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Melanoma as a Subsequent Neoplasm in Adult Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study

AS Pappo¹, GT Armstrong², W Liu³, DK Srivastava³, A McDonald², WM Leisenring⁴, S Hammond⁵, M Stovall⁶, JP Neglia⁷, and LL Robison²

¹Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN

²Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN

³Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN

⁴Cancer Prevention and Clinical Statistics Program, Fred Hutchinson Cancer Research Center, Seattle, WA

⁵Department of Pathology, The Ohio State University, Columbus, OH

⁶Department of Radiation Physics, University of Texas M.D. Anderson Cancer Center, Houston, TX

⁷Department of Pediatrics, University of Minnesota Medical School, Minneapolis, MN

Abstract

Background—Childhood cancer survivors have a six fold increased risk of developing subsequent neoplasms when compared to the general population. We sought to describe the occurrence of melanoma as a subsequent neoplasm among adult survivors of childhood cancer.

Patients and Methods—Among 14,358 5-year survivors of childhood cancer diagnosed between 1970–86, we calculated the cumulative incidence, standardized incidence ratio (SIR), and absolute excess risk (AER) of subsequent melanoma. Potential risk factors were assessed using a cause-specific hazards model.

Results—57 melanomas (46 invasive, 2 ocular and 9 *in situ*) occurred in 51 survivors. The median time to the development of melanoma was 21.0 years (range 5.6–35.4 years) and the median age at melanoma was 32.3 years (range 10.9 – 49.0 years). Initial cancer diagnoses included soft tissue and bone sarcoma (n=15), leukemia (13), lymphoma (14), central nervous system malignancy (5), Wilms' tumor (3), and neuroblastoma (1). The cumulative incidence of first subsequent melanoma at 35 years from initial cancer diagnosis was 0.55% (95% CI 0.37–0.73). The SIR of subsequent invasive malignant melanoma of the skin was 2.42 (95% CI 1.77 – 3.23), and the AER was 0.10 (95% CI 0.05 – 0.15) per 1,000 person years. No statistically significant associations were found between melanoma risk and family history of cancer, demographic, or treatment-related factors.

Conclusion—Survivors of childhood cancer have an approximate 2.5-fold increased risk of melanoma. Early screening and prevention strategies are warranted.

Corresponding Author: Alberto S. Pappo, M.D., St Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, Phone: 901-595-6765, Fax: 901-521-9005, alberto.pappo@stjude.org.

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Introduction

Improvements in therapies for childhood cancer have increased five year survival rates to over 80%.[1] This success has increased the number of childhood cancer survivors, who currently account for 3% of the total cancer survivor population in the United States.[2] Although survivors of childhood cancer face many late complications related to their initial therapy, the development of a subsequent malignant neoplasm is one of the most concerning.[3–5]. The Childhood Cancer Survivor Study (CCSS) recently reported the 30-year cumulative incidence of all subsequent neoplasms amongst five-year survivors to be 20.5% and the cumulative incidence of non-melanoma skin cancer was 9.1%. [4] In contrast to non-melanoma skin cancer, melanoma, which is estimated to account for approximately 5% of all subsequent cancers in survivors of childhood cancer, has not been extensively investigated as documented in the recent review by Braam et al. [6]

Malignant melanoma is the sixth most common cancer in the United States and its incidence continues to increase at a rate of approximately 2.9% per year.[7] It is estimated that 1.93% of men and women born today will be diagnosed with melanoma of the skin at some time during their lifetime and in 2011, 8,790 deaths will be attributed to this disease.[8,9] Risk factors associated with the development of melanoma include skin pigmentary traits, sun exposure, use of tanning beds, hereditary predisposition, and hereditary syndromes such as xeroderma pigmentosum and retinoblastoma.[10–13] In addition, several reports suggest that immunosuppressed patients including those who have received bone marrow transplantation and survivors of childhood cancer are at increased risk for the development of malignant melanoma.[4,6,14–16].

In this report we provide the most recent update of melanoma as a subsequent neoplasm in the CCSS cohort. This analysis reflects the largest evaluation to date of the descriptive characteristics, incidence, risk, and associated risk factors for subsequent melanomas among five-year survivors of the most common forms of childhood cancer.

