Analysis Concept Proposal

Title: Nonmelanoma Skin Cancer in Survivors of Childhood Cancer: An Update from the Childhood Cancer Survivor Study

Working Groups: Second Malignancy (Primary), Epidemiology/Biostatistics (Secondary)

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Background and Rationale:

Skin cancer is the most commonly diagnosed malignancy in the United States and rates are increasing.[1-3] Cutaneous malignancies are divided into two broad categories- melanoma and non-melanoma skin cancer (NMSC). Basal cell carcinoma (BCC) followed by squamous cell carcinoma (SCC) are the two most common types of NMSC. They are not tracked by most cancer registries so the incidence of NMSCs must be estimated by data such as Medicare claims. One study estimates a lifetime risk of 28-33% for BCC and 7-11% for SCC in the US.[2] The incidence rate has risen at an alarming pace over the last 30 years with SCC incidence rising 3-10% per year, and BCC incidence rising 20-80% in that timeframe.[3] A variety of factors have been implicated including the popularity of indoor and outdoor tanning, less covering clothing choices, and an aging population with increased life expectancy.[3]

Ultraviolet radiation is the most important factor in the pathogenesis of NMSC, but other exposures such as ionizing radiation therapy and immunosuppression further increase risk.[4-6] In 2005, Perkins et al. used data from the Childhood Cancer Survivor Study (CCSS) to demonstrate a high incidence of NMSC in this group.[7] Among 13,132 childhood cancer survivors diagnosed between 1970 and 1986, 213 reported being diagnosed with a NMSC. Almost half of these survivors (46%) had multiple NMSC. The median age of first skin cancer was 31 years, much younger than in the general population. In a U.S. cohort study of the general population, only 0.05% of individuals with BCC or cutaneous SCC were younger than 20 and <15% were younger than 50 years old.[8] Among CCSS participants, statistically significant risk factors included type of primary malignancy, age at diagnosis, time since diagnosis, exposure to chemotherapy or radiation, white race, and family history of skin cancer.[7] Radiation exposure was the strongest association resulting in a 6.3 fold increase in NMSC. Importantly, 90% of skin cancers in those treated with radiation occurred in the irradiated area.[7] Patients who had received radiation therapy at a dose of >/=35 Gy had an odds ratio for developing BCC to the skin site of 39.8 compared to survivors without radiation therapy exposure.[9] Additional studies confirmed that NMSC is the most common subsequent neoplasm (SN) in childhood cancer survivors, comprising nearly 60% of reported neoplasms.[10,12]

Since the publication of Perkins' study, the CCSS has expanded to include survivors diagnosed between 1987 and 1999 and now includes 25.665 participants. An additional 15 years of additional follow-up are available from the initial cohort and more recent treatment eras have not been explored in which the use of therapeutic radiation has decreased and a trend toward decreased radiation exposure with imaging studies has been observed.[13-16] Additionally, treatment with hematopoietic cell transplantation (HCT) has increased over time in the pediatric population and is a known risk factor for NMSC; immunosuppression, cutaneous graft-versus-host disease, and exposure to photosensitizing agents including voriconazole all contribute to risk.[17-19]

Awareness about the risks of UV radiation including indoor tanning has improved. Nineteen states currently have bans or restrictions on indoor tanning for minors. Recognition of skin cancer risks in cancer survivors has also heightened. The Children's Oncology Group Survivorship Guidelines recommend an annual skin check for anyone who has received radiation or HCT, a personal or family history of skin cancer, history of dysplastic nevi, or had a severe sunburn at an early age.[20] Early treatment of actinic keratoses, precursors of SCC, may impact rates of SCC in childhood cancer survivors. Additionally, as sun exposure in the first two decades of life is a risk factor for BCC, the geographic location where survivors lived or received cancer therapies during childhood may also play a role in the later development of NMSC.[21]

All of this taken together supports the need to reinvestigate rates of NMSC in childhood cancer survivors. With the proposed study we will have the opportunity to examine the long-term health outcomes among approximately 23,000 CCSS participants. Currently, among the 1468 survivors with NMSC confirmed by pathology report, medical records, or through the National Death Index ,there have been a total of 5932 reported NMSC lesions, highlighting that many individuals had multiple NMSC. In the group of patients who had at least one NMSC approximately 25% had four or more with a mean of 3.49 lesions and a median of 1 lesion per individual. This is significant as large cohort studies in the general population have found much lower rates of multiple NMSC with 7.6% of patients with BCC developing 4 or more BCC[22] and 3.4% of patients with NMSC developing 4 or more BCC and/or cSCC[23] over 17 and 21 years respectively. We hypothesize that rates of NMSC will have increased in the initial cohort given increasing attained ages of this population and the national trends cited above. It is further anticipated that a large segment of this group will have developed ≥4 NMSCs. We hypothesize the rates of skin cancer in the more recent diagnosis decade of cancer survivors (1990 – 1999) will be lower by attained age and time from diagnosis compared to CCSS survivors diagnosed with their primary cancer in the 70's and 80's. Decreased therapeutic radiation and chemotherapy dosing and improved sun protection practices are anticipated drivers of this change.[10,23,24] Similar improvements may not, however, be noted in those treated with HCT. We will address these hypotheses through the following specific aims:

