Title: Absence of basal cell carcinoma in irradiated childhood cancer survivors of black race: a report from the St. Jude Lifetime Cohort Study

Running Title: BCC in irradiated black cancer survivors

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Abstract:

Background: Cancer survivors exposed to therapeutic radiation are at increased risk for basal cell carcinoma (BCC). Despite the notable influence of race on rates of BCC in the general population, the same is not clearly defined in previously irradiated cancer survivors. We investigated the influence of race on the development of BCC in adult survivors of childhood cancer.

Methods: Using a retrospective cohort study, outcomes were collected through June 30, 2015 for 1,746 irradiated childhood cancer survivors participating in the St. Jude Lifetime Cohort Study (SJLIFE), comprising a total of 33,147 person years of follow-up. Subsequent neoplasms identified in survivors through self-report and prospective clinical assessment were validated by pathology reports. Expected numbers of each type of radiation-associated neoplasm, including BCC, were calculated for irradiated black survivors based on rates in irradiated white survivors, accounting for primary cancer diagnosis, diagnosis year, attained age, and sex.

Results: Based upon the rate of BCC in previously irradiated white survivors, 56.1 BCCs were expected among 237 black survivors, yet none observed. In contrast, the observed to expected ratio of non-BCC radiation-associated neoplasms (melanoma, brain, breast, thyroid cancer) was 0.88 (30 observed/34.2 expected, 95% confidence interval 0.59-1.25).

Conclusions: We identified an unexpected absence of BCC in irradiated black survivors in SJLIFE. We observe a similar absence of BCC in black individuals among two additional cohorts treated with irradiation for childhood cancer.

Impact: Black survivors are at a substantially reduced or absent risk for BCC from therapeutic radiation for reasons not yet fully understood.
Introduction
Childhood cancer survivors are at risk for subsequent neoplasms (SNs), which comprise basal cell carcinoma (BCC) in approximately 50-60% of cases (1, 2). BCC risk is predominantly associated with curative doses of ionizing radiation incurred during cancer therapies (1, 3). Similarly, ionizing radiation exposure has been shown to increase the risk for BCC in atomic bomb survivors, radiological health care workers, and individuals irradiated for benign medical conditions (4-13).

The incidence of de novo BCC in the general population is dependent upon demographics and geographic ultraviolet radiation (UVR) exposures; therefore estimated rates vary appreciably. It is evident, however, that in the general population whites develop BCC at higher rates than blacks (14, 15). A recent report from the United States suggested that whites had a 70-fold higher incidence of BCC than age- and sex-matched blacks (14). In addition, individuals of fair complexion, with higher UVR exposure, and exposed at younger ages are at highest risk (15). Reduced occurrences in blacks and non-sun-exposed anatomic locations in whites have led some to hypothesize that discrete pathogenic mechanisms may contribute to these variable presentations (16).

Despite the notable influence of race on rates of BCC in populations not exposed to ionizing radiation, the same is not clearly defined in cancer survivors treated with radiation therapy. Compared to irradiated non-white cancer survivors, irradiated whites have been shown to be at significantly increased risk for BCC by some (2), but not other investigators (3, 17); however, outcomes for blacks specifically were not reported. Most studies of populations other than
cancer survivors either did not report outcomes by race or were limited by the non-black racial homogeneity of their cohorts (4-8, 10-12). Apart from those occurring in individuals with nevoid basal cell carcinoma syndrome (NBCCS) (18-20), the few reports of BCC in previously irradiated blacks are limited to individuals treated with scalp radiation for tinea capitis (21, 22). These observations led us to investigate the influence of race on the occurrence of BCC in previously irradiated adult survivors of childhood cancer.

