1. Study title

Risk Factors for Melanoma among Adult Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study

2. Investigators and Working Group

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CCSS Second Malignancy Working Group

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3. Background and Rationale

3.1. Overview

As outcomes for childhood cancer patients have improved, there has been increasing attention to the late health consequences of childhood cancer therapy.[1, 2] Subsequent malignant neoplasms (SMNs) substantially contribute to the late morbidity and mortality among childhood cancer survivors.[1-3] In 2013, melanoma as an SMN was investigated among childhood cancer

patients by the Childhood Cancer Survivor Study (CCSS), and among 14,358 childhood cancer survivors the standardized incidence ratio (SIR) for melanoma was 2.42 [95% confidence interval (CI): 1.77-3.23] and the absolute excess risk (AER) was 0.10 (95% CI: 0.05-0.15) per 1,000 person-years.[4] With the expansion of the CCSS cohort, over 22,000 patients are now available for analysis, with a longer duration of follow-up for the original cohort. Further, at the time of the initial report, 57 malignant melanomas had occurred, five years post-cancer diagnosis; as of June 2021, 162 melanomas in 143 survivors have been reported and validated **(appendix 1).**

Overall, melanoma is the fifth most common cancer in the United States[5] and its incidence is steadily increasing among adults.[6] In the general population, risk factors for melanoma include UV radiation, skin pigmentation, total body nevus count, genetic predisposition, history of non-melanoma skin cancer, family history, and immunosuppression.[7] Interestingly, in contrast to older adults the incidence of melanoma has recently decreased in children and adolescents, likely due to increased awareness of the dangers of UV radiation.[6] In addition to the report by Pappo, et al., others have also observed an increased risk of melanoma among survivors of cancer and hematopoietic cell transplantation (HCT).[8-11] However, specific risk factors among childhood cancer survivors for melanoma are not well defined and various studies have shown conflicting data regarding radiation exposure, diagnosis (increased incidence with Hodgkin disease, retinoblastoma, soft tissue sarcoma, and gonadal tumors), chemotherapy (increased risk with alkylating agents and vincristine/vinblastine), family history, and genetic predisposition.[4, 10, 12-15] Conflicting risk factors in previous studies are likely due to small numbers of melanomas in individual studies. Despite an increased incidence of subsequent melanomas among childhood cancer survivors, without clear risk factors, evidence based recommendations remain non-specific. The relatively large number of melanoma cases in the CCSS cohort provides an ideal opportunity to conduct a more robust investigation, and would be the largest such study to date.

Historically, outcomes for patients with metastatic melanoma have been very poor.[16] The Dutch Childhood Cancer Oncology Group Long-Term Effects After Childhood Cancer group analyzed outcomes in childhood cancer survivors who developed melanoma as a second malignant neoplasm and population controls, and found that childhood cancer survivors who developed melanoma have similar overall survival to controls, though confidence intervals were wide.[17] In a Surveillance, Epidemiology, and End Results (SEER) analyzing melanoma outcomes in childhood cancer survivors vs. non childhood cancer survivors, and adjusting for age, overall survival was markedly worse for childhood cancer survivors (at 160 months post-melanoma diagnosis 60.1% vs. 16.2%).[18] Immune checkpoint inhibitors and BRAF- and MEK-targeted therapies have dramatically improved the prognosis for melanoma patients in the general population.[16, 19, 20] In 2011, vemurafenib, a BRAF inhibitor, and ipilimumab, an immune checkpoint inhibitor, were approved for use in metastatic melanoma, and since this time further agents have come to market, improving the outlook for these pateints.[16, 21] It is unknown if childhood cancer survivors with melanoma as a SMN have also seen improvements in outcomes.

