02-14

# CCSS Analysis Concept Proposal

1. **Title: A Cautionary Note in the Analysis of Second Malignant Neoplasm Risk in Long-Term Survivors of Childhood Cancers** (open to alternative title suggestions)

2. **Working group/Investigators:** This analysis will be conducted under Epidemiology/Biostatitsics Working Group with the following investigators:


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|---|---|---|
| Yutaka Yasui | yyasui@fhcrc.org | 206-667-4459 |
| Yan Liu | yanliu@fhcrc.org | 206-667-7408 |
| Joe Neglia | jneglia@tc.umn.edu | 612/626-2778 |
| Deb Friedman | dfried@chmc.org | 206-526-2106 |
| Smita Bhatia | SBhatia@coh.org | 626-301-8426 |
| Anna Meadows | meadows@email.chop.edu | 215-590-2804 |
| Ann Mertens | mertens@epi.umn.edu | 612-626-2187 |
| John Whitton | jwhitton@fhcrc.org | 206-667-6895 |
| Les Robison | robison@epi.umn.edu | 612-626-2902 |
| Anyone else? | | |


3. **Background and Rationale:**

Second malignant neoplasms (SMN) are a major late-effect of concern for long-term survivors of childhood cancer and their physicians. Understanding SMN risk after childhood cancers based on patients' demographic characteristics and primary-cancer types/therapies is critical in order for clinicians to provide appropriate follow-up care for the survivors as well as to potentially improve treatment protocols. Large long-term follow-up studies of childhood-cancer survivors such as Childhood Cancer Survivor Study (CCSS) and Late Effects Study Group (LESG) project aim to assess SMN risk after childhood cancers as one of their major research goals.

This paper is concerned with a methodological issue in such assessments of SMN risk in long-term follow-up studies. To make our discussion concrete, consider breast-SMN risk in female survivors and its potential association with ages at diagnosis of childhood cancers as an example. The association may be hypothesized based on the notion that exposures to chest radiotherapies during puberty, when breast cells are undergoing high mitotic activity, could increase relevant mutation rates, thereby increase subsequent breast-cancer risk. Using a popular approach to rate-ratio evaluations in follow-up studies, namely, Cox regression, a report from LESG found a significant modification of breast-SMN risk by age at diagnosis of Hodgkin disease, a finding consistent to the above hypothesis. In contrast, a report from CCSS used Poisson regression of standardized incidence ratios (SIRs) and found no association of breast-SMN

risk with age at diagnosis of childhood cancers (Neglia et al., 200?). The aim of this paper is to elucidate methodologically why the two reports came to different conclusions and illustrate the importance of accounting for certain study aspects unique to long-term follow-up studies of childhood-cancer survivors.

**4. Specific Aims/Objectives:**

- Describe the two analysis methods of long-term follow-up data for SMN risk for clinicians
- Contrast the differences between the two methods clearly with real-data examples from the CCSS and LESG
- Expand the difference explanations to regression settings (Cox vs. Poisson SIR analyses) with real-data illustrations from the CCSS and LESG

**5. Analysis Framework:**

Our analysis will focus on the association of breast SMN risk with age at diagnosis of the original cancer.

Datasets: We will use the CCSS baseline data (June 2002 version) and updated LESG data for illustration. We will use only females.

Outcomes of interest: Breast SMN (malignant)

We will first calculate rates of breast SMN among females in the two datasets stratified by age at diagnosis of the original cancer. We will then calculate the standardized incidence ratios (SIRs), stratified by the age at diagnosis, using the SEER registry data as the reference. The rates and SIRs are shown graphically to contrast the two approaches.

We will explain the cause of the differences between the two approaches using the age-incidence curve of breast cancer from the SEER registry and state the importance of accounting for the age-associated rise in the risk of breast cancer in the general population, when assessing breast SMN risk by age at diagnosis.

Finally, we will estimate the rate-ratio parameters associated with the age-at-diagnosis effects using regression methods, contrasting the estimates from the Cox regression with those from the Poisson regression.

Throughout the paper, the focus will be on a scientific question "whether or not there is an increased risk of breast SMN for girls diagnosed with Hodgkin disease or other childhood cancers during puberty, compared to those diagnosed outside of puberty?"

Special consideration: Clarity of exposition and its appropriateness to clinical audience will be emphasized during the writing of this manuscript.