Materials and Methods
The St. Jude Lifetime Cohort Study (SJLIFE) is an institutional review board-approved, ongoing clinical study designed to facilitate longitudinal evaluation of health outcomes among adult survivors of pediatric malignancies. Active patient accrual has been occurring since 2007. Informed consent for this study was obtained for all participants. The study methods have been previously described (23). Briefly, subjects eligible for SJLIFE were previously treated for childhood cancer at St. Jude Children’s Research Hospital, had survived ≥ 10 years from diagnosis, and were ≥ 18 years old at study enrollment. For the purposes of the current study, only those participants who were previously treated with ionizing radiation and had completed an on campus assessment prior to June 30, 2015 were included. Treatment exposures, cumulative chemotherapy doses, radiation doses to individual anatomic sites, and medical events during and after therapy were abstracted from medical records. All retrospective and prospective data in the current report were collected under the SJLIFE protocol. At the SJLIFE baseline clinical assessment, participants completed comprehensive questionnaires that provided self-reported health outcomes, demographic factors, and medical history. Individuals underwent risk-based screening for chronic health conditions, including
subsequent neoplasms (SNs), per the *Children’s Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer* (24). Subsequent neoplasms were confirmed by central review of pathology reports following ascertainment of previously occurring, through questionnaire/patient-report, and newly identified SNs, through prospective clinical assessment that included skin examination by SJLIFE clinicians. Suspicious lesions were referred for additional evaluation by a dermatologist. In the current analysis, radiation-associated SNs were restricted to skin (BCC and melanoma), brain, thyroid, and breast. Given prior studies reporting a lack of association with ionizing radiation, squamous cell carcinomas were not considered in the analysis of radiation-associated neoplasms (6, 13).

We calculated an expected number of each type of radiation-associated SN in irradiated blacks, assuming the same rates of development as were seen in irradiated white survivors, accounting for the effects of primary cancer diagnosis, calendar year of diagnosis, attained age, and sex. Specifically, we fitted a piecewise exponential model with these categorical covariates to irradiated whites’ person-time data of each type of the radiation-associated SNs, using the logarithm of person-years as the offset. The fitted model was applied to irradiated blacks’ person-time data of the same SN type to obtain their expected count. Multiple occurrences within individual survivors were accounted for using generalized estimating equations modifying the piecewise exponential models above. Observed to expected ratios and 95% confidence intervals (CI) were calculated by SN type in irradiated blacks based on Poisson probability models for the observed counts given the expected counts.
Results
Among 1,746 eligible survivors with 33,147 person years (PY) of follow-up, 320 SNs occurred in 160 individuals. The median (range) follow-up time was 28.8 (11.1-52.5) years. The ratio of observed to expected non-BCC radiation-associated SNs in irradiated blacks was 0.88 (30 observed/34.2 expected, 95% CI 0.59-1.25). Although not statistically significant, irradiated blacks had lower than expected subsequent thyroid and breast cancers. We expected 56.1 BCCs in irradiated blacks (mean maximum radiation dose: 33.9 Gy, range: 10.0-99.6 Gy), yet observed zero (95% CI 0.00-0.07) (Table 1). Similarly, when considering only the first-occurrence of any SN, 19.5 BCCs were expected but none observed (95% CI 0.00-0.19) (Table 2).

Discussion
We identified an unexpected absence of BCC in irradiated blacks in SJLIFE. These findings underscore a similar pattern among three distinct cohorts (Table 3). Shore and colleagues were first to report an absence of BCC in blacks treated with irradiation for tinea capitis (median follow-up 25.7 years; delivered doses of 300-600 rad). Despite a clear propensity for irradiated individuals to develop BCC (relative risk 3.8, 95% CI 2.8-5.2), none developed in blacks (3,010 PY) compared to 41 in whites (21,763 PY) (p=0.003) (9). Extended follow-up of this cohort (median 39.3 years) identified only three BCC in irradiated blacks, whereas irradiated whites remained at 10-fold higher risk for BCC (RR 10.0, 95% CI 3.2-31.4) compared to irradiated blacks (21). Similarly, Schwartz et al. investigated the occurrence of BCC after total-body irradiation (9.2-15.75 Gy) in transplant survivors with a median follow-up duration of 6.6 years (range 0.3-36.2). Despite the occurrence of 197 BCCs in 3,512 whites
(17), none occurred among 60 blacks (W.M. Leisenring; personal communication). Lastly, investigators from the Childhood Cancer Survivor Study (CCSS) identified 1,116 BCCs in 7,527 irradiated whites compared to zero in 313 blacks after a median duration of follow-up of 25.1 years (6.5-38.9) (25). Of note, only 39 (12%) of the black survivors in CCSS were also included in our study cohort.

