Melanoma as a subsequent neoplasm in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study

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Background

- Survivors of childhood cancer are at increased risk of developing secondary malignant neoplasms (SMN). Generally speaking, children treated for malignant disease are acknowledged to be at greatly increased risk for SMN following cancer treatment when compared to adult cancer survivors, with risk approaching 10-fold, corresponding to about a 21% risk at 30 years.
- Those at highest risk are females, older (adolescent) patients, those treated with radiation, and those with a primary diagnosis of Hodgkin lymphoma.
- The incidence of melanoma in the general population has increased over the past 2 years. In the United States, there are about 68,000 cases per year resulting in 8,700 deaths. Genetic factors, environmental factors, and immunosuppression are all linked to the development of the disease.
- The incidence and clinical characteristics of subsequent melanoma have not been well described in survivors of childhood cancer. One SEER-based study, found that among 23,819 pediatric cancer patients who survived 2 or more months after diagnosis, 25 developed melanoma which translated into an incidence that is 4-fold higher than that of the general population.
- The aim of this study was to describe the incidence, clinical characteristics and outcome of childhood cancer survivors who developed melanoma as a second malignant neoplasm and to identify possible risk factors that may predispose childhood cancer survivors to the development of melanoma.

Methods

- The Childhood Cancer Survivor study (CCSS) population is a multi-institutional cohort of over 14,000 patients. The CCSS population is the largest and most extensively studied cohort of individuals established for the study of late effects of cancer and its treatment in children. It is unique in that the cohort under study has been extensively characterized according to previous cancer therapy and occurrence of outcomes of interest. The majority of individuals in this cohort have now reached adulthood; thus, it is possible to investigate the occurrence of SMN.
- The population examined as part of this study included 14,358 5-year survivors of childhood cancer diagnosed between 1970-1986. In this cohort, the cumulative incidence (CIN) of first occurrence of subsequent melanoma (invasive, ocular, or in situ) was estimated.
- The CIN of melanoma and possible risk factors were tested using cause specific hazards models with age as the time scale and censoring at time of death.
- Risks for subsequent malignant melanoma as compared to those obtained from SEER database (excluding in situ and ocular melanomas) were calculated using standardized incidence ratios (SIR) and excess absolute risk (EAR) per 1000 person years.

Results

- 55 childhood cancer survivors were diagnosed with 61 malignant melanomas (invasive 50, in situ 9, and ocular 2). Of
these patients, 28 were male and 27 were female. 4 patients died as a direct consequence of their melanoma. 5 patients developed more than one melanoma.

- The median time to melanoma development was 20.7 yrs (range 5.6-35.4yrs). The median age at diagnosis of melanoma was 32 yrs (10.9 — 49.0 yrs)
- The preceding diagnoses included leukemia (16), lymphoma (15), soft tissue and bone sarcoma (n=15), brain tumor (5), Wilms' tumor (3), and neuroblastoma (1). At last contact, 82% of patients were alive.
- The CIN of first subsequent melanoma (excluding in-situ and ocular) at 36 yrs from initial cancer was 0.72% (95% CI 0.37-1.07). The excess absolute risk was 0.11. The CIN for each primary diagnosis ranged from 0.23% for brain tumors to 1.3% for soft tissue and bone sarcoma survivors.
- The SIR was 2.95 (95% CI 2.19 — 3.89), and EAR was 0.12 (95% CI 0.07 — 0.18) per 1000 person years.
- The occurrence of melanoma was not associated with age at primary cancer diagnosis, sex, race or family history of cancer. Patients with melanoma were more likely to be treated in an earlier era (70s-80s) but this was not statistically significant.

**Author's Conclusions**

- Although the incidence is low, survivors of childhood cancer are at increased risk for developing malignant melanoma. This risk appears to be approximately 3-fold compared to the general population, which may be of increasing important as the incidence of melanoma is rising.
- No specific risk factors for development of melanoma were identified which were statistically significant, although leukemia/lymphoma ad soft tissue /bone tumor patients were the most likely to develop melanoma.

**Clinical Implications**

- Increased melanoma awareness is needed for survivors of childhood cancers. There are no guidelines regarding screening for melanoma in survivors of childhood cancer, however, particularly for survivors of leukemia and sarcomas, annual full body skin examination may be useful.
- If additional information on skin type and previous sun exposure is available, determining whether an additive effect exits would be useful in identifying survivors who are at highest risk for melanoma.
- No real association has been documented regarding tumor location and radiotherapy exposure and treatment portals with regard to risk of development of melanoma. Longer follow-up may reveal an increased incidence in survivors who received radiotherapy. Other contributing factors to consider include the role of the number of nevi, genetic factors, and sun exposure.
- It will be useful to see if methods of radiotherapy that have the potential to reduce integral dose to tissues (such as proton therapy) will result in decreased second malignancy rates or melanoma. In the future, analysis of the pediatric patients treated with proton versus photon treatment would certainly be of great interest.