

**CHILDHOOD CANCER SURVIVOR STUDY
Analysis concept proposal**

1. TITLE Predictions of second malignant neoplasm incidence in a large cohort of long-term survivors of childhood cancers

2. WORKING GROUP AND INVESTIGATORS:

The proposed study will be carried out under the Epidemiology and Biostatistics Working Group. Proposed investigators include:

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3. BACKGROUND:

Second Malignant Neoplasms (SMNs) occurring after successful initial therapy for childhood cancer are a well-recognized event. Neglia et al. reported in 2000 that 314 SMNs were identified in 298 individuals among 13581 CCSS survivors. The standard incidence ratio (SIR) was 6.38 (95% CI 5.69 ~ 7.13) compared to the general population (1). The incidences of SMNs are expected to increase as we extend the CCSS follow-up of the cohort. For example, the total cumulative number of the second breast cancer cases was 95 in the January 2002 follow-up survey, whereas it was only 60 in June 2000 in the baseline data. The incidence rates jumped more than 50% in less than two years (2).

The prediction of SMN incidence is important in multiple ways. It will help us to plan future CCSS activities. It will inform the patients and clinicians of the types of second cancer that are of concern in terms of prevention and diagnosis. The statistical models built in this study will also aid the future CCSS study, budget estimation and research application.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

Predict future SMN incidence in the CCSS cohort by survivor characteristics (such as gender, radiation therapy, primary diagnosis and so on), calendar year, and the types of SMN.

5. ANALYSIS FRAMEWORK:

We will first describe the baseline data by calculating the number of cases and the incidence rates (per 100,000 person years) of SMNs stratified by gender, age at primary diagnosis and years since study entry (five years post diagnosis) (table 1). We will then build models to predict the SMN incidences and rates stratified by gender and calendar year. The model we propose is the age-cohort model, an extension to the model proposed by Breslow and Clayton (4), and Berzuini and Clayton (5). We will use the Bayesian approach with autoregressive smoothing of the cohort trend parameter.

The explanatory variables will include the radiation therapy (yes/no) and primary diagnosis. In making predictions we have to assume that current (and past) trends continue into the future. To examine the predictive performance of the models, we will compare predicted SMN numbers and rates to the observed in the follow-up data of June 2002 or later if available (table 2).

After the model is decided, we will predict the incidences and the rates (with their 95% confidence intervals) for all SMN and separately for some specific types of SMN (table 3) by survivor characteristics.

Table 1: Number of cases and rates (per 100,000 person years) of SMNs in CCSS baseline data:

Sex	Age at dx	Years Since 5 th Anniversary of DX						
		0-3	4-7	8-11	12-15	16-19	20-23
M	0-3	# of cases (rate)						
	4-7							
	8-11							
	12-15							
	16-19							
							
F	0-3							
	4-7							
	8-11							
	12-15							
	16-19							
							

Table 2: Comparing the observed and predicted number of SMN cases and rates

Sex	Data	Observed		Predicted (95% CI)	
		N	Rates	N	Rates
M	Baseline			x	x
	FU by 06/2002				
	FU 07/2002-12/2003				
	...(if available)				
F	Baseline			x	x
	FU by 06/2002				
	FU 07/2002-12/2003				
	...(if available)				

Table 3 Prediction of the SMN

Sex	Data	SMN Prediction**	
		N	Rates
M	2004-2005		
	2006-2007		
	2008-2009		
	2010-2011		
F	2004-2005		
	2006-2007		
	2008-2009		
	2010-2011		

**** We will generate this type of tables for all SMN, and some specific second cancers separately such as second breast cancer, CNS, thyroid, leukemia, bone cancer.**

6. REFERENCE

1. Neglia JP, Friedman DL, Yasui Y, Mertens AC, Hammond S, Stovall M, Donaldson SS, Meadows AT and Robison LL (2001) Second malignant neoplasms in five-year survivors of childhood cancer: Childhood Cancer Survivor Study, *J Natl Cancer Inst* 93: 618-29
2. Kenney LB, Diller L, Friedman D, Neglia J, Yasui Y, Mertens A, Inskip P, Meadows A and Robison LL (2002) Risk factors for breast cancer (BC) in women from the Childhood Cancer Survivor Study (CCSS). 7th International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer (Niagara-on-the-Lake), 2002, Oral Presentation
3. Bray I, Brennan P, and Boffetta P (2001) Recent trends and future projections of lymphoid neoplasms – a Bayesian age-period-cohort analysis, *Cancer causes and Control* 12: 813-820
4. Breslow NE and Clayton DG (1993) Approximate inference in generalized linear mixed models. *Journal of the American Statistical Association*:88(421):9-25
5. Berzuini C., Clayton DG (1994) Bayesian analysis of survival on multiple time scales, *Statistics in Medicine*, 13:823-838