3.2. Radiation and Subsequent Melanoma

Among childhood cancer survivors, non-melanoma skin cancers (e.g. basal cell carcinoma, squamous cell carcinoma) have been strongly associated with therapeutic radiation exposure.[22-24] However, studies on radiation and melanoma have not demonstrated consistent relationships, potentially due to studies being underpowered. Previously, Pappo, et al did not detect an association between the receipt of radiotherapy and the incidence of 57 melanomas.[4] Teepen and colleagues analyzed the incidence of 20 melanomas among childhood cancer survivors with a history of radiation to the specific body compartment where the SMN occurred and did not detect a significant association.[10] In a case-control study of 16 childhood cancer survivors with subsequent melanomas, radiotherapy appeared to increase the risk of melanoma for local doses

>15 Gy with an odds ratio of 13, however, the results did not reach the level of statistical significance (95% CI: 0.94-174).[15] The CCSS database currently contains data on radiation exposure and dose to body region (brain, other head, neck, chest, abdomen, pelvis, and extremities), dose of radiation, as well as site of melanoma **(appendix 1; special consideration 6.1).** The large number of cases available through the CCSS as well as the location of both melanoma and radiation exposure provides a drastically increased power to detect a potential difference.

4. Specific Aims and Hypotheses

Primary Aim 1:
Determine the cumulative incidence, standardized incidence ratio (SIR), and absolute excess risk (AER) of subsequent melanoma among five year childhood cancer survivors.

We hypothesize that the cumulative incidence, SIR, and AER will be elevated above the general population and with greater numbers of patients and longer follow-up we expect to be able to determine more precise estimates as well as access estimates at a longer time from primary cancer diagnosis than was possible by Pappo, et al.[4] This will be possible in the full cohort as well as within subgroups identified in risk factor analyses **(Aim 2).**

Primary Aim 2:
Determine the risk factors for development of melanoma as a subsequent neoplasms among five year childhood cancer survivors.

> ***Primary Aim 2a:***
> ***Determine if radiation therapy dose to a specific body region is associated with subsequent melanoma in the exposed body region***
>
> We hypothesize that radiation to a specific body region will be associated with the development of subsequent melanoma in the corresponding body region.
>
> ***Primary Aim 2b: Determine if chemotherapy exposures, bone marrow transplant, previous non-melanoma skin cancer, and other clinical and demographic factors are associated with the development of subsequent melanoma***
>
> Given this is the largest proposed study to date of subsequent melanoma in childhood cancer survivors, we hypothesize that we will be able to detect a relationship between melanoma and bone marrow transplant, chemotherapy exposure, previous non-melanoma skin cancer, and demographic factors.

Exploratory Aim 1:
Determine if the SIR and cumulative incidence of invasive melanoma has decreased across treatment eras.

We hypothesize that the SIR of invasive melanoma has decreased among survivors diagnosed in more recent treatment eras (1970s vs. 80s vs. 90s), after adjusting for attained age **(appendix 2).** We further hypothesize this is due to a reduction in the use of radiation as a therapeutic modality.

Exploratory Aim 2:
Determine if family history of melanoma is associated with the development of invasive melanoma after adjusting for other known risk factors.

We hypothesize that among other risk factors, family history is associated with increased risk of melanoma.

Exploratory Aim 3:
Determine if the survival of invasive melanoma has improved in more recent eras among five year childhood cancer survivors.

We hypothesize that the three year overall survival of those CCSS participants diagnosed with invasive melanoma has improved since 2011.

Exploratory Aim 4:
Describe the distribution of Clark's level or Breslow measurement categorically for childhood cancer survivors who develop invasive melanoma
(see special considerations 6.2)

5. Analysis framework

5.1. Outcome(s) of interest
- Occurrence of melanoma of the skin and eye, both invasive and *in situ* (time dependent), and location of the melanoma
- Vital Status/Overall Survival of CCSS participants who develop invasive melanoma

5.2. Subject Population
This proposal would encompass all CCSS participants. Comparisons would be made between those that did and did not develop melanoma. This proposal will not utilize the sibling cohort.