Patients and Methods

The CCSS is a retrospective cohort with longitudinal follow-up established through 26 participating centers in the US and Canada. The cohort consists of 14,358 five year survivors of childhood cancer diagnosed prior to 21 years of age between January 1, 1970 and December 31, 1986. Eligible cancer diagnoses included leukemia, central nervous system malignancy, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft tissue sarcoma, and bone tumors. The study design, cohort characteristics, and participation rates have been previously described in detail. [17–19]

Subsequent neoplasms were initially ascertained through self-report from the baseline and follow-up questionnaires as well as review of death certificates. Cases of subsequent neoplasms were confirmed by pathology report, or when not available, confirmed by death certificate or other medical records reviewed by study investigators. Because of the cohort eligibility criteria, only subsequent melanomas occurring five or more years following the childhood cancer diagnosis were included in this analysis. There were two additional cases of melanoma among CCSS participants prior to entry into the cohort (occurring at 31 and 43 months from initial diagnosis). To maintain the integrity of the cohort design, these events cannot be included when calculating incidence. Accordingly, these cases are not considered in any calculations described in the statistical analysis. Melanoma cases considered in this analysis included histology codes 8720–8780 listed in the International Classification of Diseases of Oncology (ICDO2).

Statistical Analysis

The distribution of participant characteristics and treatment therapies in survivors with and without melanoma as a subsequent neoplasm are summarized and compared with χ^2 tests (I). Cumulative incidence of melanoma (invasive, ocular, and *in situ*) and corresponding 95% confidence intervals (CI) were estimated with participants censored at date of last questionnaire. Death was treated as a competing risk event. Associations between demographic and treatment factors and subsequent risk of melanoma were evaluated using cause-specific hazards models with age as the time scale and censoring at time of last questionnaire or death.[20]

Risks for subsequent malignant melanoma were calculated using standardized incidence ratios (SIR) and absolute excess risk (AER). SIRs of observed-to-expected melanomas were calculated using age- and sex- and race-specific incidence rates from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. The SEER registry does not include melanoma *in situ* and thus, these cases are not included in the calculation of SIRs or AERs. In addition, the SIRs and AERs were calculated for all invasive melanomas (skin + ocular), as well as for skin and ocular alone for comparability with other studies. AER was determined by subtracting the expected number of malignancies from the observed number, dividing the difference by the person-years of follow-up, and multiplying by 1000. Person-years of follow-up were calculated from entry into the CCSS cohort at five years following cancer diagnosis up to the time of death or last contact. Multiple occurrences of melanoma within the same subject were included in SIR and AER analyses. SIR and AER were calculated for ocular melanoma separately by using SEER site codes C69.0–C69.9. All analyses were conducted using SAS 9.2 (Cary, NC).

Results

A total of 51 survivors developed 57 melanomas (46 invasive, 2 ocular and 9 *in situ*). One participant with osteosarcoma developed three subsequent malignant melanomas and four participants developed two subsequent malignant melanomas. The median time to the development of first subsequent melanoma from initial cancer diagnosis was 21.0 years (range 5.6–35.4 years) and the median age at diagnosis of the first subsequent melanoma was 32.3 years (range 10.9 – 49.0 years). Characteristics of participants with and without melanoma are provided in Table I. Among participants with a subsequent melanoma, 27 were male (53%) and 46 (90%) white non-Hispanic. Initial tumor diagnoses included soft tissue and bone sarcoma (n=15), leukemia (n=13), lymphoma (n=14), brain tumor (n=5), Wilms tumor (n=3), and neuroblastoma (n=1). When compared to CCSS participants without melanoma, patients who developed melanoma were more likely diagnosed in an earlier treatment era, to be 10 years of age or older at the time of cancer diagnosis, and had higher rates of a reported family history of cancer in a first degree relative.