Together these findings highlight a provocative series of observations suggesting that irradiated blacks are at a substantially lower risk for BCC than expected based upon the increased rate seen in irradiated compared to non-irradiated whites. Even taking into consideration the occurrence of three BCCs in irradiated blacks reported by Shore and colleagues, our finding of no BCC in irradiated blacks contrasts the earlier and more frequent occurrence of BCC observed in previously irradiated whites. This observation remains unexplained within the existing literature, leaving only speculation as to the underlying mechanism.

One might anticipate an additive effect of high intensity, short duration, ionizing radiation on UVR carcinogenesis, in which case we would expect a substantial increase in the occurrence of BCC in irradiated, compared to non-irradiated, blacks (Figure 1). The observed lack of increase among irradiated blacks emphasizes the need for a better mechanistic understanding of BCC pathogenesis in irradiated cancer survivors.

A previous report from the CCSS suggested that darker skin pigmentation is associated with a reduced risk for BCC after ionizing radiation (3). Similarly, the substantially lower risk of BCC
in blacks compared to whites irradiated for tinea capitis led investigators to speculate regarding the potentially modifying effects of UVR exposure on carcinogenesis from ionizing radiation (21). However, if this difference can be attributed to the photoprotective effects of melanocytes against UVR alone (26), one might anticipate blacks to experience a reduced, yet still tangible rate of BCC, in contrast to the complete absence we have observed in cancer survivors. Likewise, one might also expect reduced radiation treatment efficacy in black cancer cohorts. Few malignancies are treated with radiation alone, leaving this question difficult to address. Zaki and colleagues reported decreased 5-year overall survival for blacks compared to whites treated with radiation monotherapy for Hodgkin lymphoma (68% vs. 78%) (27). The same survival disparity has not been observed in children treated for Hodgkin lymphoma with a combination of radiation and systemic chemotherapy (28, 29).

Alternatively, genotypic rather than phenotypic mechanisms may be responsible for this seemingly protective effect in blacks. It is well-recognized that genetic variants can cause greater DNA damage, inhibit DNA repair, and impair chemotherapy transport mechanisms and metabolism (30). Germline mutations in the tumor suppressor gene PTCH have been linked to NBCCS, an autosomal dominant condition in which, among other anomalies, individuals are at substantially higher risk for multiple BCC (31). Despite a reduced rate of BCC in black individuals with NBCCS (32), black individuals exposed to ionizing radiation may develop numerous BCC within previous radiation fields (18). Conversely, protective germline variants may contribute to the reduced risk of BCC we have observed in irradiated black survivors. Given the ongoing genomics initiatives within childhood cancer survivor cohorts such as SJLIFE and CCSS, our findings come at a crucial juncture in time when focused investigations
to better understand potentially underlying genetic mechanisms can be performed. If identified, the implications of these findings may extend beyond surveillance strategies, impacting upfront treatment approaches for survivors of all races and ethnicities.
Acknowledgements

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References:


# Table 1. Observed and expected counts of multiple subsequent radiation-associated neoplasms in irradiated white and black survivors in the St. Jude Lifetime Cohort Study

