (J15 baseline survey original and expanded)
6. History of diabetes (E5, E6, E7 original and expanded baseline)
7. History of any Grade 3 or 4 CTCAE outcome (based on chronic disease matrix)

Data Analysis Plan

We will calculate prevalence of peripheral neuropathy at study entry (5 years after diagnosis). Cumulative incidence for peripheral neuropathy that develops more than five years from diagnosis will be calculated with curves starting at the prevalence as of 5 years to reflect the overall burden of peripheral neuropathy (Aims 1&2). Presence or absence of peripheral motor and sensory neuropathy will be based on CTCAE grade as defined above.[20,27] We will assume that peripheral neuropathy that is present at study entry will remain a prevalent condition. We acknowledge that a limitation to our analysis is that the original baseline survey does not indicate whether peripheral neuropathy is still present at the time of the survey, but for the purpose of this analysis we will assume any peripheral neuropathy reported in the original baseline survey occurring at less than five years since diagnosis is still prevalent at study entry. We will compare the distribution of peripheral neuropathy between the original and expanded cohort who report "still present" to determine if peripheral neuropathy is over-represented in the original cohort at study entry. Prevalence of peripheral neuropathy will be evaluated using log-binomial or modified Poisson models to evaluate prevalence ratios comparing between diagnosis groups and to siblings, with cubic spline attained age adjustments. For prevalence analyses, sibling data will be limited to the time period <age 26 to correspond to the possible range of ages for survivors. Since peripheral neuropathy may be extremely rare among siblings, particularly in this age range, analyses may be restricted to comparisons between survivor diagnostic groups. Cox proportional hazards models will evaluate hazard ratios for developing peripheral neuropathy more than 5 years after diagnosis among subjects who did not already have it, comparing between diagnostic groups among survivors and to siblings, if enough events. Follow-up time will be truncated at occurrence of an SMN (competing risk).

To determine predictors of peripheral neuropathy (aim 3) we will compare survivors who develop peripheral neuropathy more than 5 years after diagnosis to survivors without peripheral neuropathy. Similar to Aim 2 methodology, we will perform a time to event analysis using a cox regression to calculate hazard ratios for demographic and disease characteristics (outlined above) that predict peripheral neuropathy. For peripheral neuropathy that is present at study entry we will perform a separate cross-sectional analysis and estimate prevalence ratios for demographic, disease and treatment characteristics that predict peripheral neuropathy using similar models to those in Aim 1. Separate analyses will be performed using overall peripheral neuropathy, motor neuropathy and sensory neuropathy as the dependent variables.

To assess for the risk of subsequent comorbid physical, psychological and social outcomes in survivors with peripheral neuropathy compared to survivors without peripheral neuropathy (aim 4) bivariate and multivariable analyses will be performed within the survivor group. Predictor variables will include prior onset of overall peripheral neuropathy, motor neuropathy, and sensory neuropathy and dependent variables will include inactivity, physical impairment, obesity, low educational attainment, neurocognitive impairment, unemployment and low income as assessed on the baseline survey (and FU2 and FU5 for neurocognitive outcomes). We will include the confounders listed above as covariates in the analysis. Most outcomes will be categorized into binary measures and will be analysed using similar methods to those described for Aim 1. For measures that remain categorical or ordinal, we will explore multinomial logistic regression or proportional odds models to examine associations with these outcomes, though binary models will be explored for all outcomes as their interpretability will be preferred if the same general information is conveyed by the results.

Given that CNS tumors are a unique population at risk for multiple neurologic sequelae and also at risk for peripheral neuropathy based on their treatment exposure we will perform all analyses described above on the

entire cohort and then perform stratified analyses of CNS tumors and non-CNS tumors to determine if associations differ between groups. We will also perform a stratified analysis of osteosarcoma patients with lower limb amputations, as they are at risk for neuromuscular changes and impaired function. In full models, we will also test CNS malignancy and lower limb amputation interaction terms with key risk factors in the models above to determine whether reporting stratified analyses is warranted.

