Childhood Cancer Survivor Study
Analysis Concept Proposal

**Title:** Long-Term Survivors of Childhood Osteosarcoma

**Working Group:** Chronic Disease Working Group

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**Background and Rationale:**

One particular group of childhood cancer survivors with potentially increased sequelae are adult survivors of pediatric osteosarcoma.[1] Children diagnosed with osteosarcoma often require extensive surgical intervention (amputation or limb sparing procedures), and are exposed to significant amounts of chemotherapy. Evidence of the surgical treatment can be quite noticeable because bone tumors predominantly occur in the extremities (lower > upper). [2] Disfigurement or dysfunction related to muscle and bone loss or amputation may interfere with everyday physical function and may alter self image. Additionally, the intensive chemotherapy (and/or radiation therapy) may alter cellular structure and organ function resulting in cardiac impairments, fertility problems, second cancers, etc[3]... and have a lifelong impact on daily living. The impact these treatments have on an individual are compounded by varying levels of emotional maturity (pre-adolescence and adolescence) and skeletal maturity of the child at the time of diagnosis. Emotional maturity may play an important role in psychosocial functioning because of one’s development of body image, independence and relationships during adolescence. Skeletal maturity is another potential determinant of psychosocial sequelae because of its importance in determining the type of
surgical local control (amputation/rotationplasty/expanding prosthesis vs. limb sparing surgeries) which can alter one’s body image and infringe on self-reliance.

**Specific Aims/Objectives/Research Hypotheses:**

This study will use data from the Childhood Cancer Survivor Study (CCSS) to determine survival rates, rates of relapse, late mortality, late medical complications, and socioeconomic (education, marriage, employment, insurance) factors in survivors of childhood osteosarcoma.

**Hypotheses:**

1) Overall and event-free survival will be significantly lower among survivors of childhood osteosarcoma compared to the general U.S. population.

2) Survivors of childhood osteosarcoma therapy will experience significant late morbidity compared with a sibling control group (i.e. early cardiovascular disease, endocrine disorders, second cancers, etc.)

3) Survivors of childhood osteosarcoma will be less educated, and less likely to be employed, have insurance coverage, or be married than the sibling control group and the general population.

4) Survivors of childhood osteosarcoma will have increased disability and increased physical limitations compared to the sibling control group.

**Analysis Framework:**

A. Subject population:
   1. all osteosarcoma survivors in the CCSS cohort who have survived 5 years from diagnosis (733 have completed a baseline, 552 have completed Follow-up1 and 488 have completed Follow-up2),
   2. all eligible siblings
   3. U.S. Census Bureau data

B. Outcomes of interest: (see table of variables)
   1. Survival rates
   2. Medical Complications:
      a. Hearing
         i. Baseline: C4 (tinnitus), C5 (vertigo) and Composite of C1 (hearing aid), C2 (deafness not corrected), and C3 (deafness corrected)
         ii. Follow-up 1: Composite of 12a (hearing aid), 12b (deafness not corrected), 12c (deafness corrected)
      b. Kidney function: D4 (dialysis) from Baseline
      c. Fertility
         i. Low Sperm Count: E15 from Baseline
ii. Have you ever had a menstrual period: E16 from Baseline and 19 from Follow-up 1
iii. Pregnancy: M9 from Baseline and 8 from Follow-up 1

d. Cardiovascular
   i. Coronary Artery Disease: Composite of F2, F5, F6, F10 from Baseline
   ii. Coronary Artery Disease: Composite of 10b, 10e, 10f, 10h from Follow-up 1
   iii. Congestive Heart Failure: F4 from Baseline

e. Pulmonary
   i. Lung Fibrosis: Baseline G12
   ii. Lung Fibrosis: Follow-up 1 111
   iii. O2 need: Baseline G9
   iv. O2 need: Follow-up 1 111

f. Surgery Frequencies
   i. Amputation: Baseline I1, Follow-up 1 21
   ii. Leg shortening: Baseline I4
   iii. Joint Replacement: Baseline I5
   iv. Other bone surgery: Baseline I6