The cumulative incidence of first subsequent melanoma (invasive, ocular and *in situ*) was 0.55% (95% CI 0.37–0.73) 35 years from initial cancer diagnosis (Figure 1, Table II). The cumulative incidence of first subsequent melanoma by primary diagnosis (Figure 2) was highest for patients with bone and soft tissue sarcomas (0.87%; 95% CI 0.38 – 1.36%) and lowest for patients with brain tumors (0.29%; 95% CI 0.03–0.54%).

Excluding ocular and *in situ* disease (n=11), there were a total of 43 patients with 46 episodes of invasive melanoma of the skin. Compared to the SEER estimates, the SIR of subsequent malignant melanoma for our survivor population was 2.42 (95% CI 1.77 – 3.23), and the AER was 0.10 (95% CI 0.05 – 0.15) per 1,000 person years (Table II). The SIR of

subsequent ocular melanoma for the CCSS survivor population was 6.18 (95% CI 0.69 – 22.3), and the AER was 0.006 (95% CI 0 – 0.025) per 1,000 person years (Table II).

For patients with invasive disease, Breslow's thickness (n=26) ranged from 0.27–3.5 mm (median of 0.58), Clarks' level of invasion (n=24) ranged from II–IV (median III), and 21 of 22 specimens for which the subtype of melanoma was known were of the superficial spreading subtype. Five patients developed subsequent malignancies following diagnosis of melanoma that included intraductal breast carcinoma (2), papillary thyroid carcinoma (1) squamous cell carcinoma (1), and glioblastoma (1).

In univariate analysis, no factors were statistically significantly associated with an increased risk for developing subsequent melanoma (Table III). Family history of cancer showed an increased risk (hazard ratio of 1.78, 95% CI of 0.99 – 3.21), but did not achieve statistical significance ($p = 0.055$). Data on the precise location of the melanoma was not available for enough cases to allow for estimation of RT field location and its association with the development of subsequent melanoma. At last contact, 84% of patients who developed a melanoma were alive; in three of the eight deceased patients, death was directly attributed to melanoma.

Discussion

While large cohorts of childhood cancer survivors, including CCSS, have identified cases of subsequent melanoma [21,22], the current report represents the first to provide an in depth assessment of cumulative incidence and associated risk factors. Our analysis demonstrates that the cumulative incidence of melanoma among five-year survivors of childhood cancer treated between 1970 and 1986 is low, at less than 1% 35 years following their initial cancer. However, while the overall incidence is very low, the observed cases reflect a nearly three-fold increased risk compared to the general population. In considering this estimate of risk it is noteworthy that secondary invasive melanoma was ascertained by self-report (followed by pathology confirmation), which could result in some degree of under reporting. Thus, the lower 95% confidence limit of the risk estimate would indicate that a conservative estimate is that childhood cancer survivors have an 83% higher risk than the general population. The observed SIR in the CCSS cohort is remarkably similar to that reported by the British Childhood Cancer Survivor Study (SIR of 2.3) [21] and among the Nordic countries (SIR of 2.6).[22] Although this risk of subsequent melanoma is lower than that reported for other subsequent malignancies such as breast cancer (10-fold increased risk) and bone sarcomas (19-fold increased risk) [4], this is still a relatively young population and it can be anticipated that the magnitude of risk will increase with age. Thus, screening for melanoma as a subsequent neoplasm should be strongly considered as an integral part of surveillance strategies for childhood cancer survivors since prevention and early diagnosis are known to significantly impact the morbidity and mortality associated with this disease. [23]

The median age at diagnosis of melanoma in our patients was significantly lower than the current estimates in the general population (32 years vs. 57 years) [24], which likely reflects the young age of the CCSS cohort and has been previously reported in survivors who developed subsequent non-melanoma skin cancers and melanoma.[25,26] This earlier onset might be the result of an interaction between early introduction of therapies to treat cancer during childhood and an inherent increased susceptibility for the development of this disease. It is well known that patients with germline *CDKN2A* mutations have an earlier onset of melanoma and that other modifier genes such as *MC1R* can further shift the age at onset of this disease.[27] In our series, the majority of patients who developed subsequent melanomas were initially diagnosed with leukemia or Hodgkin lymphoma and these two

entities have been previously associated with the highest risk of developing subsequent neoplasms in childhood cancer survivors. [4,28] Although retinoblastoma has been associated with an increased incidence of melanoma, the CCSS cohort does not include survivors of retinoblastoma. Thus, our estimate of the overall incidence of secondary melanoma may be conservative relative to the rate that may be seen when considering the full spectrum of pediatric cancers.