5.3. Exploratory Variables

5.3.1. Clinical and Demographic Variables
- Age at diagnosis of primary malignancy
- Treatment era (1970s, 80s, 90s)
- Sex
- Race and ethnicity
- Age at subsequent malignant melanoma
- Year of subsequent malignant melanoma (before 2011 vs. 2011 or later)
- Primary malignancy
- Any chemotherapy for initial malignancy (yes/no)
- Alkylating agents (yes/no)
- Cyclophosphamide Equivalent Dose[25] (cumulative dose)
- Anthracycline (yes/no)
- Anthracycline (cumulative doxorubicin equivalents)
- Antibiotic chemotherapy (actinomycin and bleomycin; yes/no)
- Antimetabolites (yes/no)
- Platinum chemotherapy (yes/no)
- Steroid chemotherapy (yes/no)
- Epipodophyllotoxins (etoposide, teniposide; yes/no)
- Plant Alkyloids (Vincristine or Vinblastine; yes/no)[15]
- History of non-melanoma skin cancer (prior to melanoma diagnosis)

- History of use of immunosuppressive medication (cyclosporine, tacrolimus, mycophenolate mofetil, sirolimus; yes/no)
- History of any allogeneic HCT
- History of melanoma cancer in first degree relative

5.3.2. Radiation Variables

To analyze if radiation to a specific body region is associated with subsequent melanoma in that region (primary aim 2a)

- Radiation therapy exposure by body region (none, head, thorax, lower and upper extremities); for extremities, laterality will also be provided as left, right, right and left, or unknown **(Figure 1)**.
- Radiation maximum prescribed dose (for each body region, and maximum of all body regions)

5.4. Statistical Overview

We expect approximately 162 cases of melanoma to be identified, based on the June, 2021 report, though that number may be slightly greater at this point. We will first describe two cohorts, one with a history of melanoma as a SMN and one without, providing basic summary statistics of each of the exploratory variables using chi-square test, t-test, or Mann-Whitney test as appropriate **(table 1).**

Next we will describe the cohort of CCSS participants who developed melanoma as an SMN in more detail regarding disease characteristics. We will describe Clark's level or Breslow measurement, categorically, location of tumor (skin vs. ocular), and invasive vs. *in situ* (**table 2; special considerations 6.2, 6.3).**

Cumulative incidence of developing a first melanoma, using time from childhood cancer diagnosis as the time scale, will be estimated and factors associated with the development of melanoma will be evaluated using a fine and gray model, with death as a competing risk **(figure 2).** We will specifically estimate cumulative of first melanoma incidence at 10 and 30 years, but other point estimates may be made after reviewing the distribution of follow-up data **(table 3; special considerations 6.4)**

We will also calculate SIRs by comparing the number of observed occurrences of melanoma in the CCSS cohort to those expected in the general population based on SEER registry age, sex and calendar year specific rates of melanoma. AER will be calculated by subtracting the expected number of melanomas as SMN in the cohort from the observed number, dividing the difference by person-years of follow-up, and multiplying by 100,000.[4] The SIRs and AERs along with corresponding 95% confidence intervals of subsequent melanoma stratified by patient and treatment characteristics will be calculated based on a Poisson model utilizing expected rates as offset terms and using piecewise person-year time split into unique age and calendar year intervals. Results will be reported **(table 3),** and SIR will be shown as a figure similar to Turcotte, et al. 2017 **(figure 3)**.[3]

Univariate analysis of exploratory variables (above) will be performed and then fit into a multivariate model **(table 4)** to predict the incidence of melanoma**.** In these models for melanomas located in any region of the body, radiation exposure be coded as maximum dose to any region of the body. In the multivariate model, alpha will be set at 0.05 **(table 5, figure 4).**

To further test whether radiation exposure is associated with the development of melanoma, we will perform a similar analysis as above, but will define 6 different endpoints of interest as

melanoma occurring on the a) head, b) trunk, c) right upper extremity, d) left upper extremity, e), right lower extremity, f) left lower extremity, to analyze each in a separate model with the relevant radiation exposure variable for that region **(see primary aim 2a; table 4).** In this analysis, we will specifically examine whether radiation to each region is associated with the development of melanoma in each region, respectively. Additionally, the maximum target dose of radiation will be categorized and analyzed. Body region radiation data will then be compared to the development of melanoma in the corresponding region **(figure 1)**. Adjustments based on additional risk factors found significant will be incorporated as needed **(table 5)**.

