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**CHILDHOOD CANCER SURVIVOR STUDY****Analysis Concept Proposal**

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1. **Title:** Dental health 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 are at risk for increased dental abnormalities related to their primary disease and therapy. Numerous studies have investigated the immediate effects of chemotherapy and/or radiation on the oral mucosa and other perioral soft tissues, but few have addressed late dental sequelae of cancer treatment received at an early age. The purpose of this study is to describe the types and frequencies of altered dental development in pediatric patients who have survived childhood cancer.

Many of the chemotherapy agents used to treat childhood malignancies disrupt tooth formation <sup>[1, 2]</sup>. The known long-term effects associated with chemotherapy include

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agenesis, microdontia, root stunting, enamel hypoplasia, and alteration of facial growth. Previous reports have observed treatment-related hypodontia, microdontia, enamel hypoplasia, root stunting, taurodontia, over-retention of primary teeth, and an increased caries index in survivors of childhood cancer<sup>[3-6]</sup>. Impaired root development decreases the growth of alveolar bone, thus impairing the vertical development of the mandible and the lower third of the face<sup>[7]</sup>. Other reported adverse sequelae include malocclusion<sup>[8]</sup>, narrowing of the pulp canal<sup>[9]</sup>, and reduced temporomandibular joint mobility<sup>[10]</sup>.

Alteration of odontogenesis by high dose chemotherapy or radiation in the context of hematopoietic stem cell transplantation can also result in dental problems including hypodontia. Furthermore, post transplant complications such as graft versus host disease has also been implicated in adverse oral outcomes<sup>[11-15]</sup>. However, hypodontia is a common occurrence in the healthy population, with a reported incidence of 35%<sup>[4]</sup>. When third molars are excluded, hypodontia rates of 2.2%-10.1% have been reported; the maxillary lateral incisor and mandibular second premolar are the teeth most commonly affected<sup>[16-19]</sup>. Though dental abnormalities often occur in the general population as a result of genetic inheritance or as part of a syndrome, the frequency of microdontia, taurodontia, and enamel pearls have reportedly been increased in childhood cancer survivors<sup>[1, 4-6, 9]</sup>.

In the evaluation of factors that lead to dental complications from cancer therapy, consideration of elements which affect the population at large must be taken into account. Access to medical and dental care has previously been shown to affect overall health and be related to socioeconomic factors<sup>[20-22]</sup>. Specifically, socioeconomic status has been shown to correlate to poor oral health. Thus, in addition to causations for dental abnormalities described above, the socioeconomic issues also need to be studied to understand their impact on dental care and oral health.

4. **Specific Aims:** This proposed project is designed to provide a comprehensive analysis of dental abnormalities reported among childhood cancer survivors in CCSS as detailed within the designated section of the Follow-up2 survey. Specifically, we plan to do the following (aims d and e will be analyzed and published in a separate manuscript):

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- a. Determine the prevalence of dental abnormalities in the CCSS cohort, overall and by diagnostic subcategories. Specific dental abnormalities will include: microdontia (question O-3), hypodontia (O-1), caries in excess of 5 (O-8), root stunting (O-4), enamel hypoplasia (O-2), severe gingivitis (O6, 9), tooth loss of at least 6 teeth (O-6, 11), use of a dental bridge and/or dentures (O-10, 11), oral prosthesis (O-12), xerostomia (O-1 to 15).
- b. Identify patient and therapy characteristics that affect the risk of developing dental abnormalities
- c. Determine the frequency of dental abnormalities among childhood cancer survivors compared to the CCSS sibling controls.
- d. Determine survivor access to and use of dental and orthodontic care in the CCSS cohort (O-15 to 19; LTFU-2 [A6, M2] ).
- e. Estimate access to and predictors of dental insurance coverage of survivors (O16-19).

## **5. Hypotheses:**

- a. Childhood cancer survivors are at increased risk for dental abnormalities compared to their sibling controls.
- b. Childhood cancer survivors with the following characteristics will have a greater risk of dental abnormalities:
  - i. Head and neck irradiation
  - ii. Treatment at younger ages
  - iii. Received chemotherapy (specifically glucocorticoids, cyclophosphamide and vincristine)
  - iv. Underwent bone marrow transplantation
- c. Access to dental care for childhood cancer survivors will be influenced by availability of dental insurance (O-16). Those with dental insurance will be more likely to seek dental care and will do so more often (O-16, 17, 18, 19).