g. Bone Health: Follow-up 2: Section N

3. Second Cancers:
   a. Baseline: section K
   b. Follow-up 1: question 17
   c. Follow-up 2: section R

4. Education:
   a. Baseline: section O, questions 1-4
   b. Follow-up 1: question 1
   c. Follow-up 2: question 1

5. Employment:
   a. Baseline: section O, questions 5-11, section Q, questions 8, 9
   b. Follow-up 2: question 3
   c. Follow-up 3: questions 4, 5, 6

6. Insurance:
   a. Baseline: section Q, questions 1-6
   b. Follow-up1: question 16
   c. Follow-up 2: section M

7. Marriage:
   a. Baseline: section L
   b. Follow-up 1: question 2
   c. Follow-up 2: questions 2 and 3

8. Pregnancy history:
   a. Baseline: section M
   b. Follow-up 1: question 8
   c. Follow-up 2: section N

9. Physical Disability
   a. Baseline: N10 and N11
   b. Follow-2: SF-36 - Role Physical
10. Physical Limitation
   a. Baseline: N12, N14a, N14b, N14c, N14d, N14e
   b. Follow-2: SF-36 - Physical Function

C. Explanatory variables: (see table of variables)
   1. Age at cancer diagnosis
   2. Age at response to CCSS questionnaire
   3. Time from diagnosis
   4. Gender
   5. Type of treatment (chemotherapy, radiation, surgery) – Yes/No
   6. Type and cumulative doses of chemotherapy
      a. Anthracycline Yes/No
      b. Anthracycline <300 or > 300 mg/m2
      c. Cisplatinum Yes/No
      d. Alkylator use
         i. Cytoxan
            1. Yes/No
            2. <5gm. 5-10 gm, and > 10gm
         ii. Ifosfamide
            1. Yes/No
            2. <30gm, 30-60gm, and >60 gm
   7. Radiation site and dose
      a. Site: Pelvis, abdomen, thorax/lung, arm, leg, head/neck
         i. Yes/No to site
         ii. Dose: Gross doses (<2000, 2000-4000, >4000)
   8. Types of surgery
   9. Site of disease

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<thead>
<tr>
<th>Dependent and Outcome Variables</th>
<th>Outcome Variables</th>
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<tbody>
<tr>
<td>Dependent Variable</td>
<td>Medical Complications</td>
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<tr>
<td>Age at Cancer Dx</td>
<td>Baseline: Section C (Hearing)</td>
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<td>Age at questionnaire</td>
<td>Baseline: Section D (Urinary)</td>
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<tr>
<td>Gender</td>
<td>Baseline: Section E (Hormonal)</td>
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<tr>
<td>Type of Treatment (chemo/XRT/surgery)</td>
<td>Baseline: Section F (cardiovascular)</td>
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<tr>
<td>Type and cumulative dosages of chemotherapy</td>
<td>Baseline: Section G (Pulmonary) Baseline: Section H (Gl)</td>
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<tr>
<td>Radiation (site and dose)</td>
<td>Baseline: Section I (Surgical)</td>
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<td>Types of Surgery</td>
<td>Follow-up 1: Question 9 (medical condition)</td>
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<td>Site of Disease</td>
<td>Follow-up 1: Question 10 (cardiovascular)</td>
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<td>Follow-up 1: Question 11 (Respiratory)</td>
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<td>Follow-up 1: Question 12 (Hearing)</td>
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<td>Follow-up 1: Ovarian failure and menopause data</td>
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<td>Follow-up 2: Section N (bone health)</td>
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Second Cancers
D. Analysis Plan:
1. Descriptive Epidemiology/Summary statistics:
   a. Characteristics of osteosarcoma survivors and siblings will be described using frequencies, means (SD) or medians (range).