Finally, for those patients developing invasive melanoma, we will calculate their three year overall survival, and compare this among patients who were diagnosed with melanoma as a SMN prior to 2011 and in 2011 or later using the Kaplan-Meier method. Analysis will be performed for all invasive melanoma (*in situ excluded;* **figure 5).**

6. Special considerations

6.1. Laterality

Laterality of extremity radiation was not previously available in the CCSS database, but can now be provided by the MD Anderson Radiation Physics Center *(personal communication with Rebecca Howell, Susan Smith) as described in section 5.3.2.* Laterality of extremity subsequent melanoma is available for the vast majority of cases, however for those that remain unknown, some may be determined after analyzing additional text fields.

6.2. Depth of Invasion

Clark's level or Breslow measurement will require supplemental manual review of path reports. If this information was available from previous review of pathology reports of second malignant neoplasms, it was placed in a text field in the CCSS database. Data is expected to be incomplete, but the percent completion is not known until review of these text boxes is undertaken (*personal communication with Lucie Turcotte, Joseph Neglia).*

6.3. Ocular Melanoma

All initial analysis will also include patients who developed ocular melanoma (n=4). As the risk factors for ocular melanoma may differ from cutaneous melanoma, and the numbers of ocular melanomas in this dataset is small, we will also perform sensitivity analysis excluding ocular melanomas.

6.4 Survivors with Multiple Occurrences of Melanoma

In total, 168 melanomas have been diagnosed as of June, 2021 with 162 occurring at least 5-years post-cancer diagnosis. These melanomas occurred among 143 survivors.

7. Appendices

Appendix 1. Site Code		
Cancer Site	**Frequency**	**Percent**
C44.2 Skin of ear and external auricular canal	7	4.3%
C44.3 Skin of other and unspecified parts of face	9	5.6%
C44.4 Skin of scalp and neck	13	8.0%
C44.5 Skin of trunk	57	35.2%
C44.6 Skin of upper limb, including shoulder	35	21.6%
C44.7 Skin of lower limb, including hip	30	18.5%
C44.9 Malignant neoplasm of skin, unspecified	7	4.3%
C69.0 Conjunctiva	1	0.6%
C69.3 Choroid	2	1.2%
C69.9 Eye, unspecified	1	0.6%

Appendix 2. Decade of Treatment		
Decade of Treatment	**Frequency**	**Percent**
1970-1979	73	45.1%
1980-1989	50	30.9%
1990-1999	39	24.1%

8. Examples of Specific Tables and Figures

Table 1. Overall Cohort			
Characteristic	**Melanoma (n=~162)**	**No Melanoma (n=~22,000)**	**P-Value**
Age at diagnosis of primary cancer, years (median, range)			
Decade of Original Diagnosis (count, %)			
1970s			
1980s			
1990s			
Sex (% female)			
Current age, years			
Age at subsequent malignant melanoma (median, range)		n/a	n/a
Year of subsequent malignant melanoma (before 2011 vs. 2011 or later)		n/a	n/a
Race/ethnicity, n (%)			
White, non-Hispanic			
Black, non-Hispanic			
Hispanic			
Other			
Primary Cancer Diagnosis, n (%)			
Leukemia			
CNS Tumor			
Hodgkin Disease			
Non-Hodgkin Lymphoma			
Renal Tumors			
Neuroblastoma			
Soft Tissue Sarcoma			
Bone Tumors			
Any Chemotherapy (Y/N)			
Alkylating Agents (Y/N)			
Cyclophosphamide Equivalent Dose (median)			
Anthracycline (Y/N)			
Anthracycline (median, cumulative doxorubicin equivalents)			
Antibiotic chemotherapy (actinomycin and bleomycin; yes/no)			
Antimetabolites (yes/no)			
Platinum chemotherapy (yes/no)			
Steroid chemotherapy (yes/no)			
Epipodophyllotoxins (etoposide, teniposide; yes/no)			
Plant Alkyloids (Vincristine or Vinblastine; yes/no)			
Radiation therapy exposure (Any y/n)			
Radiotherapy (region)			
None			
Head			
Trunk			
Upper Extremity			
Lower Extremity			
Other			
Maximum prescribed radiation dose (of all regions)			
Radiotherapy maximum prescribed dose (by region)			
Head			
Trunk			