Tables/Figures

Table 1: Patient Characteristics

Patient Characteristics	Survivors n %	Sibling n %	p-value
Total			
Age at survey completion			
<20			
20-29			
30-39			
>40			
Age at diagnosis			
0-4			
5-9			
10-14			
15-20			
Sex			
Male			
Female			
Race			
White			
Black			
American Indian/Alaskan Native			
Asian or Pacific Islander			
Other			
Unknown			
Hispanic			
Yes			
No			
Unknown			
Diagnosis			
Acute lymphoid leukemia			
Acute myeloid leukemia			
Other leukemia			
CNS Tumor			
Hodgkin lymphoma			
Non-Hodgkin lymphoma			
Wilms tumor			
Neuroblastoma			

Soft tissue sarcoma Ewing sarcoma Osteosarcoma			
Chemotherapy Yes No			
Type of chemotherapy Vinca Platinum Etoposide Intrathecal Methotrexate Other Intrathecal			
Radiation Therapy Cranial Radiation TBI Spinal Radiation Other XRT			
Cranial Radiation High dose Moderate dose Low dose			

Table 2: Prevalence and PR of peripheral neuropathy in survivors compared to sibling group

	Sibling n (%)	Survivor n (%)	PR	95% Confidence Interval	p-value
Overall prevalence of peripheral neuropathy Motor Sensory					
Prevalence of neuropathy by diagnosis Acute lymphoid leukemia Acute myeloid leukemia Other leukemia CNS Tumor Hodgkin lymphoma Non-Hodgkin lymphoma Wilms tumor Neuroblastoma Soft tissue sarcoma Ewing sarcoma Osteosarcoma					

Table 3: Risk of peripheral neuropathy in survivors based on demographic and treatment characteristics (table will be repeated for prevalence ratios as of 5 years post diagnosis and post-5 year intervals for Hazard Ratios)

	Overall Neuropathy		Motor Neuropathy		Sensory Neuropathy	
	n (%)	PR/HR	n (%)	PR/ HR	n (%)	PR/HR
Total						
Age at survey completion						
<20						
20-29						
30-39						
>=40						
Age at diagnosis						
0-4						
5-9						
10-14						
15-20						
Years since treatment						
0-4						
5-9						
10-14						
15-19						
>=20						
Sex						
Male						
Female						
Race						
White						
Black						
American Indian/Alaskan Native						
Asian or Pacific Islander						
Other						
Unknown						
Hispanic						
Yes						
No						
Unknown						
Diagnosis						
Acute lymphoid leukemia						
Acute myeloid leukemia						
Other leukemia						
CNS Tumor						
Hodgkin lymphoma						
Non-Hodgkin lymphoma						
Wilms tumor						
Neuroblastoma						
Soft tissue sarcoma						
Ewing sarcoma						

Osteosarcoma						
Chemotherapy Yes No						
Type of chemotherapy Vinca Alkaloid Platinum Intrathecal Etoposide						
Radiation Therapy Cranial Radiation TBI Spinal Radiation Other XRT						
Cranial Radiation High dose Moderate dose Low dose						

Table 4: Educational and employment outcomes in survivors with neuropathy compared to those without neuropathy

	Survivors with neuropathy (n, %)	Survivors without neuropathy (n, %)	PR	p-value
Highest educational attainment Grade school High school College Graduate school				
History of special education				
History of advance placement				
Income None <$9,999 $10,00-$19,999 $20,000-$39,999 $40,000-$59,999 >$60,000				
Never employed				
Unemployed at time of survey				

Table 5: Risk of inactivity and obesity in survivors with neuropathy compared to survivors without neuropathy

	Survivors with neuropathy (n, %)	Survivors without neuropathy (n, %)	PR	p-value
Overweight				
Obese				
Impaired activity				

Table 6: Risk of emotional and neurocognitive outcomes in survivors with neuropathy compared to survivors without neuropathy

	Survivors with neuropathy (n, %)	Survivors without neuropathy (n, %)	PR	p-value
Anxiety				
Depression				
Neurocognitive impairment Task Efficiency Emotional Regulation Memory Organization				

