

CHILDHOOD CANCER SURVIVOR STUDY Analysis Concept Proposal

Revised January 6, 2005

- 1. **Title:** The risk of adverse bone outcomes among long-term survivors of childhood cancer
- 2. **Working Group and Investigators:** This proposed publication will be within the Chronic Disease Working Group. Proposed investigators include:

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3. **Background and Rationale:**

Survivors of childhood cancer may be at increased risk for the debilitating bone processes of osteoporosis and osteonecrosis (also referred to as avascular necrosis). These conditions represent different pathophysiological phenomena, but can both result in considerable morbidity because of the associated pain, immobility, financial burden, and risk of related serious medical complications.

Treatment of childhood cancer is associated with numerous processes that may be disruptive to normal bone metabolism during childhood and adolescence. Bone mass may be impaired by poor nutritional intake and decreased physical activity. Chemotherapeutic agents such as corticosteroids and methotrexate have been shown to adversely affect bone mineral density in small cross-sectional and longitudinal studies of patients still receiving therapy or only a few years after the completion of therapy. In several small studies, cranial radiation has been associated with osteopenia that can persist for many years after treatment, presumably because of growth hormone and sex hormone deficiencies. Similarly, steroid therapy and radiation therapy have been associated with avascular necrosis. In patients with high risk acute lymphoblastic leukemia, girls who are treated during adolescence are at greatest risk for this outcome.

The magnitude and extent of osteopenia/osteoporosis and osteonecrosis have not yet been established in a large sample of long-term childhood cancer survivors. The Childhood Cancer Survivor Study (CCSS), because of its retrospective cohort study design and large sample size, provides an unprecedented opportunity to evaluate these bone conditions. Using the Follow-Up 2 data, the goal of this analysis is to describe the prevalence of (1) osteopenia/osteoporosis and (2) osteonecrosis in the CCSS cohort, as well as to identify patient and treatment characteristics that are associated with increased risk. Such an analysis will determine the importance of previously described risk factors and potentially identify unrecognized risk mediators. Frequencies of reports of osteopenia/osteoporosis, osteonecrosis, and fractures in childhood cancer survivors will also be compared to that of

sibling controls to determine if there is excess beyond that which would be expected. Conclusions from such an analysis can be used to decide which childhood cancer survivors should be targeted for screening bone mineral density, presence of osteonecrosis, and possible pharmacological prophylaxis/therapy

*Because osteopenia and osteoporosis are both usually sub-clinical conditions, they can not be distinguished from each other reliably by self-report. Therefore, they are mentioned together in the questionnaire and will be analyzed together in this analysis.

4. Specific Aims

This project is designed to provide a comprehensive descriptive analysis of osteopenia/osteoporosis and osteonecrosis reported among the childhood cancer survivors in the CCSS. Specifically, we plan to do the following:

- a) Determine the prevalence of osteopenia/osteoporosis reported in the CCSS cohort, overall and by diagnostic subcategories.
- b) Determine the prevalence of osteonecrosis reported in the CCSS cohort, overall and by diagnostic subcategories
- c) Identify patient and therapy characteristics that affect the risk of osteopenia/osteoporosis and osteonecrosis
- d) Determine the incidence of fractures reported in the CCSS cohort, overall and by diagnostic subcategories.
- e) Determine the frequency of osteopenia/osteoporosis, osteonecrosis, and fractures among childhood cancer survivors compared to their sibling controls.

5. Hypotheses:

- a) Childhood cancer survivors are at increased risk for osteopenia/osteoporosis and osteonecrosis compared to their sibling controls.
- b) Childhood cancer survivors will have a greater risk of osteopenia/osteoporosis if they have the following characteristics:
 - i. Increasing dose of radiation to the hypothalamus/pituitary regions (<24 Gy vs \geq 24Gy)
 - ii. Ovarian failure (as already classified by Dr. Sklar from review of the data)
 - iii. Increasing dose of testicular radiation (<20 Gy vs > 20Gy)
 - iv. Increasing dose of thyroid radiation (<20 Gy vs >20Gy)
 - v. History of steroid therapy. Within steroids, we hypothesize that past therapy with dexamethasone (vs. prednisone or methylprednisilone) therapy confers greater risk.
 - vi. History of methotrexate therapy
 - vii. Post-pubertal age at diagnosis
 - viii. Caucasian race
 - ix. Female gender
 - x. Less physical activity (D1-D7)
- c) Childhood cancer survivors will have a greater risk of osteonecrosis if they have the following characteristics:
 - i. Post-pubertal age at diagnosis

