**CCSS Study Analysis Concept Proposal**

**Epidemiology and Biostatistics Working Group (Primary)**

## 1. Study Title: Burden of Morbidity after Basal Cell Carcinoma in Childhood Cancer Survivors

**2. Working Group and Investigators:** Epidemiology/ Biostatistics Working Group, Second Malignancies Working Group and Chronic Diseases Working Group

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## 3. BACKGROUND AND RATIONALE

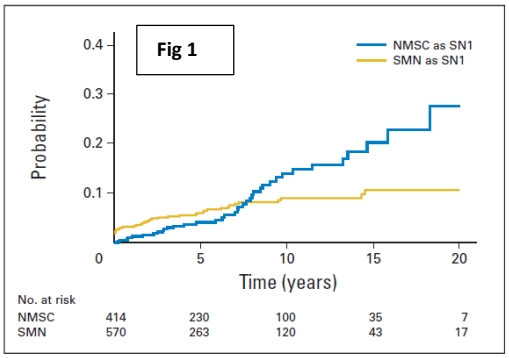
***Basal cell carcinoma among cancer survivors:*** Childhood cancer survivors are at an increased risk of developing NMSC. In a prior analysis among 13,132 Childhood Cancer Survivor Study (CCSS) participants, 213 reported NMSC (97% were BCC); 99 (46%) had multiple occurrences.[1] Median age of occurrence was 31 years (range, 7 to 46 years). Ninety percent of the patients had received radiation therapy; 90% of the tumors occurred within the radiation field. Radiation was associated with a 6.3-fold increased risk of developing NMSC (95% CI, 3.5-11.3).

***Risk factors for BCC:*** Ultraviolet radiation (UVR) is a proven human carcinogen;[2] over 90% of BCC are associated with exposure to solar UVR.[3] Both long-term sun exposure as well as occasional extended, intense exposure (typically leading to sunburn) combine to cause damage that can lead to BCC. Indoor tanning devices have been now included on the list of most dangerous cancer-causing substances (along with plutonium, cigarettes and solar UVR) by the International Agency for Research on Cancer (IARC), an affiliate of the World Health Organization,[4] and have also been classified by the FDA as class II devices (those associated with moderate to high risk of cancer).[5] Incidence rates of BCC are noted to increase with increasing ambient solar UV exposure. Length of exposure, exposure at an early age, and total accumulated exposure are important factors in BCC development.[6-9] Phenotypic risk factors for BCC include family history of melanoma, blond/red hair color, higher number of extremity moles, higher susceptibility to sunburn as a child/ adolescent, and higher lifetime number of severe/blistering sunburns.[10] People who have had one BCC are at risk for developing others over the years.

Exposure to ionizing radiation is also an established risk factor for BCC.[11-16] Evidence of this association has been documented in workers using early radiation devices,[17] individuals treated with low-dose ionizing radiation for tinea capitis or thymic enlargement in childhood,[11,12,14] and survivors of the atomic bombings.[11] A strong positive dose-response association was observed in the latter population.[11] Stem cell transplant recipients exposed to total body irradiation (TBI) are reported to have an absolute excess risk of 24 cases of BCC per 10,000 person-years compared with those not exposed to TBI.[15] Among childhood cancer survivors, radiation therapy, either alone or in combination with chemotherapy, was associated with an increased risk of BCC compared with no chemotherapy or radiation. The odds ratio for subjects who received 35 Gy or more to the skin site vs no radiation therapy was 39.8 (95% CI = 8.6 to 185). Radiation doses to the skin of more than 1 Gy are associated with an increased risk of BCC. Results were consistent with a linear dose–response relationship, with an excess odds ratio per Gy of 1.09 (95% CI = 0.49 to 2.64).

No other treatment variables were statistically significantly associated with an increased risk of BCC.[18] The rate of BCC occurrence continues to grow with increasing time since irradiation exposure.[12]

***BCC is associated with an increased risk of subsequent neoplasms among cancer survivors:*** Radiation-exposed survivors who developed an SN1 of BCC had a cumulative incidence of subsequent malignant neoplasm (SMN; i.e., malignancies excluding BCC) of 20.3% (95% CI, 13.0% to 27.6%) at 15 years compared with only 10.7% (95% CI, 7.2% to 14.2%) for those who were exposed to radiation and whose SN1 was an invasive SMN (excluding BCC) (**Fig 1**).[19]




**The strong evidence of the association between personal histories of BCC with increased risk of developing other malignancies, indicates that a common mechanism, perhaps a defect in DNA damage response when faced with carcinogens could explain these associations.**