Our analysis failed to identify statistically significant demographic or treatment-related factors associated with an increased risk for the development of melanoma. It is possible that the low event rate (0.36%, 52 out of 14358) in the small and heterogeneous population, in conjunction with the lack of full information regarding the anatomic location of the tumor relative to the field of radiotherapy treatments, could have prevented us from identifying meaningful associations, particularly for radiation exposure. The role of radiotherapy in the pathogenesis of melanoma remains controversial.[25,29,30] In an earlier publication by Guerin et al.[25] which included 16 cases of melanoma among survivors of childhood cancer, no significant risk was found for radiation exposure when considered as a dichotomous (yes/no) variable. However, a statistically significant association ($p=0.05$) was identified with dose of radiation when considered as a continuous variable, with an estimated 7% increase in risk for each Gy of exposure. While their sample size was limited, the results do suggest that further investigation of radiation therapy as a risk factor is warranted. In another study by Inskip, the use of radiotherapy was not found to be associated with an increased risk of developing melanoma when compared to patients who did not receive radiotherapy.[31] Because of a lack of precision for reporting on the site of the melanoma among CCSS participants, we were not able to evaluate the effect of radiation exposure in a dose-dependent fashion. None of the individuals who developed a subsequent melanoma had a history of total body irradiation. Efforts are currently underway to attempt to more precisely identify the location of the lesions, to permit conduct of a nested case-control study to evaluate risk according to radiation exposure of the affected area.

It is of interest that a family history of cancer in a first degree relative was of borderline significance, further substantiating the possible contributing role of hereditary factors in the development of melanoma in our population. However, there were no consistent patterns observed for the type of cancers reported among first degree relatives, with only one family member reported with melanoma. Other cancers reported among first degree relatives included three breast, three prostate, two non-melanoma skin cancer, two cervix, one leukemia, one Hodgkin lymphoma, and one with an unknown cancer type. Furthermore, five of our survivors had more than one melanoma, a feature has been reported to be associated with germline p16 mutations in up to 15% of patients.[32] Two patients with ocular melanoma did not have previously described predisposing conditions such as xeroderma pigmentosum or ocular melanocytosis.[33] Phenotypic traits known to be associated with the development of adolescent and adult melanoma were not available for all members of the CCSS cohort. However, information was available for a sub-set of 9,308 cohort members where we identified an increased risk of melanoma to be associated with blue eyes (Odds Ratio 2.44, 95% CI 1.11–5.33 compared to brown eyes) and red hair (Odds Ratio 4.68, 95% CI 1.57–13.97, compared to brown/black hair) whereas survivors with white skin were at increased risk but the presence of this trait did not achieve statistical significance (Odds Ratio 1.44, 95% CI 0.64–3.26, compared to brown/black skin).

It is likely that the etiology of subsequent melanomas in our patient population is polygenic in origin. Chronic immunosuppression has been linked to the development of melanoma and increased number of nevi in renal transplant recipients and childhood survivors of acute lymphoblastic leukemia.[15,34] An interplay of environmental factors including inherited genetic variants with a modest individual effect, could ultimately increase the risk of

melanoma in this population. For example, individuals diagnosed with Hodgkin lymphoma and who lack the gene glutathione S-transferase M1 have been reported to have an increased risk for subsequent malignancies. [35] More recently, genome wide association studies have identified that certain variants of the tyrosinase, *MC1R* and *CDKN2A* genes are associated with an increased risk of melanoma and variants of the *MTAP* and *PLAS2G6* genes are also associated with an increased risk of developing melanocytic nevi and melanoma.[36,37] Familial melanoma has been associated with the presence of mutations in two genes: *CDKN2A* (which encodes p16 and p14ARF), and *CDK4*. [11]