- ii. History of steroid therapy. Within steroids, we hypothesize that past therapy with dexamethasone (vs. prednisone or methylprednisilone) therapy confers greater risk.
- iii. Female gender
- iv. Previous radiation to affected site
- v. History of alcohol use

6. Analysis Framework:

- a) Outcome of interest:
 - i. Primary: History of osteopenia/osteoporosis (P1), History of osteonecrosis (P4)
 - ii. Secondary: History of fractures (A4 medical care in last 2 years, baseline surgical section), history of medication for osteopenia/osteoporosis or osteonecrosis (P2, P3, P5, P6)
- b) Subject Population: All CCSS cases.
- c) Explanatory variables:
 - i. Radiation dose: continuous variable representing direct radiation to that site
 - whole brain
 - hypothalamus/pituitary (segment 2 of brain)
 - ii. Radiation dose: categorical variable (for the following sites, direct radiation dose is expressed as one of the following categories: no radiation anywhere, no direct radiation to site of interest, 1-999 cGy, 1000-2499 cGy, 2500-3499 cGy, 3500-4499 cGy, 4500-5499 cGy, >5500 cGy)
 - Ovaries. The CCSS database already contains ovarian dose estimates for almost all females >18 yr treated with RT
 - testes (in males, treatment to pelvis)
 - thyroid (from neck, full spine, and total body treatments)
 - extremities affected by osteonecrosis for reported instances of osteonecrosis
 - iii. history of corticosteroids (yes/no and individual preparations)
 - iv. history of methotrexate
 - v. cumulative alkylator score
 - vi. history of cyclosporine therapy (open field medication section)
 - vii. gender
 - viii. race
 - ix. age at diagnosis
 - x. elapsed time since diagnosis
 - xi. cigarette smoking (N.1)
 - xii. alcohol use (N.3)
 - xiii. body mass index
 - xiv. calcium supplement use
 - xv. vitamin D use
 - xvi. estrogen replacement
 - xvii. physical activity (N.9)
 - xviii. history of growth hormone replacement
 - xix. history of testosterone replacement.
 - xx. history of hyperthyroidism or hypothyroidism

d) Analyses:

- i. Prevalence of osteopenia/osteoporosis and osteonecrosis reported by CCSS participants, overall and stratified by patient and therapeutic characteristics.
- ii. Case-Case Analyses
 1. Univariate regression of the explanatory variables described above
 2. Multiple Poisson regression of the factors found to be significant in univariate analysis.
 3. Interactions to be tested: gender and age at diagnosis, steroids and cranial radiation, therapy and age at diagnosis
- iii. Case-Control Analysis: multiple logistic regression adjusted for age, race, and gender.
- iv. Other: If cranial radiation is confirmed as a risk factor, the role of growth hormone deficiency, hypothyroidism, and hypogonadism (including secondary ovarian failure) will be examined, presumably as events in the causal pathway of the outcome of interest.

7. Special Considerations:

Because osteoporosis is often a sub-clinical condition, we recognize that the prevalence of osteopenia/osteoporosis may be under-estimated by self-report in the CCSS cohort. Though cases were not directly asked about fractures, we are likely able to get fracture data from other open questions in the FU2 and baseline questionnaires, as described above. Due to ascertainment bias (subjects more likely to get bone mineral studies compared to controls), the relative risk in subjects may be over-estimated. Despite this limitations (which will be clearly stated in any manuscripts emerging from this analysis), we are keen to proceed with this analysis because CCSS data will provide the best available data regarding the burden of these adverse bone outcomes in survivors and help better delineate the groups at greatest risk.