**DNA damage Response and Human Disease**

Each of the ~$10^{13}$ cells in the human body develops tens of thousands of DNA lesions per day.[20] These lesions can block genome replication and transcription, and if they are not repaired or are repaired incorrectly, they lead to additional genomic aberrations that threaten cell viability. The most pervasive environmental DNA-damaging agent is UV light. UV-A and UV-B in strong sunlight can induce ~100,000 lesions per exposed cell per hour. Ionizing radiation has been proven to be an iatrogenic cancer-causing agent.[1,18,19,23,24] Cells have evolved mechanisms – collectively termed the DNA damage response (DDR) – to detect DNA lesions, signal their presence and promote their repair.[25-27] Cells defective in these mechanisms generally display heightened sensitivity towards DNA-damaging agents and many such defects cause human disease. Although responses differ for different classes of DNA lesions, they operate collectively and share many components.

**Cancer and DNA damage**

Most carcinogens operate by generating DNA damage and causing mutations.[28,29] A fundamental feature of cancer is genome instability[30], as illustrated by mismatch repair defects (MMR) (and associated microsatellite instability) and the predisposition to colorectal and endometrial cancer[31], and chromosomal instability observed in most solid tumors[32]. Inherited DDR defects predispose to cancer, contribute to "mutator phenotype" of many malignancies, and may allow tumor-cell survival and proliferation. Aberrant cell proliferation, caused by oncogene activation or tumor suppressor inactivation, elicits DNA-replication stress and ongoing DNA damage. While the DDR is activated in early neoplastic lesions and likely protects against malignancy, [33,34] breaches to this barrier (arising through mutational or epigenetic inactivation of DDR components) are subsequently selected for tumor development, thus allowing malignant progression. This model helps explain the high frequency of DDR defects in human cancers.[35]

***DNA Repair defects and BCC-subsequent cancer association:*** Common, low-penetrant DNA repair gene variants could possibly play a role in the observed increased susceptibility among BCC patients to develop visceral invasive malignancies. A cohort study was conducted to examine the association between *XPD* Lys751Gln polymorphism and risk of a second primary cancer in individuals with BCC.[36] Persons with at least one Gln allele had an increased risk of a second primary cancer compared with the reference Lys/Lys genotype (adjusted IRR 2.22, 95% CI 1.30-3.76). When the reference category was limited to never smokers with the Lys/Lys genotype, the risk of developing a second primary cancer associated with having at least one Gln allele was increased >3-fold in both never smokers (IRR 3.93, 95% CI 1.36-11.36) and ever smokers (IRR 6.14, 95% CI 2.17-17.37). These findings suggest that individuals with BCC who have the variant *XPD* Gln allele are at increased risk of developing a second primary cancer.

Results from another recent study are indeed suggestive of the contribution of DNA repair genes to the BCC cancer prone phenotype.[37] A promising lead was a genetic variant in *TDG* (thymidine DNA glycosylase gene; OR=1.5, 95% CI, 1.2–1.9; P=0.0001). This gene plays a role in base excision repair (BER) as well as in regulating the epigenome and gene expression. An additional eight SNPs were associated with the BCC cancer-prone phenotype (additive model: *P*-values < 0.01); these SNPs were located in six pathways and seven genes: two nucleotide excision repair (*ERCC8*, *ERCC3*), two homologous recombinational repair (*PALB2*, *DMC1*) and one each from direct reversal repair (*MGMT*), DNA damage signal transduction (*CHEK2*) and mismatch repair (*MSH6*).

**Neurodegenerative Disorders and DDR**

Accumulation of DNA lesions in neurons is associated with neurodegenerative disorders, such as Alzheimer's and Parkinson's.[38,39] The high mitochondrial respiration and associated reactive-oxygen-species (ROS) production exhibited by neurons makes the mitochondrial and nuclear DNA susceptible to damage.[40] BER and SSBR play a critical role in repairing such mitochondrial and DNA lesions; defects in these pathways trigger neuronal dysfunction and degeneration.[38,41] Furthermore, the limited capacity for neuronal cell replacement in adulthood possibly leads to accumulation of damaged but irreplaceable terminally differentiated neurons. Adding further insult, being in G0, neuronal cells do not repair double strand breaks (DSB) by homologous recombination (HR) but must employ the error-prone non-homologous end joining (NHEJ).[38] Finally, neurons rely on transcription and oxidative DNA damage can block this. Thus, accumulation of DNA lesions in repair-defective patients – and possibly in aging normal individuals – might progressively deprive neurons of vital transcripts, leading to cell dysfunction or apoptosis.[42] Such processes presumably contribute to the neurodegeneration observed in ataxias and in Cockayne syndrome, caused by defects in DNA strand break repair and transcription-coupled NER, respectively.[38,39] Finally, such processes likely play a role in the development of treatment-related structural/ functional defects in the brain among childhood cancer survivors.

