

CHILDHOOD CANCER SURVIVAL STUDY CONCEPT PROPOSAL

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I- Title: Neurocognitive and Psychosocial Correlates of Adaptive Functioning in Survivors of Childhood Leukemia and Lymphoma.

II- Working Group and Investigators: Psychology Working Group. Proposed investigators will include:

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III- Background and Rationale:

The impressive gains in childhood cancer cure rates have led to an obligation to assess long-term complications that can affect the quality of life in the growing population of survivors. Outcome studies suggest that, compared to their siblings and normative populations, survivors are more likely to live with their parents as adults [1], need special education services [2], have lower educational attainment [3], and not to marry [4]. One model hypothesized in the literature is that these failures in adaptive functioning are due to observed changes in neurocognitive functioning, particularly problems in executive functioning. Executive functioning, the bringing together and coordinating of information for a purpose, is a multifaceted process with at least two clearly identified elements: attention and working memory. Additionally or even alternatively, these problems in adaptive functioning may be largely caused by psychological distress. It is key to know the relative contribution of psychosocial and neurocognitive factors to determine how to best design interventions to improve adaptive functioning outcomes.

Several treatment exposures have been associated with impaired neurocognitive functioning in survivors of childhood cancer. These therapies include cranial radiation, methotrexate, cytarabine, and intrathecal therapy. Histological changes associated with cranial radiation include subacute leukoencephalopathy, mineralizing microangiopathy, and cortical atrophy, most often becoming apparent several months to years after cranial radiation [5-7]. Domains of neurobehavioral impairment after cranial radiation include intelligence, attention, short term memory impairment, distractibility, fine motor

coordination, visual-spatial ability, and somatosensory functioning [8-13]. Patients previously treated with methotrexate without cranial radiation also experience significant declines in attention, verbal and non-verbal memory as well as nonsignificant declines in visual-spatial abilities. Glucocorticoid therapy, another mainstay of many pediatric cancer protocols, has been associated with attentional problems in non-cancer pediatric populations, including premature infants and asthmatics [14, 15]. Intrathecal administration of agents directly into the cerebrospinal fluid may compound neurotoxicity.

Past studies indicate that most long-term survivors of childhood cancer have relatively normal psychological outcomes, but a significant proportion experience debilitating problems in psychosocial adjustment. Zebrack et al. analyzed findings from the baseline questionnaire in the Childhood Cancer Survivor Cohort [16]. He concluded that survivors were more likely than sibling controls to report symptoms of depression and somatic complaints, especially in those who received more intensive therapy. Kornblith et al. administered the Brief Symptom Inventory to 273 adult survivors of Hodgkin Disease and concluded that 22% met the criteria for a psychiatric diagnosis [17]. Psychological distress was particularly marked in the areas of somatization and depression. In a study limited to long-term survivors of adolescent cancer, Lansky et al reported the prevalence of treated depression to be higher than the general population [18]. In her study of ALL patients previously enrolled in Children's Cancer Group cooperative trials, Zeltzer et al. found an elevated incidence of negative mood in survivors. This finding was independent of reported energy level differences, and was most prominent in females and non-white patients [19].

The Childhood Cancer Survivor Study provides a unique opportunity because the Follow-Up survey measured psychological status, neurocognitive functioning, and adaptive outcomes simultaneously in a large sample of childhood cancer survivors. In this proposal, we would like to determine the relative contribution of psychosocial vs. neurocognitive functioning in outcomes of adaptive functioning. We will limit our analysis to survivors of leukemia and lymphoma because 1) this represents the most frequent group of childhood cancers and 2) the chemotherapy agents are similar in terms of those known to cause neurotoxicity.

IV- Specific Aims/Objectives/Research Hypotheses:

A- Primary aim: Determine the relative contribution of psychological status, including post-traumatic growth, and impaired executive functioning to outcomes of adaptive functioning.

B- Hypotheses:

1. Both psychological distress and impaired executive functioning are associated with limited adaptive functioning, but impaired executive functioning will be a more robust predictor.

2. Survivors who have experienced post traumatic growth, or a feeling of enhanced quality of life after their cancer experience, will display better adaptive functioning.
3. There will be an interaction between post-adolescent age at diagnosis and psychological functioning as a predictor of adaptive functioning, i.e. survivors with psychological distress diagnosed as adolescents will experience worse adaptive functioning than those with psychological distress diagnosed as pre-adolescents.

V- Analysis Framework:

1. Outcomes of interest:
 - Marriage status
 - Special education service use
 - Independence in living status
 - Educational status
 - Annual income
2. Study population:
Leukemia, Hodgkin Lymphoma, and Non-Hodgkin Lymphoma CCSS cohort members
3. Predictor variables to be analyzed:
 - a. Executive functioning as measured by the BRIEF (J1-25)
 - b. Psychological distress as measured by the Brief Symptom Inventory (G1-20)
 - c. Post-traumatic stress disorder status as measured by K 1-17
 - d. Personal growth / post-traumatic growth as measured by H1-21
 - e. Other predictor variables appearing to be associated with adaptive living in survivors from previous literature
 - i. Gender
 - ii. Age at diagnosis
 - iii. Current age
 - iv. Intensity of therapy
 - f. We will validate findings of anxiety and depression from BSI with reported antidepressant and anxiolytic use on Q8-9 (history of medications)
4. Analysis:
Univariate and multivariate regression analyses to determine the association between psychological status and executive functioning and the outcomes of altered adaptive functioning, adjusted for factors found to be significant in univariate analyses. We will check for colinearity between predictor facts before constructing our multivariate model.

V. Other considerations

Dr. Kadan-Lottick is working on this proposal as part of her K grant to examine psychosocial and neurocognitive outcomes in leukemia survivors. Dr. Schultz is per primary mentor for the K grant and Dr. Meadows is a co-mentor.

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