Another interesting subset of patients who developed melanoma included those with osteosarcoma and rhabdomyosarcoma. In 1987, Birch described an association between melanomas in close relatives of children who developed osteosarcoma.[38] Germline p53 mutations have been described in 3% of pediatric patients with osteosarcoma and over half of these patients did not have a family history of cancer.[39] Thus, it is possible that some of our patients had a germline mutation of p53. About 20% of children younger than three years of age with rhabdomyosarcoma will have germline mutations of p53.[40] Although only one of our patients was three years of age, two others had a family history of melanoma and breast cancer in first degree relatives suggesting that either a p53 mutations or a p14 mutation that provided an alternative mechanism for p53 inactivation could be present in these patients.[41] Unfortunately, we do not have information on the germline p53 status of these families, but the history and pattern of cancers observed are highly suggestive of an alteration in this pathway.

The characteristics of the melanomas in our patient population were overall favorable with a median thickness of 0.5 mm. Studies in immunosuppressed patients confirm that the outcome of melanoma is favorable amongst patients whose tumors were detected early and the thickness of the melanoma did not exceed 1 mm. [42] These observations further strengthen the need for early intervention and prevention in survivors of childhood cancer.

Our findings emphasize the importance of integrating into clinical practice increased awareness of childhood cancer survivors to practice enhanced sun protection, decreasing sun exposure and avoiding tanning beds along with other preventive measures such as non-initiation or cessation of smoking. Although routine screening for melanoma in the general population or in populations at relatively low risk for the development of the disease such as the one described in our paper is not routinely recommended, there is preliminary evidence from systematic skin cancer screening programs such as the SCREEN project in Germany can identify larger number of cases and decrease mortality.[43] However, our current recommendations would be to follow the Children's Oncology Group long-term survivor follow-up guidelines, which currently recommend "inspection and palpation of skin and soft tissues in irradiated fields annually". Accordingly, 72% of the cases included in our report would fall under the current surveillance guidelines. In addition, in order to improve compliance with these practices, education, scheduled medical care, and knowledge of the therapy received should be part of the routine follow up for survivors of childhood cancer. [44]

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Figure 1.
Cumulative incidence of first subsequent melanoma.

CIN at 35 years from initial diagnosis and 95% CI for each primary diagnosis group:

- 0.87% (0.38 – 1.36%) for bone and soft tissue sarcomas

- 0.39% (0.15-0.63%) for Leukemia

- 0.55% (0.26 – 0.84%) for lymphoma

- 0.29% (95% CI 0.03 – 0.54%) for brain tumors

CIN at 35 years from initial diagnosis and 95% CI for each primary diagnosis group:

- 0.87% (0.38 – 1.36%) for bone and soft tissue sarcomas

- 0.41% (0.16-0.66%) for Leukemia

- 0.55% (0.26 – 0.84%) for lymphoma

- 0.29% (95% CI 0.03 – 0.54%) for brain tumors

Figure 2.
Cumulative incidence of subsequent melanoma by primary tumor diagnosis.

Table I

Characteristics of survivors who developed melanoma as a subsequent neoplasm compared to those who did not develop melanoma