**Cardiovascular disease and DDR**

There is a growing body of evidence that points to atherosclerosis being characterized by enhanced DNA damage and DDR signaling leading to senescence of vascular smooth muscle cells and death of other cells, yielding atherosclerotic lesions.[43] Patients with defective DDR commonly exhibit insulin resistance and glucose intolerance.[44,45] There is a growing body of evidence pointing to an increased risk of cardiovascular disease among cancer survivors that is directly related to chest radiation; this risk is modified by cardiovascular risk factors such as diabetes mellitus.[46-48] Furthermore, several studies have implicated the role for abdominal radiation or total body irradiation in the development of insulin resistance and diabetes mellitus.[49,50]

## SIGNIFICANCE

***Basal cell carcinoma in the general population:*** Basal cell carcinoma (BCC) is the most common form of cancer; an estimated 2 million are diagnosed annually in the US.[51] The incidence of BCC exceeds the combined incidence of cancers of the breast, prostate, lung and colon.[52] The incidence peaks at approximately 70 years of age, and the lifetime risk is estimated at 33%, with the risk for men greater than that of women.[10] By age 70 years, nearly 1 in 6 non-Hispanic white US residents has had at least 1 BCC. However, only three thousand deaths directly related to advanced BCC occur annually in the US.[53]

***Risk of subsequent neoplasms after BCC in the general population:*** Several studies have reported that individuals diagnosed with BCC have 20% to 60% higher risk of subsequent malignancies.[54-69] Furthermore, several studies have shown that the increased risk of cancer after BCC cannot be fully explained by known cancer risk factors.[56,58,66,69] The prior diagnosis of BCC is associated with a broad spectrum of malignancies.[68] The strongest statistically significant associations have been reported between a personal history of BCC and the subsequent development of melanoma, lip, oropharynx, non-Hodgkin lymphoma, and lung cancer. These cancers have demonstrated significant associations with environmental exposures (tobacco, UVR, therapeutic radiation).

***Implications of association between BCC and subsequent malignant and non-malignant chronic health conditions in the general population and among cancer survivors:*** An association between BCC and other chronic health conditions that are dependent on an impaired DDR would mean that a personal history of BCC could serve as a marker for select malignant and non-malignant conditions. Ultimately, identification of those at greatest risk of key malignant and non-malignant chronic health conditions through the discovery of novel biomarkers will aid in implementation of targeted screening and intervention.

## SPECIFIC AIMS

The analysis will be restricted to childhood cancers with prior exposure to radiation. Each case of BCC (occurring as a first event after cohort entry) will be matched with CCSS survivors without BCC for at least the same length of follow-up time from primary cancer diagnosis to the case's BCC development + ≥10 years, on site of radiation (head, neck, thorax, spine, LU, LL, RU, RL extremity, abdomen and pelvis) and dose of prescribed radiation to that site. Using this cohort of childhood cancer survivors, we will:

**Aim 1.** Determine the risk of non-BCC SMNs among childhood cancer survivors with BCC, when compared with childhood cancer survivors without BCC

*Aim 1.1* *Determine the risk of first non-BCC SMN among childhood cancer survivors with BCC, when compared with childhood cancer survivors without BCC*

*Aim 1.2* *Determine the risk of first non-BCC SMN among childhood cancer survivors with multiple BCCs, when compared with childhood cancer survivors with a single BCC*

*Aim 1.3* *Determine the risk of site specific non-BCC SMNs (for the most common non-BCC SMNs) among childhood cancer survivors with BCC, when compared with childhood cancer survivors without BCC*

**Hypothesis 1.** **Childhood cancer survivors with BCC will be at increased risk for developing SMNs when compared with those without BCC, after adjusting for chemotherapy and demographic risk factors.**

**Aim 2.** Determine the risk of subsequent chronic health conditions among childhood cancer survivors with BCC, when compared with childhood cancer survivors without BCC

*Aim 2.1* *Determine the risk of any subsequent grade 3-5 chronic health condition among childhood cancer survivors with BCC, when compared with childhood cancer survivors without BCC*

*Aim 2.2* *Determine the risk of any subsequent grade 3-5 chronic health condition among childhood cancer survivors with multiple BCCs, when compared with childhood cancer survivors with a single BCC*

*Aim 2.3* *Determine the risk of specific chronic health conditions (for most common chronic health conditions) among childhood cancer survivors with BCC, when compared with survivors without BCC*