Figure 1: Cumulative incidence of overall peripheral neuropathy in survivor and sibling groups

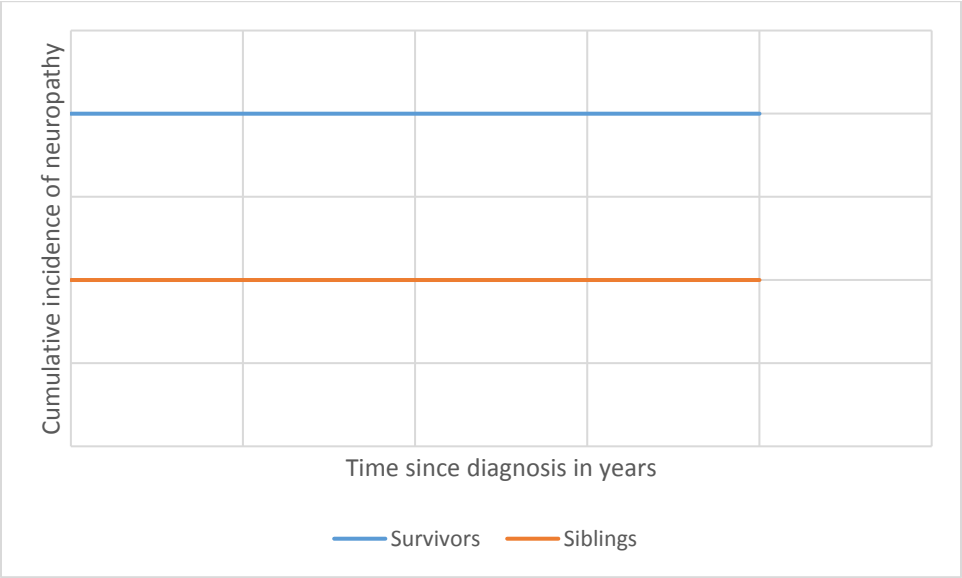


Figure 2: Cumulative incidence of peripheral motor neuropathy in survivor and sibling groups

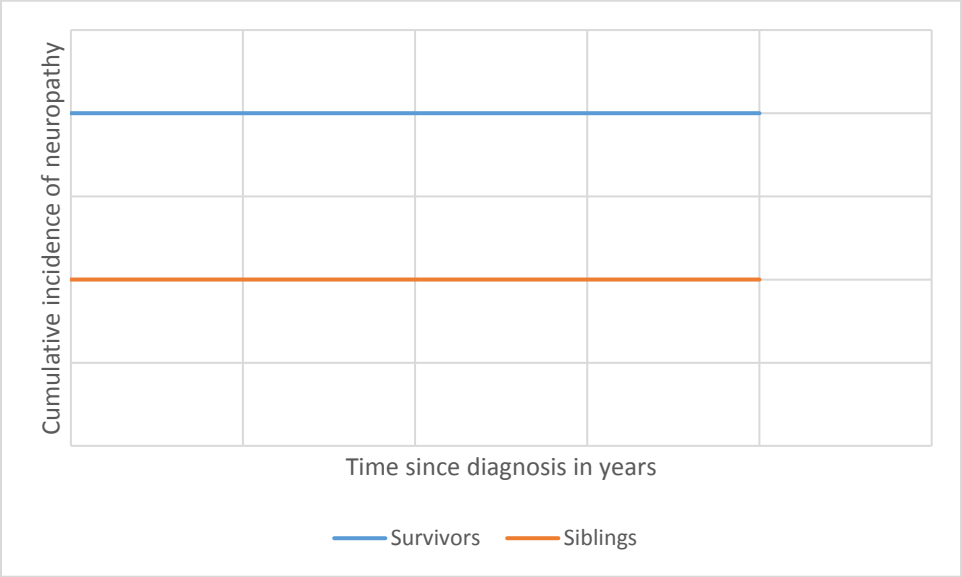
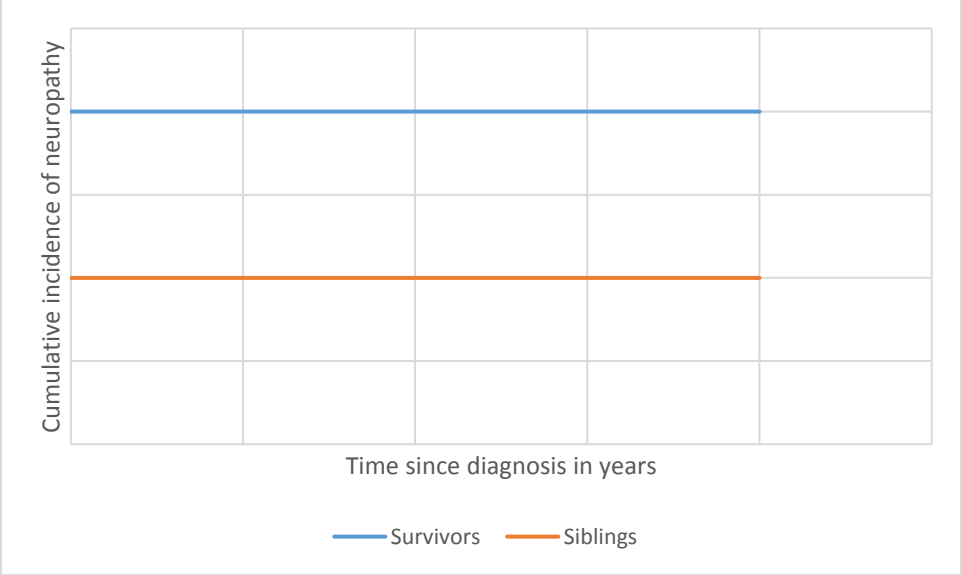


