04-12

CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

Submitted:

Title: Sun sensitivity, sun exposure, sun protection behavior and risk of skin cancer (melanoma and NMSC)

Working Group and Investigators: This proposed publication will be within the SMN Working Groups and Cancer Control. Proposed investigators will include (name/email):

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Background and Rationale:

Skin cancer is the most common form of malignancy in the United States, accounting for over 1.3 million cases in 2003, and rates are continuing to increase[1]. Ironically, it is also the most preventable type of cancer. The American Cancer Society has estimated that UV exposure is associated with more than one million cases of basal cell and squamous cell cancers annually. Skin cancer is capable of extensive tissue destruction and invasion of adjacent organs, and is responsible for considerable morbidity and health care expenditures in the United States each year. The Surveillance, Epidemiology, and End Results Program (SEER) does not collect incidence data on NMSC, limiting the ability to track overall rates and trends in the United States. In a population-based study in New Hampshire, Karagas et al. found that between 1979-1980 and 1993-1994, the incidence rates of BCC increased by 82% in both men and women, and incidence rates of SCC increased by 235% in men, and 350% in women[2]. Incidence rates of newly diagnosed SCC and BCC over a one-year period in residents of New Hampshire, shows that the rates increase with age. In 1993-1994, the incidence rates per 100,000 person years for BCC in NH were 8.7, 113.4, 283.8 in age groups of < 35 years, 35-44, and 45-54 respectively. These incidence rates continued to increase with age, with a rate of 1081.8 per 100,000 for individuals between the ages of 65-74.

In the general population, the likelihood of developing skin cancer is related to genetic predisposition and subsequent exposure to environmental risk factors. Skin color is the major constitutional risk factor for skin cancer of all types[3]. Dark-skinned populations show much lower incidence than white populations living in the same climates. In the white population red hair and light skin color emerge strongly as independent risk factors. Sun exposure is the

strongest environmental risk factor for skin cancer. All types of skin cancer have been associated to the number of sunburns. Intermittent sun exposure has been shown to be associated with both melanoma and BCC whereas cumulative exposure is associated with SCC[4-8].

Skin cancer was the first type of cancer documented as being associated with exposure to ionizing radiation[9]. Researchers found an increased risk of BCC in atomic bomb survivors in Japan, with risk highest in individuals exposed at younger ages[10]. In later studies of radiation therapy for treatment of tinea capitis, similar results were seen, with increased risk associated with lower age at exposure, and with fair skin[11]. Available evidence also suggests that the excess risk of skin cancer increases from time of exposure and continues for 45 years or more following radiation[12]. Some evidence exists for an interaction between radiation treatment and amount of subsequent ultraviolet radiation exposure from sunlight[13]. Other studies have not confirmed these findings, possibly because these studies involved ethnic groups less sensitive to UV radiation, or had insufficient power to detect a possible interaction between UV and ionizing radiation.

The incidence rate of NMSC in survivors of childhood cancer has rarely been reported in the literature. However, several studies have reported the frequency of NMSC in cohorts designed to evaluate SMN, accounting for 6-29 % of all reported NMSC [14-16]. In the Childhood Cancer Survivor Study (CCSS), skin cancer is the most frequently occurring subsequent malignancy in the CCSS cohort, with nonmelanoma skin cancer accounting for 41% of all confirmed subsequent cancers, and melanoma for 3%. The incidence rate of BCC was 84.1, 446.1, and 973.9 per 100,000 person years for survivors who were < 35 years, 35-44 years, and 45-54 years of age respectively[17]. The incidence rate of the CCSS population was greater that what was seen in the population on New Hampshire, with survivors less than 35 years of age having almost 10 times the incidence rate seen in NH. Survivors aged 45-54 had incidence rates comparable to NH residents who were 65-74 years of age. Review of the radiation records found that 91% of the NMSC occurred within the previous radiation fields.

We have recently collected data on the Follow-up 2 survey regarding sun sensitivity, past sun exposure, and present sun protection behavior. This allows us the opportunity to determine whether there is an interactive effect between radiation exposure, hair/skin color and previous sun exposure. It will also allow us the opportunity to investigate current sun exposure behaviors for possible future intervention studies.

Specific Aims/Objectives/Research Hypotheses: One of the major goals of the CCSS is to educate survivors' about possible risk posed by their past exposure to radiation during treatment and current exposure to ultraviolet radiation in sunlight. This analysis will determine whether there is a multiplicative or additive effect between radiation exposure and known risk factors (sun sensitivity and sun exposure). It will also determine current sun protection behaviors. This information can be applied to future intervention studies regarding behavior change toward sun protection measures.

Hypotheses:

1. Among survivors of childhood cancers who received radiotherapy, those with fair skin, have a higher risk of skin cancer than darker skinned individuals.
2. Among survivors of childhood cancers who received radiotherapy, those with a history of sunburns are at higher risk for skin cancer than those without a history of sunburns.

