

1. STUDY TITLE: *Neurocognitive and emotional problems predict health behavior outcomes.*

2. WORKING GROUP AND INVESTIGATORS:

2.1. Working Groups: Prevention and Control; Psychology

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3. BACKGROUND AND RATIONALE:

Neurocognitive functioning has been identified as an important factor for consideration in examining health behaviors and utilization of health care in cancer survivors.¹ This proposal aims to evaluate the relation between self-reported neurocognitive and emotional impairment and healthy behaviors and health care utilization in the CCSS survivor cohort.

Cognitive impairment, and in particular memory problems and executive dysfunctions, are reported to be related to health behaviors. Low general intelligence has long been identified as a risk factor for poor self-care and for poor health behaviors in the general population, as well as in individuals with serious mental illness.^{2,3} However, specific neurocognitive abilities may underlie this relation. Hall and colleagues recently reported that, in a community sample, good executive functioning predicted engagement in health protective behaviors, while poor executive functioning predicted higher levels of risky health behaviors.⁴ Similarly, poor memory skills have been related to poor health behavior in chronic illness.³

This connection between neurocognitive functioning and health-related behavior also extends to treatment adherence. In a sample of adult HIV patients, those with neurocognitive impairment were reported to be 2.5 times more likely to demonstrate non-adherence to treatment recommendations compared to patients without neurocognitive impairment.⁵ Reduced adherence to HIV treatment is reported in patients with poor memory skills and poor executive functions.⁶ Similarly, in a treatment paradigm designed to lower serum cholesterol in patients at risk for cardiovascular events, Stille and colleagues reported that patients with impaired executive functioning demonstrated significantly lower medication adherence rates compared to patients without executive dysfunction.⁷ Poor medication adherence has also been reported in a community sample of elderly patients with impaired memory and

executive functioning.⁸ Thus, impaired memory and/or executive functions may limit an individual's ability to adhere to treatment recommendations specific to their medical condition.

Engagement in healthy behaviors has also been associated with current emotional state. In a chronic pain sample, Vines and colleagues reported that increased symptoms of depression were related to lower engagement in healthy behaviors.⁹ Depression has also been associated with insufficient exercise and physical activity in medical samples.^{10, 11} Similar findings have been reported in a large community sample. Specifically, Stine and colleagues reported frequent symptoms of anxiety to be related to poor health behavior, including physical inactivity.¹² Thus, in order to fully understand the relation between neurocognitive functioning and health behaviors, it will be important to consider the moderating effect of current emotional functioning.

Neurocognitive and emotional functioning has also been associated with healthcare utilization in a variety of adult populations. In a nationally representative community sample of 6,651 elderly individuals, Walsh and colleagues identified reduced global cognitive functioning as a barrier to accessing outpatient health care services.¹³ However, several studies have also suggested that increased emotional pathology is related to increased healthcare utilization.¹⁴⁻¹⁶ For example, in a study of over 40,000 patients recruited by the Department of Veterans Affairs, Chen and colleagues reported increased healthcare utilization in patients who were reporting symptoms of depression.¹⁴ Similarly, using data from the National Health Survey, Levinson and colleagues reported increased primary care utilization to be associated with current symptoms of mood and anxiety.¹⁵ Although level of neurocognitive functioning may moderate an individual's ability to access appropriate healthcare, it would appear important to also consider the role of current emotional symptoms in stimulating attempts to access care of any type.

The Neurocognitive Questionnaire (NCQ) is a self-report measure of neurocognitive functioning collected during the Follow-Up 2 survey of the Childhood Cancer Survivor Study (CCSS). In a recent analysis of the factor structure of the NCQ in CCSS, four primary factors were identified: Task Efficiency, Emotional Regulation, Organization, and Memory.¹⁷ The Emotional Regulation and Organization factors are primarily measures of executive functions. The Task Efficiency and Memory factors include aspects of executive functions, though are also comprised of skills related to attention and memory abilities, respectively. Given the previous literature reporting relations between memory and executive functions and engagement in health behaviors and health care utilization, we expect the Memory, Organization, and Emotional Regulation factors to be associated with health behaviors and healthcare utilization in the CCSS cohort.

The Brief Symptom Inventory (BSI) is a self-report measure of emotional functioning, also collected during the Follow-Up 2 survey of the Childhood Cancer Survivor Study (CCSS). This questionnaire produces reliable measures of depression, anxiety, and somatization in long-term adult survivors of childhood cancer.¹⁸ Given the previous literature in other diseases, we expect symptoms of depression and anxiety to be related to positive health behaviors. In addition, since emotional functioning has been identified as a predictor of

healthcare utilization, we will use the BSI as a covariate in the NCQ prediction model of risk-based healthcare utilization.