**Hypothesis 2.** **Childhood cancer survivors with BCC will be at increased risk for grade 3-5 health conditions when compared with those without BCC, after adjusting for chemotherapy and demographic risk factors.**

## 4. ANALYSIS FRAMEWORK

- ***Outcome of interest:*** The primary outcomes of interest are:
    - Subsequent malignant neoplasms
    - All CTCAE grades ≥3 chronic health conditions
- ***Exposure of interest:*** The primary exposure of interest is the occurrence of BCC prior to development of Outcomes of Interest in childhood cancer survivors with prior exposure to radiation.
- ***Population of interest:*** Original CCSS cohort. Eligibility criteria for our study will mirror the eligibility for the CCSS cohort with history of exposure to radiation for management of primary cancer.
- ***Exploratory variables:*** The following information will be requested from CCSS Medical Records Abstraction Form (MRAF) or questionnaire data:
    - Primary cancer diagnosis
    - Subsequent malignant neoplasms
    - Chronic health conditions ≥grade 3
    - Age at primary cancer diagnosis
    - Age at diagnosis of BCC
    - Age at diagnosis of SMN
    - Age at diagnosis of chronic health conditions
    - Age at most current questionnaire completion
    - Date of death (and cause)
    - Gender
    - Race/ethnicity
    - Treatment history, including:
        - Radiation field and dose to prescribed radiation field
        - Chemotherapy: yes/ no
        - Anthracycline cumulative dose
    - Sun exposure and sun burn history (for the subset where this information is available)

- ***Statistical analysis:*** The baseline characteristics of participants according to BCC status will be compared by use of Student *t* test for continuous and Pearson $\chi^2$ test for categorical variables.

  Cox regression analysis with time-dependent covariates will be used to determine the hazard ratios (henceforth referred to as relative risks [RR]) and 95% confidence intervals (CIs) of subsequent malignant neoplasms associated with a previous diagnosis of BCC when compared with no previous diagnosis of BCC. For this study, the independent variable of interest will be the presence or absence of a pathologically confirmed BCC diagnosis among childhood cancer survivors. The follow-up time for each survivor with BCC and his/her matched survivors without BCC will start at the case's BCC incidence. The second and subsequent BCC development will be treated as time dependent and studied in relation to the risk of subsequent malignancies other than BCC. The follow-up time for all analyses will end at the earliest of the date of completion of the most current questionnaire, the first diagnosis of a subsequent malignancy other than BCC, or death. Estimates of RR and 95% CI of developing subsequent malignancies other than BCC associated with BCC incidence will be derived from a model that adjusts for age at primary cancer diagnosis, sex, BMI (continuous), cigarette smoking (never, former, or current), chemotherapy (yes/ no), skin type, sunburn history, and time from the study entry, with strata being the matched sets. To more carefully account for the possible confounding or modifying effects of age and primary cancer diagnosis, we will also conduct a primary cancer-stratified and age-stratified analysis.

- Similar analyses will be conducted using subsequent development of grades 3-5 chronic health conditions as the outcome of interest overall, and by specific type (the most prevalent types).

- ***Power analysis:*** Among the 14,364 participants in the original CCSS cohort, 602 survivors have reported 1,274 BCCs (ICD03 codes of 8090, 8091, 8093 or 8097). For 538 of these subjects, a BCC was their first cancer.

  We currently plan to utilize the original portion of the CCSS cohort for this analysis, since in current data for the expanded addition to the CCSS cohort, among the 10,004 participants only 98 BCCs have been reported by 48 survivors, for whom a BCC was the first SN experienced for 43 subjects.

  Based on the original cohort numbers of BCC cases, a rough power calculation indicates that with the numbers of subjects with and without a BCC we will have at least 80% power to detect the following Relative Risks (with two-sided type I error of 0.05):

| Cumulative incidence of Outcome among non-BCC | Minimum detectable Relative Risk for BCC vs. no BCC |
|---|---|
| 1% | 2.4 |
| 2% | 2.0 |
| 3% | 1.8 |
| 5% | 1.6 |
| 10% | 1.4 |
| 20% | 1.3 |
| 40% | 1.2 |
| 50% | 1.1 |

  Only when the cumulative incidence of a condition falls below 2% does the minimum detectable RR fall below 2. For the outcomes we plan to examine, cumulative incidence is generally above 2%

