CHILDHOOD CANCER SURVIVOR STUDY PROPOSAL

1. TITLE: The psychosocial sequelae of cancer survivorship from leukaemia, brain tumors, Wilms, sarcomas and neuroblastomas diagnosed in infancy versus after infancy.

2. WORKING GROUP AND INVESTIGATORS

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3. BACKGROUND:

Several important studies on childhood cancer survivors’ quality of life and adjustment have been performed from the CCSS database, and impressive progress in understanding the long-term sequelae of childhood cancers has been made by such investigations. Despite these efforts, as yet no study has undertaken to use the CCSS data-base to examine the effects of specific periods in childhood of the onset or diagnosis of cancers for psycho-social sequelae. A major limitation of studies of the psychosocial consequences of childhood cancer is that they usually do not recruit ample numbers of participants to address issues of the potential impact of patient age at onset/diagnosis of specific types of cancer on specific aspects of later child and adult adjustment and quality of life. Our aim in this proposal is to begin to fill this developmental gap in the existing literature based on the CCSS database by focusing on cancers diagnosed and treated in infancy (0 to 2 years) versus the immediate post-infancy period.

The age of the patients at diagnosis was used by Zebrack and his associates in two published CCSS studies which failed to find an age effect on depression in survivors of childhood leukaemia and lymphomas or brain tumors. However, neither study considered cancer in infancy as opposed to cancer at later ages of childhood as a design variable. In developmental science, there is universal consensus that infancy is a special stage in human development that, as different from other identifiable stages of childhood (toddlerhood, middle childhood, adolescence), is associated with specific developmental accomplishments and with particular developmental tasks. For example, the human brain undergoes crucial forms of development and the infant achieves vital developmental tasks such as advances in locomotion, the onset of language and communication, and abstract cognition and symbolization. In a parallel way, following Piagetian theory, the American Heart Association, recently recommended an infancy (birth to 2 years) versus early childhood (2 to 7 years) contrast for analyzing the outcomes of invasive cardiac procedures for children and adolescents.

These developments invoke at least two sets of considerations. First, there is the psychosocial experience of having cancer. Such experience involves the infant’s separation from parent and family, hospitalization, restriction of movement, and so forth that may deprive the infant of the stimulation and social conditions necessary for normal development. In addition, cancer treatment may directly affect the developing CNS not only from the effects of medications and/or radiation.
per se, but potentially also from other associated experiences such as repeated painful complications of therapy administration. Medications may thus affect the CNS leading to identifiable deficits, and they may exert more subtle effects by diminishing or altering children’s adaptive skills (e.g., memory or temperament) for months or years to come. We propose therefore to assess and compare the various impacts of the onset/diagnosis of different forms of cancer during two different periods of human development: infancy (0-2 years) versus the period immediately after infancy (3-6 years).

We believe that the size of the CCSS sample allows us to examine a) type of cancer diagnosis (leukaemia, brain tumors, Wilms, sarcomas, and neuroblastomas); b) treatments (chemotherapy, cranial vs other site radiation); c) relevant individual factors (gender, ethnicity); and d) relevant sociodemographic (SES) factors. We should thus be able to offer empirical answers for our two main questions:

1. How do depression, anxiety, and somatizations as measured by BSI-18 in maturity vary in cancer survivors who were diagnosed at two different early stages of life?
2. How does cognition as measured by academic achievement and mental retardation in maturity vary in cancer survivors who were diagnosed at two different early stages of life?

To address these central developmental questions, we propose to analyze the outcomes which influence the quality of life of childhood cancer survivors. We plan to assess the role of particular cancers at these two stages of early childhood for specific adverse outcomes.

**Anxiety, Depression, and Somatizations Outcomes**

Two reports from the Childhood Cancer Survivor Study used the Brief Symptom Inventory as dependent measure \(^1\)\(^2\). In the first, it was shown that survivors of childhood leukaemia, Hodgkin’s disease, and non-Hodgkin’s lymphoma have more somatic and depressive symptoms than sibling controls. Such symptoms are exacerbated by intensive chemotherapy. Related to the present proposal, age of diagnosis (0-10 years vs. 11 years and older) was significant for somatic distress but not for depression. A study of long-term survivors of childhood brain cancer showed a similar pattern of results, but in this case age (0-4 vs. 5-11) was not a significant factor. However, these studies failed to selectively segregate very young patients (0-2 years) from older ones, thus overlooking the possibly meaningful developmental perspective.