Figure 2: Cumulative incidence of peripheral sensory neuropathy in survivor and sibling groups



Special considerations

Rozalyn is starting her second year of pediatric hematology-oncology fellowship and will have two years of protected research time without clinical responsibilities to focus on this project, with mentorship and guidance from Dr. Nina Kadan-Lottick.

References:

1. Mora E, Smith EML, Donohoe C, Hertz DL. Vincristine-induced peripheral neuropathy in pediatric cancer patients. *American Journal of Cancer Research.* 2016;6(11):2416-2430.
2. Gilchrist LS, Tanner LR, Ness KK. Short-term recovery of chemotherapy-induced peripheral neuropathy after treatment for pediatric non-CNS cancer. *Pediatr Blood Cancer.* 2017;64(1):180-187.
3. Ness KK, Hudson MM, Pui CH, et al. Neuromuscular impairments in adult survivors of childhood acute lymphoblastic leukemia: associations with physical performance and chemotherapy doses. *Cancer.* 2012;118(3):828-838.
4. Gilchrist L. Chemotherapy-induced peripheral neuropathy in pediatric cancer patients. *Semin Pediatr Neurol.* 2012;19(1):9-17.
5. Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-Induced Peripheral Neuropathy: A Current Review. *Annals of neurology.* 2017;81(6):772-781.
6. Lavoie Smith EM, Li L, Chiang C, et al. Patterns and severity of vincristine-induced peripheral neuropathy in children with acute lymphoblastic leukemia. *J Peripher Nerv Syst.* 2015;20(1):37-46.
7. Bjornard KL, Gilchrist LS, Inaba H, et al. Peripheral neuropathy in children and adolescents treated for cancer. *Lancet Child Adolesc Health.* 2018;2(10):744-754.
8. Ramchandren S, Leonard M, Mody RJ, et al. Peripheral neuropathy in survivors of childhood acute lymphoblastic leukemia. *J Peripher Nerv Syst.* 2009;14(3):184-189.
9. Tay CG, Lee VWM, Ong LC, Goh KJ, Ariffin H, Fong CY. Vincristine-induced peripheral neuropathy in survivors of childhood acute lymphoblastic leukaemia. *Pediatr Blood Cancer.* 2017;64(8).
10. Jain P, Gulati S, Seth R, Bakhshi S, Toteja GS, Pandey RM. Vincristine-induced neuropathy in childhood ALL (acute lymphoblastic leukemia) survivors: prevalence and electrophysiological characteristics. *J Child Neurol.* 2014;29(7):932-937.
11. Lehtinen SS, Huuskonen UE, Harila-Saari AH, Tolonen U, Vainionpaa LK, Lanning BM. Motor nervous system impairment persists in long-term survivors of childhood acute lymphoblastic leukemia. *Cancer.* 2002;94(9):2466-2473.
12. Kandula T, Farrar MA, Cohn RJ, et al. Chemotherapy-Induced Peripheral Neuropathy in Long-term Survivors of Childhood Cancer: Clinical, Neurophysiological, Functional, and Patient-Reported Outcomes. *JAMA Neurol.* 2018.
13. Ness KK, Jones KE, Smith WA, et al. Chemotherapy-related neuropathic symptoms and functional impairment in adult survivors of extracranial solid tumors of childhood: results from the St. Jude Lifetime Cohort Study. *Arch Phys Med Rehabil.* 2013;94(8):1451-1457.