Right Upper Extremity			
Left Upper Extremity			
Right Lower Extremity			
Left Lower Extremity			
Other			
History of Non-melanoma skin cancer (Y/N)			
Family History of First Degree Relative with Melanoma (Y/N)			
History of use of immunosuppressive medication (Y/N)			
History of Allogeneic BMT			
Current Vital Status			

Table 2. SMN Melanoma Details (N=~162)	
Invasive Skin and Ocular	N (%)
Skin Breslow Depth I II III IV Clark's Level I (*in situ)* II III IV V	
Invasive Ocular	
Body Location Upper Extremity Lower Extremity Trunk Head Other	

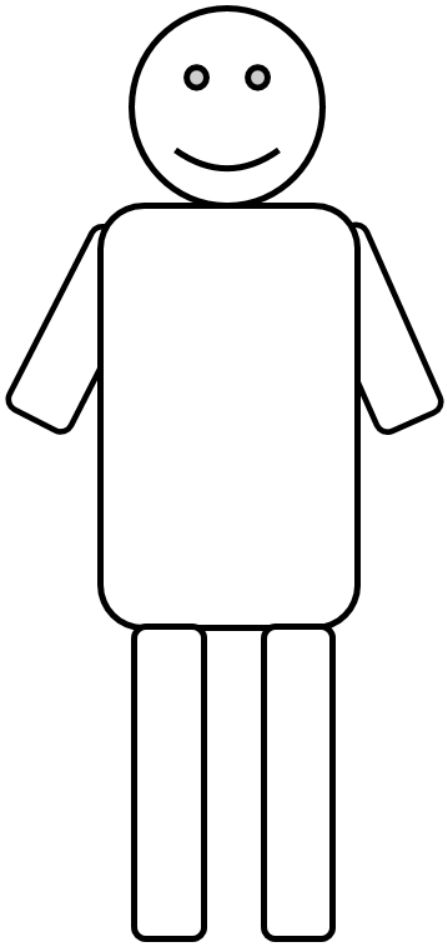
Table 3. Epidemiologic Data				
	Cumulative Incidence of First Melanoma at 10 years (95% CI)	**Cumulative Incidence of First Melanoma at 30 years (95% CI)**	**SIR (95% CI)**	**AER (95% CI)**
All Cases			**n/a**	**n/a**
Invasive Skin and Ocular				
Ocular Only				
Invasive Skin Only				
In Situ			**n/a**	**n/a**

Note: SEER doesn't have *in situ* data

Table 4. Univariate Analysis of Risk factors for Development of ALL Subsequent Melanoma with Radiation by Body Region														
Melanoma Location	**All**		**Head**		**Trunk**		**Right Upper Extremity**		**Left Upper Extremity**		**Right Lower Extremity**		**Left Lower Extremity**	
Characteristic	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at diagnosis of primary cancer, years														
Decade of Original Diagnosis (count, %)														
1970s														
1980s														
1990s														
Sex (% female)														
Race/ethnicity, n (%)														
White, non-Hispanic														
Black, non-Hispanic														
Hispanic														
Other														
Primary Cancer Diagnosis, n (%)														
Leukemia														
CNS Tumor														
Hodgkin Disease														
Non-Hodgkin Lymphoma														
Renal Tumors														
Neuroblastoma														
Soft Tissue Sarcoma														
Bone Tumors														
Any Chemotherapy (Y/N)														
Alkylating Agents (Y/N)														
Cyclophosphamide Equivalent Dose (median)														
Anthracycline (Y/N)														
Anthracycline (median, cumulative doxorubicin equivalents)														
Antibiotic chemotherapy (actinomycin and bleomycin; yes/no)														
Antimetabolites (yes/no)														
Platinum chemotherapy (yes/no)														
Steroid chemotherapy (yes/no)														
Epipodophyllotoxins (etoposide, teniposide; yes/no)														