It is also of interest to specifically address the issue of anxiety symptoms, which can be reliably measured by the BSI-18. Infants (as opposed older children) are especially vulnerable to separation anxiety and trauma that is known to affect later development of anxiety in personality. It is well recognized that infants develop secure or insecure attachments in the first 2 years of life, attachments that reverberate in their personality, mental health and social relationships life-long \(^5\). For this reason it would be especially valuable to look at the BSI-18 in conjunction with the age contrasts proposed.

To our knowledge no CCSS report on the BSI-18 outcomes of cancer in infancy as opposed to post-infancy has been published.

**Hypothesis 1** Long-term survivors of leukaemia, brain tumors, Wilms, sarcomas, and neuroblastomas diagnosed at 0-2 years will display more persistent symptoms of psychological malfunctioning (especially anxiety and depression) in maturity compared to long-term survivors of cancers diagnosed in post-infancy years.

**Cognitive Outcomes**
A study for the CCSS data base showed that 23% of the survivors and 8% of siblings were in need of special education services, with the greatest differences observed among survivors who were diagnosed before age 6 years. The type of cancer and of treatment were also significantly associated with the use of special education services. It is of interest, therefore, to assess whether different types of cancer in infancy attenuate achievement later in school or result in greater frequency of mental retardation. It is useful to know which types of cancer may be more debilitating and which aspects of adaptation to school are placed at greater risk (i.e., learning problems versus behavioural problems versus missed school days). Such information may be useful in planning intervention strategies to minimize the effects of cancer in infancy on later developing learning skills.

Hypothesis 2 We expect that survivors of different types of cancer in infancy (0-2 years) will attain lower levels of schooling and will be more likely to require special education services than survivors of cancer diagnosed in the post-infancy years.

4. ANALYSIS FRAMEWORK
   a) **Participant population**: Survivors of cancer in childhood (≤ 18 yrs of age at time of onset or diagnosis of cancer) defined into specific ages of diagnosis (0 to 2, 3 to 6 years).
   b) **Comparison groups**: Survivors of cancer diagnosed at infancy (0-2 years) versus preschool (3-6), and their sibling controls.
   c) **Example outcomes of interest**
      Depression, anxiety and somatizations
      Three numerical dependent variables (mean scores) will be used as identified by Zebrack et al: Anxiety (J20,24,32,33,34), Depression (J19,21,22,23,25,30,35) and Somatization (J16,17,18,26,27,28,29,31).
      Cognition
      Four categorical variables will be examined: Highest degree or level of schooling (O1,O2), Special Education (present vs absent, O4), Motivation for special education program (O3), Mental retardation (J3)
   d) **Independent variables**
      Age at diagnosis: infancy (0-2 years), preschool (3-6)
      Gender: female, male
      SES
      Ethnicity
      Diagnosis – leukaemia, brain tumors, Wilms, sarcomas and neuroblastomas.
      Treatment – We intend to treat separately the direct effects of therapy on CNS and the effect of therapy globally. From the CCSS database we propose to create 2 variables: 1. CNS direct treatment, composed by cranial radiation, intrathecal therapy and CNS surgery; 2. Therapy which may have a significant psychological impact, composed by therapy duration, disfiguring surgeries, radiation therapy (all or part the brain versus other sites), bone marrow transplant.
      SES
   e) **Data analysis plan**

<table>
<thead>
<tr>
<th>Age at dx</th>
<th>Leuk</th>
<th>CNS</th>
<th>Wilms</th>
<th>NBL</th>
<th>STS</th>
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<tbody>
<tr>
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<td>366</td>
<td>597</td>
<td>791</td>
<td>270</td>
</tr>
<tr>
<td>3-6</td>
<td>2002</td>
<td>505</td>
<td>545</td>
<td>116</td>
<td>287</td>
</tr>
</tbody>
</table>
Table 1 reports the cases on which reliable statistical analyses can be done. (HD, NHL, and Bone are not considered in the proposed analyses, due to the small cell sizes for infants)

The first steps in data analysis will be: to score any variables that need summing or combining in any way and to create subsets of data that are specific to different ages of diagnosis.

The second step will be to report basic descriptive statistics of all critical variables by different age groups. Depending upon the distributions, some measure may be eliminated from further analyses.

The ultimate analyses will look at anxiety, depression, somatizations and highest level of schooling, special education, motivation, and mental retardation in seriatim as dependent measures in hierarchical linear and logit regression analyses with other non-age variables and later age variables entered before infancy diagnoses.

The CCSS Statistical Center will carry out the statistical analyses

REFERENCES