3. Survivors of childhood cancers who received radiation therapy will have similar sun protection behavior as survivors who did not receive radiation therapy.
4. Survivors of childhood cancers will have similar sun protection behavior as siblings with similar skin color.

Analysis Framework:

a) Outcomes of interest:
- From the baseline, Follow-up 1, and Follow-up 2 survey, the occurrence of a NMSC (basal cell carcinoma or squamous cell carcinoma) or melanoma.
- From the Follow-up 2 survey, Sun protection questions (C7-13)

b) Subject population: all member of the CCSS cohort (both cases and controls)

c) Explanatory variables:

-Diagnosis
-Age at diagnosis
-Time since diagnosis
-Treatment
- Chemotherapy Y/N
- Radiation Y/N,
- Location of skin cancer occurred within the field of radiation (Y/N).

-Current age
-Sex (M, F)
-Race (White, Black, Hispanic, American Indian, Asian, other)

<u>From Follow-2 survey:</u>
- Sun sensitivity questions (C.1-3)
- Sun exposure questions (C.4-6)
- Previous sunburn questions (C.5-6)

d) Types of analysis: Initial analysis will be descriptive in nature (tables 1-2). Categories of skin, eye, and hair color will first be looked at individually, and will likely be grouped after initial numbers are determined. Previous literature have categorized these as:
- eye color: 1) dark brown/black, 2) light brown, 3) hazel, grey-blue, blue, or green
- hair color: 1 dark brown/black, jet black 2) light brown, medium brown, red-brown, 3) light blond, blond, strawberry blond, or red
- skin color: 1) brown, dark brown, black, 2) light tan, brown, or olive, 3) pale or milky white, very light brown, sometimes freckles

Previous sunburns and sun sensitivity will also be evaluated with the occurrence of skin cancer (Yes/No). Possible categorizations cited in previous literature are:
- previous sunburns: before age of 21 (none, 1-2, 3+ times) , after age of 21 (none, 1-2, 3+ times)
- sun sensitivity: 1) usually tan sometimes burn, always tan rarely burn, 2) never tan always burn, sometimes tan usually burn

The primary analysis of interest is to determine whether the magnitude of the association between radiation and risk of skin cancer is modified by hair/eye/skin color, previous sunburns, or sun sensitivity. Each of these variables will be stratified as discussed above, and relative risks between radiation exposure and skin cancer will be calculated within each stratum.

Sun protection behavior (C.7-13) will be evaluated comparing survivors with and without radiation, and will also be compared to behavior in siblings. Behaviors will also be evaluated by looking at the explanatory variables listed above and other health behaviors (smoking, alcohol use, general check-ups, and cancer screening).

Due to our increase in the number of skin cancers since the first analysis, other multivariate modeling will be considered. For example, in the previous analysis we observed a higher proportion of NMSC cases in Hodgkin's disease cases. Attempts will be made to determine the role of age at original cancer diagnosis, cancer type, radiation exposure, and current age.

Cumulative incidence curves of developing a NMSC for survivors and siblings will also be constructed, to show the rate of increase of NMSC in this population over time.

e) Specific tables:

Table 1: **Comparison of Cancer Characteristics in CCSS Cohort**

	Overall cohort	**NMSC cases**	**Melanoma**	**No skin cancer**
Total				
Age at Diagnosis				
0-4				
5-9				
10-14				
15-20				
Cancer Diagnosis				
Bone				
CNS				
Hodgkin's Disease				
Kidney (Wilms)				
Leukemia				
Neuroblastoma				
Non-Hodgkin's lymphoma				
Soft tissue sarcoma				
Second Cancer				
Malignant				
None				
Recurrence of Cancer				
Yes				
No				
Years Since Diagnosis				
5-9				
10-14				
15-19				
20+				

Table 2. Comparison of sun sensitivity and sun exposure in CCSS Cohort

	Overall cohort	NMSC cases	Melanoma	No skin cancer
Natural Skin color				
Pale white				
Very light brown				
Light tan, brown, olive				
Brown, dark brown, black				
Eye color				
Blue				
Blue-grey				
Hazel				
Green				
Light brown				
Dark brown/black				
Mixed/other				
Natural hair color				
Light blond				
Blond				
Light brown				
Medium brown				
Red-brown				
Strawberry blond				
Red				
Dark brown/black				
Jet black				
Sun sensitivity				
Never tan, always burn				
Sometimes tan, usually burn				
Usually tan, sometimes burn				
Always tan, rarely burn				
Number of sunburns < 21 years of age				
Never				
1-2 times				
3-5 times				
6+ times				
Number of sunburns > 21 years of age				

Never				
1-2 times				
3-5 times				
6+ times				

Additional comments: The determination of whether the location of the NMSC was within the radiation field was ascertained by Joanna and Joe for the first 618 NMSC. Additional skin cancers (NMSC and melanomas) that have been reported subsequently, and all melanomas will be evaluated for location in an identical manner.

References:

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