Plant Alkyloids (Vincristine or Vinblastine; yes/no)														
Radiotherapy (any, Y/N)														
Radiotherapy maximum prescribed dose (to any body region)														
Radiotherapy (region, Y/N)														
Head														
Trunk														
Right Upper Extremity														
Left Upper Extremity														
Right Lower Extremity														
Left Lower Extremity														
Other														
Radiotherapy maximum prescribed dose (by region)														
Head														
Trunk														
Right Upper Extremity														
Left Upper Extremity														
Right Lower Extremity														
Left Lower Extremity														
Other														
History of Non-melanoma skin cancer (Y/N)														
Family History of First Degree Relative with Melanoma (Y/N)														
History of use of immunosuppressive medication (Y/N)														
History of Allogeneic BMT														

Table 5. Multivariate Model for any Subsequent Melanoma with Radiation Overall and by Body Region														
Melanoma Location	**All**		**Head**		**Trunk**		**Right Upper Extremity**		**Left Upper Extremity**		**Right Lower Extremity**		**Left Lower Extremity**	
Characteristic	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Variables Retained from Univariate Analysis Table 4														



Radiation

Head
- Brain
- Other head
- Neck

Trunk
- Abdomen
- Pelvis
- Chest

Extremities
- Left v Right v Both v Unknown
- Upper v Lower

Melanoma Site

Head	
• Ear	7
• Unspecified face	9
• Scalp and neck	14
• Eye, Choroid, Conjunctiva	4
• **Total**	34
Trunk	
• Trunk	60
Extremities	
• Left Upper	18
• Left Lower	12
• Right Upper	14
• Right Lower	16
• **Total**	62
Unknown	6

Figure 1. Location of Subsequent Melanoma Sites and Available Delineated Body Region of Radiation Exposure. Note, additional data fields allow for more specific categorization than provided in appendix 1.

Figure 2
Cumulative incidence curve of all melanoma, invasive skin melanoma, melanoma *in situ* vs. time since cancer diagnosis.

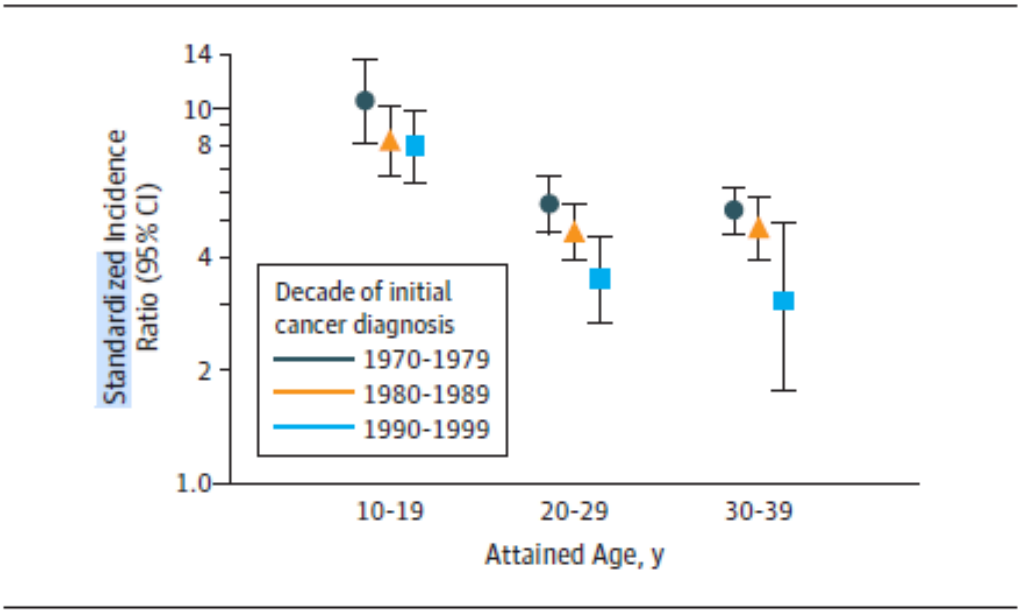


Figure 3
Standardized incidence ratio for secondary melanoma by attained age and decade of diagnosis. To be similar to Turcotte, et al. 2017 (Example above)

Figure 4
Potential cumulative incidence curves based on factors found significant in multivariate model, particularly treatment decade

Figure 5
K-M curve of OS for patients with any invasive melanoma, before and after 2011.

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