Specific Aims and Hypotheses:

1. Quantify NMSC cumulative incidence and total burden in CCSS participants
   a. Estimate cumulative incidence of NMSC (BCC, SCC) for the overall cohort, by primary cancer diagnosis, key treatment exposures and by decade of diagnosis.
   b. Evaluate differences in NMSC incidence based on decade of diagnosis.
   c. Assess cumulative burden of NMSC in CCSS participants
   Hypotheses: Incidence of NMSC will continue to increase over time from initial cancer diagnosis. Data from the 1990s compared to the 1970s will show a decrease in incidence of NMSC in more recent eras.

2. Identify risk factors for development of NMSC in CCSS participants
   a. Estimate age-adjusted relative rates of NMSC based on demographic information (sex, race, geographic regions of birth, childhood cancer treatment facility and of current location), family history of skin cancer, primary cancer subtype, and treatment exposures (chemotherapy agents, cumulative chemotherapy dose, radiation exposure and dose, HCT).

b. Perform multivariable regression analyses to assess associations between the above variables and NMSC.
c. Assess cumulative incidence of NSMC in CCSS participants who received chemotherapy without radiation
Hypothesis: Rates of NMSC will be higher in survivors with risk factors including white race, family history of skin cancer, radiation exposure, platinum, alkylating agent, or anthracycline-based chemotherapy, and a history of HCT.

3. Identify risk factors in survivors with four or more BCC and/or SCC
   a. Quantify the proportion of childhood cancer survivors, by attained age and years since diagnosis, experiencing more than one NMSC.
   b. Perform regression analyses to assess associations between the variables listed in 2a and cumulative number of NMSC.
   Hypothesis: Rates of multiple NMSC will increase with age and time since cancer diagnosis.

4. Identify body site(s) of NMSC in the entire cohort and those with radiation exposure
   a. Delineate the anatomic site (head/neck, back, chest, abdomen/pelvis, extremity, unknown) of NMSC based on BCC vs SCC subtype.
   b. Identify the percentage and subtype of NMCS to arise in the zone of irradiation when applicable.
   Hypothesis: Rates of NMSC will be highest in those anatomical sites that were treated with radiation. Among survivors without radiation exposure, sun exposed sites will be the most common location of skin cancer.

Analysis Framework:

a. Population of interest: This analysis will include patients enrolled in the CCSS cohort, diagnosed 1970-1999, with any primary childhood cancer diagnosis.
b. Outcome variable of interest: NMSCs. All subsequent neoplasms, including NMSCs, are ascertained by self-report and subsequently confirmed by pathology report, medical record or National Death Index review. The age at diagnosis is based on calculations using date of birth and date of NMSC diagnosis (as abstracted from pathology reports or medical records). Anatomic site is also abstracted from pathology reports or medical records by CCSS pathologists and oncologists. Pathology reports from re-resections and/or Mohs procedures are not counted as additional NMSC events.
   1. NMSC (yes/no; number confirmed)
   2. BCC (yes/no; number confirmed; age at diagnosis of first lesion; anatomical site of each- head/neck, abdomen/pelvis, back, chest, extremity, other/unknown)
   3. SCC (yes/no; number confirmed; age at diagnosis of first lesion; anatomical site of each- head/neck, abdomen/pelvis, back, chest, extremity, other/unknown)
c. Descriptive characteristics of the cohort:
   1. Age at diagnosis, sex, race, childhood cancer diagnosis, attained age, time from initial diagnosis, decade of diagnosis (1970s, 80s, 90s)
   2. Environmental/lifestyle exposures: smoking status (yes [ever smoked]/no)
   3. Family history of skin cancer (yes/no)
   4. Personal history of basal cell nevus syndrome (Gorlin), xeroderma pigmentosum (or XP-variant), Fanconi anemia, Rothmund-Thompson syndrome, DeSantis Cacchione syndrome, Bloom syndrome.
   5. Therapeutic exposures
      1. Therapeutic radiation
         a. Any site, Yes/No
         b. TBI, Yes/No
         c. Maximum target dose (maxTD) to exposed body region
      2. Chemotherapy class and cumulative doses (mg/m^2)

a. Chemotherapy (yes/no)
b. Alkylating agents (yes/no), cumulative dose as Cytoxan equivalent dose (mg/m^2)
c. Epipodophyllotoxins (yes/no), cumulative dose (mg/m^2)
d. Anthracyclines (yes/no), cumulative dose (mg/m^2)
e. Platinum agents (yes/no), cumulative dose (mg/m^2)