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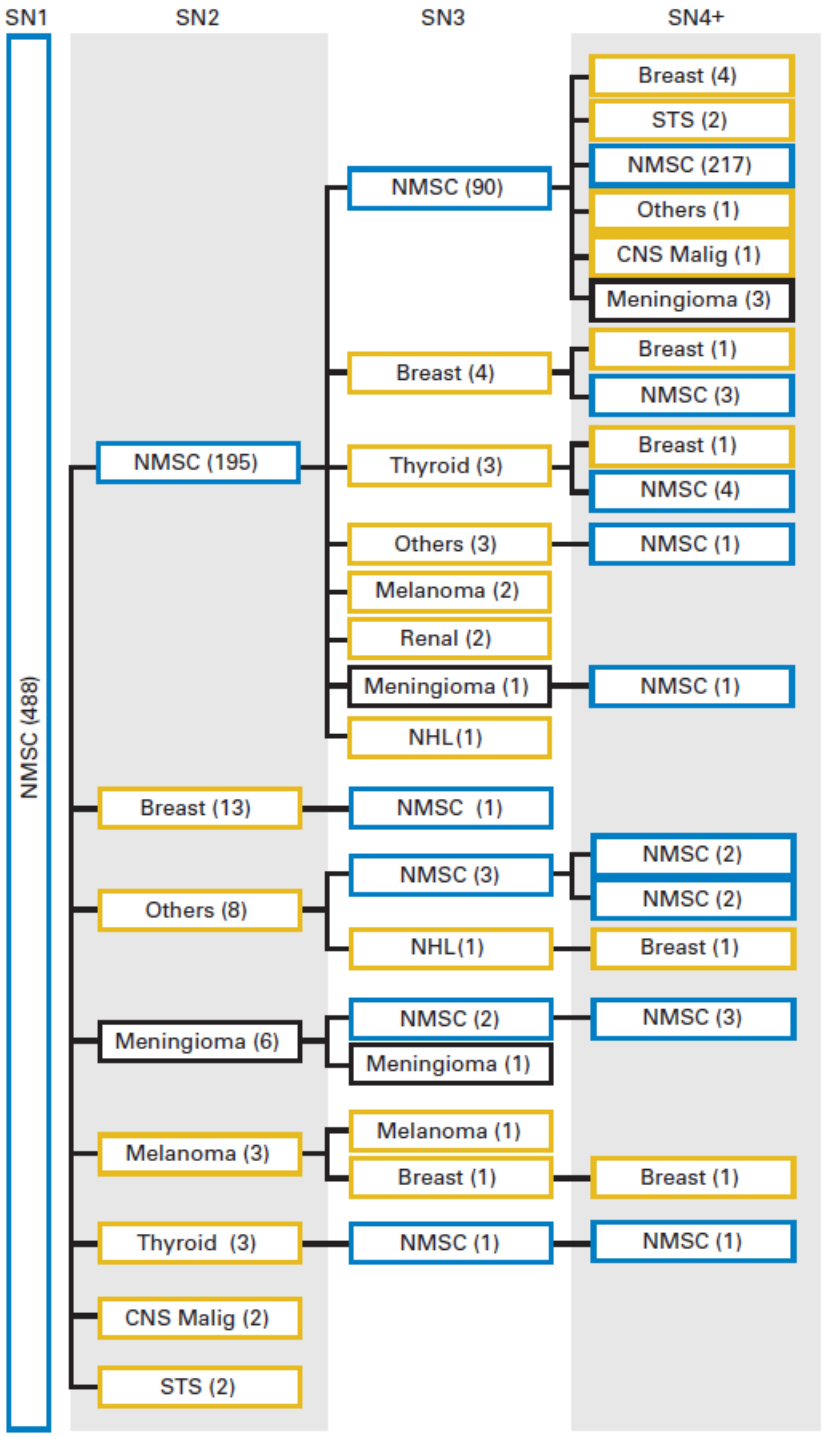
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SN2
SN3
SN4+
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NMSC (195)
Breast (13)
Others (8)
Meningioma (6)
Melanoma (3)
Thyroid (3)
CNS Malig (2)
STS (2)
NMSC (90)
Breast (4)
Thyroid (3)
Others (3)
Melanoma (2)
Renal (2)
Meningioma (1)
NHL(1)
NMSC (1)
NMSC (3)
NHL(1)
NMSC (2)
Meningioma (1)
Melanoma (1)
Breast (1)
NMSC (1)
Breast (4)
STS (2)
NMSC (217)
Others (1)
CNS Malig (1)
Meningioma (3)
Breast (1)
NMSC (3)
Breast (1)
NMSC (4)
NMSC (1)
NMSC (1)
NMSC (2)
NMSC (2)
Breast (1)
NMSC (3)
Breast (1)
NMSC (1)