## **6. Analysis Framework:**

- a. Outcome of interest:

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- i. Primary: History of dental abnormality (O1-19.)
- ii. Secondary: Availability of dental insurance, socioeconomic status, association with smoking
- b. Subject population: All CCSS cases and siblings
- c. Exploratory variables: (A 1-4 LTFU-1)
  - i. Age at diagnosis
  - ii. Age at completion of LTFU survey (elapsed time since diagnosis)
  - iii. Primary diagnosis
  - iv. Gender
  - v. Race
- d. Analyses:
  - i. Overall and age-specific prevalence rates of dental abnormalities reported by CCSS participants, overall and stratified by patient and therapeutic characteristics
  - ii. Case-case analyses
    1. Univariate regression of the exploratory variables listed 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, chemotherapy and head and neck radiation therapy, therapy and age at diagnosis
  - iii. Case-control analysis: multiple Poisson regression adjusted for age, race, and gender
  - iv. If socioeconomic status is confirmed to be a risk factor for the use/access to dental care and insurance, then analysis of dental abnormalities to socioeconomic level will be explored (S 1-3 LTFU-2; M-1 LTFU-2; O 5-11 LTFU-1)

## **7. Special Considerations:**

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Due to ascertainment bias (subjects more or less likely to seek dental follow-up than controls), the relative risk may be over- or underestimated. Further, the availability of dental insurance coverage for this cohort may affect their access to dental care. Such insurance may also be related to socioeconomic status and type of employment of the patient and/or parent-guardian. We should be able to obtain socioeconomic data from the CCSS database. Despite these limitations, we are anxious to proceed with this analysis as the CCSS dataset will provide the best and most comprehensive resource available to assess the frequency and burden of these adverse dental sequelae on childhood cancer survivors. Such information is crucial to identify groups at greatest risk and for the design of prospective interventional studies. Behavior tendencies such as smoking and tobacco use can also contribute to poor oral hygiene. We have the opportunity of investigating this relationship through the LTFU database (N1-2 LTFU-1; L1-6 LTFU-2).

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Table \_\_. Patient characteristics

Characteristic	<i>N</i> (%)	Characteristic	<i>N</i> (%)
Age at diagnosis (years)		Age at study	
Median		Median	
Range		Range	
Race		History of dental abnormality	
White		Yes	
Black		No	
Hispanic			
Diagnosis		Treatment with XRT alone	
Brain tumor		Yes	
Leukemia/Lymphoma		No	
Solid tumor			
Other			
Gender		Treatment with chemotherapy alone	
Female		Yes	
Male		No	
		Treatment with chemotherapy and XRT	
		Yes	
		No	



Table \_\_ . Characteristics of sibling cohort.

Characteristic	<i>N</i> (%)
Age at study (years)	
Median	
Range	
Race	
White	
Black	
Hispanic	
Gender	
Female	
Male	
History of dental abnormality	
Yes	
No	

Table \_\_. Comparison of Characteristics between patients and siblings who reported yes versus those reporting no to dental abnormalities

Characteristic	Patients			Siblings		
	Yes N=___	No N=___	p-value	Yes N=___	No N=___	p-value
Gender						
Female						
Male						
Race						
White						
Black						
Other						
Risk Group						
Better						
Worse						
Treatment						
Chemotherapy						
XRT alone						
Chemo + XRT						
Surgery						
Age at Dx in years						
Median (range)						
Mean (SD)						

Table \_\_. Dental abnormalities reported as yes, or no in childhood cancer survivors and siblings.

Dental characteristic	Patients		Siblings		P-value
	Yes	No	Yes	No	
Microdontia					
Hypodontia					
>5 caries					
Root stunting					
Enamel hypoplasia					
Gingivitis					
≥6 teeth lost					
Dental bridge/dentures					
Oral prosthesis					
Xerostomia					



Table \_\_: Characteristics of tobacco use reported of survivor cohort and siblings and association with dental abnormalities.

Characteristic	Survivor cohort			Sibling cohort			Comparison
	n	yes	no	n	yes	no	p-value
Dental abnormality							
Gingivitis							
Tobacco use							
Cigarettes							
Chewing tobacco							
Snuf tobacco							
Pipes							
Cigars							
Age onset tobacco use							

Table \_\_: Comparison of access to medical/dental care and insurance as reported by survivors and siblings.

Characteristic	Survivor cohort			Sibling cohort			Comparison
	n	yes	no	n	yes	no	p-value
Medical insurance							
Dental insurance							
Visit to dentist or dental clinic in last year							
Dental cleaning in last year							
Difficulty finding a dentist							