3. HCT (full details available for 1987-99; will use previous methods to identify HCT for 1970-86 [may not be able to differentiate auto and allo])
    a. Any HCT, Yes/No
    b. Autologous, Yes/No
    c. Allogeneic, Yes/No

6. Subsequent malignant neoplasm (SMN) diagnoses
    a. Any SMN, Yes/No
    b. SMN type

Statistical Approach:
Descriptive statistics will be calculated for baseline demographics, smoking status, and therapeutic exposures. These will include mean, standard deviation, median, minimum and maximum for continuous measures and frequency and proportion for categorical measures. Results will be reported based on presence of none, one or multiple NMSCs.

Aim 1: Quantify cumulative incidence and relative rates (compared to siblings) of first NMSC, first BCC, and first SCC and cumulative burden of NMSCs in individuals 5 years or more post initial cancer diagnosis. NMSC (BCC, SCC) cumulative incidence and 95% confidence intervals will be estimated using time from initial diagnosis as the time scale (for siblings' this would be time from their survivor sibling's dx), treating death as a competing risk event. Incidence will be estimated for the whole cohort and by decade of diagnosis (1970, 80, 90). Cumulative incidence curves will be compared using the Gray's test. Cumulative burden will be estimated for NMSCs by type and decade of diagnosis, using methods previously described.[26] For estimating relative rates compared to siblings, we will employ s piecewise exponential regression model for NMSC (BCC, SCC) comparing survivors vs. siblings, adjusting for attained age, sex, and race, as well as the time from initial diagnosis.

Aim 2. Identify risk factors for development of NMSC (BCC, SCC) in CCSS participants. Perform a 15 or 20 year regression analysis of first NMSC by sex, race, age at diagnosis, geographic regions of childhood cancer treatment facility and of current location, family history of skin cancer, primary cancer diagnosis, and treatment exposures (chemotherapy agents, radiation, HCT), again using time from initial diagnosis as the time scale and treating death as a competing risk. Construct a piecewise exponential regression model to estimate attained-age-sex-race-adjusted relative rates for the patient characteristics and therapeutic exposures listed above. Factors that are significant at the level of P </=0.20 will be included in a multivariable model to assess their simultaneous impact on the rate of NMSC.

Aim 3. Identify risk factors in survivors with four or more NMSC. Develop frequency tables, examining the number of NMSCs by attained age (<20, 20-29, 30-39, 40-49, 50-59, 60+) and years since diagnosis (<10, 10-19, 20-29, 30-39, 40-49, 50+) at last contact. As above, construct a piecewise exponential regression model for individuals with more than three NMSCs to estimate attained-age-sex-race-adjusted relative rates for developing 4th NMSC in association with the patient characteristics and therapeutic exposures listed above. Factors that are significant at the level of P </=0.20 will be included in a multivariable regression model to assess their simultaneous impact on the rate of developing more than 3 NMSCs.

Aim 4. Identify body site(s) of NMSC in the entire cohort and those with radiation exposure. Create frequency tables showing the number and subtype (overall, BCC, SCC) of NMSCs by anatomic site

(head/neck, back, chest, abdomen/pelvis, extremity, unknown). Calculate the percentage and subtype of NMCS to arise in the zone of irradiation when applicable. Rates of NMSC will be evaluated using the same regression method above but considering the anatomical sites that were treated with radiation. Sun exposed sites will be considered for the unirradiated survivors in the regression analysis.

Proposed Tables and Figures:

Table. 1: Survivor characteristics and exposure history

	Overall N= (%)	No NMSC N= (%)	1-3 NMSC N= (%)	≥4 NMSC N= (%)	p
Age at Diagnosis 0-5 6-10 11-15 16-20					
Sex Male Female					
Race/ethnicity White Black Hispanic Other Unknown					
Decade of diagnosis 1970-79 1980-89 1990-99					
Region of therapy Northeast Midwest West South					
Location at last follow-up Northeast Midwest West South Unknown					
History of syndrome with skin cancer risk Basal cell nevus syndrome Xeroderma pigmentosum (or XP-variant) Fanconi anemia Rothmund-Thompson syndrome DeSantis Cacchione syndrome Bloom syndrome					
Childhood cancer diagnosis Hodgkin's disease Non-Hodgkin's lymphoma Wilms' tumor/renal tumor Leukemia Brain/CS tumor Soft tissue sarcoma Bone Neuroblastoma Other					
Attained age <20 20-29 30-39 40-49 50-59 60+					
Years since diagnosis <10 10-19 20-29					