Based on the analysis conducted during the validation of the NCQ, we have determined that 6,739 survivors in the CCSS cohort have completed both the NCQ and the BSI. The breakdown for cancer diagnoses within this sample is: 33.1% survivors of leukemia, 13.5% survivors of Hodgkin lymphoma, 11.9% survivors of CNS tumors, 9.6% survivors of Wilms tumor, 9.1 survivors of soft tissue sarcoma, 8.8% survivors of bone cancer, 7.6% survivors of non-Hodgkin lymphoma, and 6.4% survivors of neuroblastoma. With this sample size and disease distribution, we can expect sufficient variability in neurocognitive and emotional symptoms and in health behaviors and expectations for healthcare utilization to identify significant associations.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

4.1. Primary Aim:

- 4.1.1. To examine the association between neurocognitive and emotional functioning and health behaviors and health care utilization among adult survivors of childhood cancer.

4.2. Objectives:

- 4.2.1. To examine the impact of memory problems, executive dysfunction, and emotional symptoms on engagement in positive health behaviors.
- 4.2.2. To examine the impact of memory problems and executive dysfunction on engagement in appropriate healthcare utilization.

4.3. Hypotheses:

- 4.3.1. Patients with memory problems, executive dysfunction, and/or significant emotional symptoms will be less likely to meet CDC guidelines for weekly physical exercise.
- 4.3.2. Patients with memory problems, executive dysfunction, and/or significant emotional symptoms will be less likely to use sunscreen while in the sun.
- 4.3.3. Patients with memory problems and executive dysfunction will be less likely to engage in routine medical care with physicians.
- 4.3.4. Patients with memory problems and executive dysfunction will be less likely to engage in routine dental care.
- 4.3.5. Patients with memory problems and executive dysfunction will be less likely to engage in risk-based medical testing as outlined in the COG Long-term Follow-up Guidelines.

5. ANALYSIS FRAMEWORK:

5.1. Primary Outcomes Variables:

- 5.1.1. Positive health behaviors
 - 5.1.1.1. Weekly physical exercise meets CDC guidelines (Yes/No)
 - 5.1.1.2. Regular sunscreen use while in sun (Yes/No)

5.1.2. Health care utilization.

- 5.1.2.1. Physician Care (no care, general care, general survivor focused care, risk-based survivor-focused care)
- 5.1.2.2. Dental visits (Yes/No)
- 5.1.2.3. Echocardiogram (classified based on treatment risk)
- 5.1.2.4. Colonoscopy (classified based on treatment and population risk)
- 5.1.2.5. Bone density exam (classified based on treatment risk)
- 5.1.2.6. Mammogram (classified based on treatment and population risk)
- 5.1.2.7. Pap smear (classified based on treatment risk)

5.2. Primary predictors:

- 5.2.1. CCSS-NCQ : Task Efficiency, Emotional Regulation, Organization, Memory. Factor scores will be dichotomized based on whether the performance is considered “impaired” or not (Yes/No), with impairment defined as a performance falling $\leq 10^{\text{th}}$ percentile based on sibling group norms.
- 5.2.2. BSI: Anxiety, Depression, Somatization. Factor scores will be dichotomized based on whether the performance is considered “impaired” or not (Yes/No), with impairment defined as a performance falling $\leq 10^{\text{th}}$ percentile based on standardized norms.

5.3. Covariates:

- 5.3.1. Cancer Diagnosis
- 5.3.2. Radiation therapy (used to identify risk-based recommended medical testing)
- 5.3.3. Chemotherapy agents (used to identify risk-based recommended medical testing)
- 5.3.4. Age
- 5.3.5. Sex
- 5.3.6. BMI
- 5.3.7. Protective clothing
- 5.3.8. Sun avoidance
- 5.3.9. Health Insurance (Canadian/Yes/No)
- 5.3.10. Household Income
- 5.3.11. Psychotropic medication use: Antidepressants, Anxiolytics

5.4. Related to the specific hypotheses, the following analyses will be conducted:

- 5.4.1. Frequency distributions will be examined to categorize relevant outcome variables and covariates according to reasonable groupings and consistent with previous CCSS manuscripts.
- 5.4.2. Physical exercise will be classified based on whether or not the survivors meet CDC guidelines.
- 5.4.3. Physician care will be categorized into four groups as indicated in 5.1.2.1 above and as previously reported by Nathan et al.
- 5.4.4. Specific risk-based medical testing (e.g. echocardiogram) will be classified based on treatment exposure and, when appropriate, by population risk (e.g. colonoscopy):