<table>
<thead>
<tr>
<th>SNs</th>
<th>Irradiated White Survivors</th>
<th>Irradiated Black Survivors</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total N = 1509</td>
<td>Total N = 237</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. of pts. with SNs</td>
<td>No. of SNs</td>
<td>Rate$^a$</td>
</tr>
<tr>
<td>BCC</td>
<td>150</td>
<td>560</td>
<td>19.17</td>
</tr>
<tr>
<td>Non-radiation-associated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>33</td>
<td>41</td>
<td>1.40</td>
</tr>
<tr>
<td>Non-BCC radiation-associated$^b$</td>
<td>160</td>
<td>320</td>
<td>10.95</td>
</tr>
<tr>
<td>Brain</td>
<td>98</td>
<td>232</td>
<td>7.94</td>
</tr>
<tr>
<td>Thyroid</td>
<td>53</td>
<td>63</td>
<td>2.16</td>
</tr>
<tr>
<td>Breast$^c$</td>
<td>18</td>
<td>22</td>
<td>1.59</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3</td>
<td>3</td>
<td>0.10</td>
</tr>
</tbody>
</table>

$^a$ Per 1,000 person-years  
$^b$ Any of melanoma, brain, breast, thyroid neoplasms  
$^c$ Females only (N=703 White; N=115 Black)

SNs indicates subsequent neoplasms; No., number; pts., patients; SCs, squamous cell carcinoma; BCC, basal cell carcinoma

Person years: 29206.06 for males and females combined in white survivors, 3940.65 for males and females combined in black survivors, 13801.66 for female white survivors, and 1918.93 for female black survivors.
Table 2. Observed and expected counts of first subsequent radiation-associated neoplasms in irradiated white and black survivors in the St. Jude Lifetime Cohort Study

<table>
<thead>
<tr>
<th>SNs</th>
<th>Irradiated White Survivors</th>
<th>Irradiated Black Survivors</th>
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</thead>
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<tr>
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<td>Total N = 1509</td>
<td>Total N = 237</td>
</tr>
<tr>
<td>No. SNs</td>
<td>Rate^a</td>
<td>No. SNs [O]</td>
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<td>Melanoma</td>
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<td></td>
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<td>0.00</td>
</tr>
</tbody>
</table>

^a Per 1,000 person-years
^b Any melanoma, brain, breast, or thyroid neoplasms
^c Females only (N=703 White; N=115 Black)

SNs indicates subsequent neoplasms; No., number; pts., patients; SCs, squamous cell carcinoma; BCC, basal cell carcinoma
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Description</th>
<th>Median (range) follow-up duration (years)</th>
<th>White BCC/total irradiated</th>
<th>Black BCC/total irradiated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walther, et al. 1981</td>
<td>Case report of child irradiated for tinea capitis</td>
<td>36</td>
<td>NA</td>
<td>1/1</td>
</tr>
<tr>
<td>Schwartz, et al. 2009c</td>
<td>Fred Hutchinson Cancer Center hematopoietic stem cell transplant survivors</td>
<td>6.6 (0.3-36.2)</td>
<td>197/3,512</td>
<td>0/60</td>
</tr>
<tr>
<td>Liu, et al. 2016</td>
<td>Childhood Cancer Survivor Study participants</td>
<td>25.1 (6.5-38.9)</td>
<td>1,116/7,527</td>
<td>0/313d</td>
</tr>
</tbody>
</table>

a Irradiated individuals among all races included in cohort
b Estimated from percentages provided in descriptive study table
c W.M. Leisenring; personal communication
d 39 out of 313 also included in SJLIFE cohort
Figure Legends:

**Figure 1.** Effect of ionizing radiation on the development of basal cell carcinoma (BCC) in childhood cancer survivors.
**Shared Risk Factors**

**Age-specific BCC Rate**
(per 100,000 Person-years)

- **White**
  - General Population:
    - <40 years: 51
    - 40-64 years: 987
  - Pediatric Cancer Survivors:
    - <40 years: 1,205
    - 40-64 years: 5,921

- **Black**
  - General Population:
    - <40 years: 0
    - 40-64 years: 12
  - Pediatric Cancer Survivors:
    - No increase

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* High exposure of short duration

**Rates for general population from Asgari, et al.**

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* Ionizing radiation*