14. Mols F, Beijers T, Vreugdenhil G, van de Poll-Franse L. Chemotherapy-induced peripheral neuropathy and its association with quality of life: a systematic review. *Support Care Cancer.* 2014;22(8):2261-2269.
15. Bao T, Basal C, Seluzicki C, Li SQ, Seidman AD, Mao JJ. Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: prevalence, risk factors, and fall risk. *Breast Cancer Res Treat.* 2016;159(2):327-333.
16. Gurney JG, Krull KR, Kadan-Lottick N, et al. Social Outcomes in the Childhood Cancer Survivor Study Cohort. *Journal of Clinical Oncology.* 2009;27(14):2390-2395.
17. Reinders-Messelink HA, Schoemaker MM, Snijders TA, Goeken LN, Bokkerink JP, Kamps WA. Analysis of handwriting of children during treatment for acute lymphoblastic leukemia. *Med Pediatr Oncol.* 2001;37(4):393-399.

18. Kirchhoff AC, Krull KR, Ness KK, et al. Occupational outcomes of adult childhood cancer survivors: A report from the Childhood Cancer Survivor Study. *Cancer.* 2011;117(13):3033-3044.
19. Common Terminology Criteria for Adverse Events v4.03 (CTCAE Version 4.03). *National Cancer Institute, National Institute of Health, U.S. Department of Health and Human Services.* 2010.
20. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med.* 2006;355(15):1572-1582.
21. Packer RJ, Gurney JG, Punyko JA, et al. Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: childhood cancer survivor study. *J Clin Oncol.* 2003;21(17):3255-3261.
22. Recklitis CJ, Parsons SK, Shih MC, Mertens A, Robison LL, Zeltzer L. Factor structure of the brief symptom inventory--18 in adult survivors of childhood cancer: results from the childhood cancer survivor study. *Psychol Assess.* 2006;18(1):22-32.
23. Zeltzer LK, Lu Q, Leisenring W, et al. Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: a report from the childhood cancer survivor study. *Cancer Epidemiol Biomarkers Prev.* 2008;17(2):435-446.
24. Krull KR, Gioia G, Ness KK, et al. Reliability and Validity of the Childhood Cancer Survivor Study Neurocognitive Questionnaire. *Cancer.* 2008;113(8):2188-2197.
25. Ellenberg L, Liu Q, Gioia G, et al. Neurocognitive Status in Long-Term Survivors of Childhood CNS Malignancies: A Report from the Childhood Cancer Survivor Study. *Neuropsychology.* 2009;23(6):705-717.
26. Kadan-Lottick NS, Zeltzer LK, Liu Q, et al. Neurocognitive Functioning in Adult Survivors of Childhood Non-Central Nervous System Cancers. *JNCI Journal of the National Cancer Institute.* 2010;102(12):881-893.
27. Common Terminology Criteria for Adverse Events v3.0 (CTCAE) *Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events,* 2003; https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed August 23, 2018, 2018.