Characteristic	Sub Group	Malignant or <i>in situ</i> melanoma	Others CCSS participants	p-value ¹
Age at initial diagnosis (Yrs)	< 10 yrs	19 (37.25)	8937 (62.47)	
	10 yrs	32 (62.75)	5370 (37.53)	<0.001
Sex	Male	27 (52.94)	7686 (53.72)	
	Female	24 (47.06)	6621 (46.28)	0.91
Race	White Non-Hispanic	46 (90.20)	11897 (83.16)	
	Black Non-Hispanic	0 (0.00)	668 (4.67)	
	Hispanic	1 (1.96)	737 (5.15)	
	All Others	4 (7.84)	1005 (7.02)	0.29
Primary malignancy	Bone and soft tissue sarcoma	15(29.41)	2419 (16.91)	
	Osteosarcoma	5 (33.33)	728 (30.10)	
	Ewings sarcoma	2 (13.33)	401 (16.58)	
	Rhabdomyosarcoma	4 (26.67)	382 (15.79)	
	Fibrosarcoma	1 (6.67)	70 (2.89)	
	Hemangioendothelioma	1 (6.67)	5 (0.21)	
	Leiomyosarcoma	1 (6.67)	20 (0.83)	
	Synovial sarcoma	1 (6.67)	92 (3.80)	
	Other Bone or STS	0 (0.00)	721 (29.81)	
	Leukemia	13 (25.49)	4817 (33.67)	
	Lymphoma	14 (27.45)	2993 (20.93)	
	Hodgkin	12 (85.71)	1915 (63.98)	
	Non Hodgkin	2 (14.29)	1078 (36.02)	
	Brain tumor	5 (9.80)	1872 (13.08)	
	Kidney (Wilms' tumor)	3 (5.88)	1253 (8.76)	
	Neuroblastoma	1 (1.96)	953 (6.66)	
Treatment era	1980–1986	17 (33.33)	7732 (54.04)	
	1970–1979	34 (66.67)	6575 (45.96)	0.003
Radiation exposure *	Any	35 (71.43)	8511 (68.03)	
	None	14 (28.57)	3999 (31.97)	0.61
Family history of cancer in a first degree relative	Yes	17 (33.33)	2342 (16.37)	
	No	34 (66.67)	11965 (83.63)	0.001
Alkylating score *	0 (none)	28 (63.64)	5777 (50.09)	
	1 to 2	11 (25.00)	4452 (38.60)	
	3 to 4	5 (11.36)	1305 (11.31)	0.16
Age at subsequent malignant or in situ Melanoma	10–19	5 (9.80)		

Characteristic	Sub Group	Malignant or <i>in situ</i> melanoma	Others CCSS participants	p-value ¹
	20–29	12 (23.53)		
	30–39	27 (52.94)		
	40+	7 (13.73)		
Current vital status	Alive	43 (84.31)	12251 (85.64)	
	Dead	8 (15.69)	2055 (14.36)	0.79

* Percentages of individuals who received radiation therapy were calculated on total number of participants who provided authorization for release of treatment information and for whom adequate information was available within the medical record to accurately assess treatment exposure.

Table II

Cumulative incidence, standardized incidence ratios and absolute excess risk of melanoma in childhood cancer survivors

	Cumulative Incidence of first melanoma at 35 years (95% CI)	Standardized Incidence Ratio (SIR) (95% CI)	Absolute Excess Risk (AER) (95% CI)
All reported cases	0.55 (0.37–0.73)	-- *	-- *
Invasive (skin + ocular)	0.49 (0.31–0.67)	2.49 (1.83–3.3)	0.10 (0.06 – 0.16)
Invasive (skin only)	0.47 (0.29–0.65)	2.42 (1.77–3.23)	0.10 (0.05 – 0.15)
Invasive (ocular only)	0.02 (0–0.04)	6.18 (0.69– 22.33)	0.006 (0 – 0.025)
<i>In situ</i>	0.08 (0.02–0.14)	-- *	-- *

* The SEER registry does not capture *in situ* melanoma and thus it is not possible to calculate SIR or AER for groups including or restricting *in situ* cases

Table IIIUnivariate analysis of risk factors for development of subsequent melanoma (SMN, ocular or *in situ*)

Characteristic		Hazard Ratio (95% CI)	p-value
Sex	Male	0.99 (0.57–1.71)	0.97
	Female	1.00	
First degree relative with cancer	Yes	1.78 (0.99–3.21)	0.055
	No	1.00	
Treatment Era	1970–79	1.10 (0.61–2.01)	0.75
	1980–86	1.00	
Alkylating score	3 to 4	0.76 (0.29–1.96)	0.56
	1 to 2	0.58 (0.29–1.17)	0.13
	0 (none)	1.00	
Race	Others	0.67 (0.26–1.68)	0.39
	White Non-Hispanic	1.00	
RT (Any)	Yes	0.99 (0.53–1.84)	0.98
	No	1.00	