- 5.4.4.1. Echocardiogram: risk based on exposure to anthracyclines, TBI, and localized radiation to chest, mantle, mediastinum, etc...
- 5.4.4.2. Colonoscopy: risk based on spinal radiation (i.e. thoracic, lumbar, sacral), TBI, and radiation localized to abdomen and/or pelvis. Risk also based on current age.
- 5.4.4.3. Bone density exam: risk based on exposure to antimetabolites, steroids, TBI
- 5.4.4.4. Mammogram: risk based on TBI, and radiation localized to chest, mantle, mediastinum, axilla. Risk based on age of female.
- 5.4.4.5. Pap smear: Risk based on age of female.
- 5.4.5. Descriptive statistics will be reported for all predictors, outcomes, and covariates. For outcomes, only patients who are at risk, based on treatment, and in need of specific medical testing will be evaluated for adherence (Yes/No).
- 5.4.6. Generalized linear regression analyses will be conducted for each outcome variable, using dichotomized factors (as described in 5.2.1 and 5.2.2) from the CCSS-NCQ and BSI as primary predictors and covariates as indicated above. Patient groups will be determined for each Health Care utilization outcomes based on treatment exposures. Patients who are deemed at risk will then be included in the model to determine which predictors/covariates are associated with adherence to the recommended medical testing for that risk.
- 5.4.7. Univariate analyses will be conducted first to identify variables contributing to each outcome.
- 5.4.8. Variables that are significant in univariate analyses will be included in multi-variate analyses for each outcome.
- 5.4.9. Relative risk ratios will be reported for predictors and covariates that significantly contribute to the multi-variate models.

5.5. Subject population:

- 5.5.1. CCSS Survivor Cohort for Follow-up 2 survey (i.e. Follow-up 2003)
 - 5.5.1.1. Inclusion criteria
 - Cancer survivors who completed CCSS-NCQ and BSI questionnaires
 - 5.5.1.2. Exclusion criteria
 - Paralysis
 - Mental Retardation
 - 5.5.1.3. Variables
 - Cancer Diagnosis
 - Radiation Therapy
 - Chemotherapy Variables
 - Age
 - Sex
 - Current BMI (7, 8)
 - Health care in past 2 years (A1)
 - Cancer-related health care in past 2 years (A5)
 - Risk-based medical testing in past 2 years – Echo (B1)
 - Risk-based medical testing in past 2 years – Colonoscopy (B2)
 - Risk-based medical testing in past 2 years – Bone strength/density (B3)
 - Risk-based medical testing in past 2 years – Mammogram (B4)

- Medical testing – Pap smear (B5)
- Suscreen use (C11)
- Min/wk vigorous exercise (D3, D4)
- Min/wk moderate exercise (D6, D7)
- BSI (G1-18)
- CCSS-NCQ (J1-25)
- Insurance (M1)
- Dental visits (O17)
- Dental cleaning (O18)
- Current Psychopharm (Q8)
- Current Household Income (S2)

5.6. Examples of specific tables and figures:

Descriptive Statistics at Follow Up 2		
	No	%
Sex		
Female		
Male		
Age		
<i>Categories TBD</i>		
Diagnosis		
Leukemia		
CNS		
HD		
NHL		
Wilms'		
Neuroblastoma		
Soft tissue sarcoma		
Radiation Therapy		
Cranial		
Total Body		
Chest		
Pelvic		
...etc		
Chemotherapy		
Anthracycline		
Antimetabolite		
Corticosteroid		
...etc		

Current Health Characteristics

	No	%
BMI Classification		
Underweight		
Normal Range		
Overweight		
Obese		
Exercise		
None	#	%
Moderate Physical Activity	Min/wk	
Vigorous Physical Activity	Min/wk	
Sun Protection		
Sunscreen		
Protective Clothing		
Use Hat		
Limit Exposure		
Stay in Shade		

Current Health Care Utilization

	No	%
Health Care		
No health care in past 2 years		
General health care		
General survivor-focused care		
Risk based, survivor-focused care		
Dental Care in last yr		
No		
Yes		
Health Insurance		
Yes		
No		
Visit to a cancer center in last 2 yrs		

Odds ratios for the prediction of health behaviors

	<i>Physical Exercise</i>			<i>Sun Screen Use</i>		
	RR	95% CI	P	RR	95% CI	p
CCSS-NCQ: Task Efficiency						
CCSS-NCQ: Emotional Regulation						
CCSS-NCQ: Organization						
CCSS-NCQ: Memory						
BSI: Depression						
BSI: Anxiety						
BSI: Somatization						

Odds ratios for the prediction of healthcare utilization

	<i>General Physical Care</i>			<i>Cancer Related Care</i>			<i>Dental Care</i>		
	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p
CCSS-NCQ: Task Efficiency									
CCSS-NCQ: Emotional Regulation									
CCSS-NCQ: Organization									
CCSS-NCQ: Memory									

Odds ratios for the prediction of risk-based medical testing

	<i>Echo</i>			<i>Colonoscopy</i>			<i>Bone test</i>			<i>Mammography</i>			<i>Pap smear</i>		
	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p
CCSS-NCQ: Task Efficiency															
CCSS-NCQ: Emotional Regulation															
CCSS-NCQ: Organization															
CCSS-NCQ: Memory															

6. SPECIAL CONSIDERATION:

- 6.1. Kiri Ness has agreed to conduct the statistical analyses at St. Jude Children's Research Hospital, under the supervision of Wendy Leisenring. We believe that we can complete the statistical procedures locally and, thus, not add to the list awaiting the Statistical Centers. Wendy will review all analyses and methods prior to sending the paper to the publications committee for review.

7. REFERENCES:

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