30-39 40-49 50+					
Family history of skin cancer					
Smoking status: **Non-smoker** **Current smoker** **Ever smoked**					
Chemotherapy Anthracycline (mg/m2) None 0-100 101-250 >250 Epipodophyllotoxin (mg/m2) None 1-1000 1001-4000 >4000 Alkylating agent (CED) (mg/m2) None 1-3999 4000-7999 8000+ Platinum Cumulative Dose (mg/m2) None 1-400 401-750 >750					
Radiation None Cranial radiation Total body irradiation Other radiation site(s) Maximum radiation dose to any body region (Gy) (range)					
Hematopoietic cell transplantation Autologous Allogenic					
Other SMN diagnosis (yes)					

Table 2. Twenty year cumulative incidence of NMSC, based on survivor characteristics.

	Cumulative Incidence (95% confidence interval)	*P*
Age at Diagnosis 0-5 6-10 11-15 16-20		
Sex Male Female		
Race/ethnicity White Black Hispanic Other Unknown		
Region of therapy		

Northeast Midwest West South		
Region of birth Northeast Midwest West South Unknown		
Location of current residence Northeast Midwest West South Unknown		
History of syndrome with skin cancer risk Basal cell nevus syndrome Xeroderma pigmentosum (or XP-variant) Fanconi anemia Rothmund-Thompson syndrome DeSantis Cacchione syndrome Bloom syndrome		
Childhood cancer diagnosis Hodgkin's disease Non-Hodgkin's lymphoma Wilms' tumor/renal tumor Leukemia Brain/CS tumor Soft tissue sarcoma Bone Neuroblastoma Other		
Family history of skin cancer		
Smoking status: Non-smoker Current smoker Ever smoked		
Chemotherapy (yes/no) Anthracycline (mg/m2) None 0-100 101-250 >250 Epipodophyllotoxin (mg/m2) None 1-1000 1001-4000 >4000 Alkylating agent (CED) (mg/m2) None 1-3999 4000-7999 8000+ Platinum Cumulative Dose (mg/m2) None 1-400 401-750 >750		

Radiation None Cranial radiation Total body irradiation Other radiation site(s) Maximum radiation dose to any body region (Gy) (range)		
Hematopoietic cell transplantation Autologous Allogenic		

Table 3. Univariate and Multivariate analysis for NMSC (one table for any # NMSCs, separate table for >/= 4 NMSCs)

	Age adjusted RR	95% CI	P	RR from Multiple Regression	P	95% CI
Age at Diagnosis 0-5 6-10 11-15 16-20						
Sex Male Female						
Race/ethnicity White Other Unknown						
Decade of diagnosis 1970-79 1980-89 1990-99						
Region of therapy Northeast Midwest West South						
Region of birth Northeast Midwest West South						
Region of current residence Northeast Midwest West South						
Primary Malignancy Hodgkin's disease Non-Hodgkin's lymphoma Wilms' tumor/renal tumor Leukemia Brain/CS tumor Soft tissue sarcoma Bone Neuroblastoma Other						
Age at follow-up <20 20-29 30-39 40-49 50-59						

60-69						
Years since diagnosis <10 10-19 20-29 30-39 40-49 50-59						
Family history of skin cancer						
Family history of Genetic conditions						
Smoking status: Non-smoker Current smoker Ever smoked						
Chemotherapy Anthracycline (mg/m2) None 0-100 101-250 >250 Epipodophyllotoxin (mg/m2) None 1-1000 1001-4000 >4000 Alkylating agent (CED) (mg/m2) None 1-3999 4000-7999 8000+ Platinum Cumulative Dose (mg/m2) None 1-400 401-750 >750						
Radiation None Cranial radiation Total body irradiation Other radiation site Maximum radiation dose to any body region (Gy) (range)						
HCT						

Table 4. Anatomic site of NMSC in association with radiation therapy

	SCC			**BCC**		
	Total lesion number	% In radiation field (in those with radiation)	No radiation	Total lesion number	% In radiation field	No radiation
Head/Neck						
Abdomen/Pelvis						
Back						
Chest						
Extremity						
Other/unknown						

Table 5. Characteristics of patients with multiple NMSC

	BCC n=	SCC n=	BCC and SCC n=
Total number of patients with >1 lesion			
% male			
Mean age (+/- SD)			
Median number of lesions [range]			
Mean years since primary cancer diagnosis [range]			
% with HCT			
% with radiation			
% with chemotherapy			

Figures:

Figure 1. Cumulative incidence of NMSC (overall and by decade of diagnosis).
Figure 2. Absolute overall NMSC, BCC and SCC counts.
Figure 3. Risk of NMSC as a function of maximum radiation dose.

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