2. Survival Analysis:
   a. Standardized mortality ratios (SMR) (observed number of deaths divided by the expected number) and their 95% confidence intervals will be calculated. SMR will be calculated using age- and sex-specific United States mortality rates, reported by the National Center for Health Statistics. Patients will be grouped by age into 5-year intervals. (Yausai) All-cause SMRs and cause-specific SMRs for secondary or subsequent cancer (ICD 140 to 239), cardiac causes (ICD 390 to 398, 402, 404, 410 to 429), pulmonary causes (ICD 460 to 519), external causes (accidents, suicides, poisonings, and so on; ICD 800 to 999), and other causes (all other ICD codes) will be computed for all deaths. (Only deaths with known causes not due to recurrence of the original cancer will be included).
   b. Overall survival and event-free survival will be analyzed from the 5th and 10th anniversary dates of diagnosis with the life table method (Kaplan-Meier curves). Survival curves for this cohort will be compared with the comparable United States population, based on the United States age- and sex-specific mortality rates. An expected number of deaths for each year since diagnosis will be calculated based on US age and sex specific mortality rates, yielding and expected survival function for each sex.(Le)
   c. Cumulative incidence of relapse, SMN, pulmonary complications, cardiovascular complications and death during remission will be calculated, treating death prior to the event of interest or relapse, as appropriate, as competing risk events. Hazard ratios for these outcomes comparing the osteosarcoma survivors and siblings will be calculated with Cox proportional hazards regression adjusted for age at diagnosis, and gender, race, treatment era and site of disease.

3. The chi-square test of independence (or Fisher’s exact test if expected frequencies are less than 5) will be used to compare proportions of medical complications, educational levels, physical limitations and disability, employment status, insured status, marital status of cases, siblings, and the general population. (Breslow & Day)

4. Multiple logistic regression, log linear regression, or Poisson regression will be used to compare rates of medical complications, physical limitations and disability, educational
levels, employment status, insured status, marital status between cases and siblings. (Homer & Lemeshow) adjusted for current age, age at diagnosis and gender.

5. Multiple logistic regression, log linear regression, or Poisson regression will be used to compare rates of medical complications (cardiovascular, pulmonary and fertility), and physical limitations/disability between those that received radiation and those who did not (Homer & Lemeshow) adjusted for current age, age at diagnosis and gender and site of disease.

6. Multiple logistic regression, log linear regression, or Poisson regression will be used to compare rates of hearing and kidney complications between those that received cisplatinum and those who did not (Homer & Lemeshow) adjusted for current age, age at diagnosis and gender and site of disease.

7. Multiple logistic regression, log linear regression, or Poisson regression will be used to compare rates of medical complications (cardiovascular and fertility) and physical limitations/disability between those that received anthracyclines and those who did not (Homer & Lemeshow) adjusted for current age, age at diagnosis and gender and site of disease.

8. Multiple logistic regression, log linear regression, or Poisson regression will be used to compare rates of medical complications (fertility) between those that received alkylators and those who did not (Homer & Lemeshow) adjusted for current age, age at diagnosis and gender and site of disease.

E. Tables and Figures:

1. Demographic table of CCSS osteosarcoma cases and siblings(if applicable):
   - sex
   - diagnosis
   - site of disease
   - age at diagnosis
   - age at follow-up
   - treatment
     - Radiation
     - Chemotherapy
     - Surgeries
   - treatment era
   - medical complications

2. Survival curves: overall survival, overall survival vs US population
3. SMR tables
4. Table of frequencies of medical outcomes and SMNs
5. Cumulative incidence curves: late medical outcomes (cardiovascular, pulmonary, hearing, kidney), second cancers
6. Tables: educational attainment, employment status, insurance status, marital/family status demonstrating frequencies and rates of each of these social indicators compared to the sibling control group and national data

7. Table: Physical disability and physical limitations compared to sibling control group

**Special Consideration:**
This concept proposal is submitted in response to the CCSS steering committee’s request for disease-focused initiatives within the CCSS cohort.

