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A Nested Case Control Study Assessing the Risk of Basal Cell Carcinoma in Childhood Cancer Survivors Treated with Varying Doses of Radiation

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An abstract of

A thesis submitted to the Faculty of the Graduate School of Emory University

In partial fulfillment of the requirements for the degree of

Master of Science

In Clinical Research

2009

Abstract

A Nested Case Control Study Assessing the Risk of Basal Cell Carcinoma in Childhood Cancer Survivors Treated with Varying Doses of Radiation

By Tanya C. Watt

Childhood cancer survivors are at risk for secondary malignancies due to the initial therapy they received. Skin cancer is the most common malignancy in the United States, and has a growing incidence, primarily due to increased sun exposure. Recently, ionizing radiation has been added to the list of risk factors for skin cancer, specifically basal cell carcinomas. This study serves to analyze whether there is a dose dependent increase in the risk of development of BCCs in childhood cancer survivors. 215 cases and 645 controls were sampled from the Childhood Cancer Survivor Study database in a nested case-control study. With multivariate analysis, treatment with ionizing radiation was the predominant risk factor for development of a BCC. This appeared to be dose dependent, with a plateau at the highest doses, suggesting that above 4500 cGy of radiation, the skin cells were so destroyed as to not undergo oncogenesis. Other risk factors included a history of Hodgkin disease, the likelihood to burn when exposed to the sun, skin color, and a family history of non-melanomatous skin cancers. No interactions were found between these other risk factors and radiation therapy. The results of this study will help to provide better guidelines for patients, their families, and their providers when assessing the risks of BCCs in childhood cancer survivors.

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Introduction

In the United States, skin cancer is the most common malignancy, with basal cell carcinoma (BCC) comprising 75% of all non-melanomatous skin cancers (1). BCC has a 95% cure rate, but the treatment often leads to poor cosmesis due to surgical procedures (2). The incidence in the United States is rising due to the increase in sun exposure, the predominant risk factor in the general population (3).

Approximately 10% of subjects who received ionizing radiation will develop non-melanomatous skin cancers, primarily BCCs, making ionizing radiation an important risk factor (4). The first information on the development of BCCs associated with ionizing radiation stemmed from research done in Hiroshima and Nagasaki after the atomic bombs. The overall excess relative risk was 1.9 for a person exposed at the age of 30 years. This risk was dose dependent, and led to more BCCs in non sun-exposed areas (5). Further studies in patients receiving ionizing radiation for tinea capitis had a relative risk for development of BCC of 4.2 (6). This was significantly increased to 10 in Caucasian participants, suggesting some interaction between sun sensitivity and radiation therapy.

With this information, the Childhood Cancer Survivor Study (CCSS), a cohort study of survivors diagnosed with cancer before the age of 21 years, was analyzed for rates of non-melanomatous skin cancers. In a multivariate analysis of survivors with non-melanomatous skin cancers (97% of which were BCCs), Caucasians, family history of skin cancer, longer follow-up, radiation therapy, and a history of older age at the time of diagnosis were associated with higher rates of BCCs (7).

This information is powerful in providing families and providers with documentation that there is an increased risk of skin cancer in childhood cancer survivors, particularly those who received ionizing radiation as part of their initial treatment. However, there is no information to determine if the dose of radiation affects the subsequent risk of development of BCCs. The primary aim of the study will be to determine the dose effect of ionizing radiation on the risk of BCC development. As other study populations have suggested interaction between sun sensitivity and radiation, our sample population will also be studied for possible interactions.

There are 215 cases of BCCs in the current CCSS database. Using incidence-density sampling, we matched 3 controls per case based on age at original cancer diagnosis and time to follow-up. Univariate and multivariate analysis were done to determine risk factors associated with the development of BCC in childhood cancer survivors. Finally, using the dose effect of radiation, we determined if there was a plateau of the effects of radiation on the skin. This information will be critical to provide information about the risks of radiation therapy, in addition to supporting preventive care in the future for childhood cancer survivors. As shown in an earlier study, a significant anxiety provoking factor for people already surviving one cancer is the development of a secondary malignancy (8). It is imperative to be able to better counsel survivors and their families to help decrease the rate of BCCs and other secondary malignancies.

Background

Skin Cancer

Skin cancer is the most common malignancy in the United States. Of the three major types of skin cancer, melanoma, basal cell carcinoma, and squamous cell carcinoma, basal cell carcinoma (BCC) comprises 75% of cases, and has a 95% cure rate (1, 2). Despite the favorable prognosis, treatment with surgical excision often leads to disfiguring scars, and poor cosmetic appearance (9). BCC and squamous cell carcinoma (SCC) comprise non-melanomatous skin cancers, with an incidence of 1 million cases per year and a lifetime risk of 33% (7). The incidence of BCC in the United States is rising, with an estimated increase of 3-10% per year, thought to be secondary to greater sun exposure (3). The most important risk factor for the development of BCC is sun exposure, with a higher risk for patients with a longer total exposure, an earlier age at first exposure, and fairer skin color (10). Thus, up to 85% of BCCs occur in the head and neck regions, those most exposed to UV radiation (11). It is thought that the major carcinogenic factor in sunlight is UV-B radiation, specifically rays between 290 and 400 nm (1, 12). Melanin, found in darker skin colors, provides some protection from UV-B rays (13). A recent study demonstrates that approximately 80% of the variance in incidence of NMSCs is due to ambient UV radiation. Further variance is explained by the average atmospheric temperature, demonstrating that temperature in patients exposed to the sun might play a role in the incidence of skin cancer (14).

Other risk factors include male sex, older age (with a peak age of 70 years), polycyclic hydrocarbons, and arsenic (15). In addition those with a family history of Gorlin syndrome or xeroderma pigmentosum or other syndromes associated with

abnormal DNA repair mechanisms are more at risk for non-melanomatous skin cancers (NMSC) (7, 16). Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome, is an autosomal dominant condition with variable penetrance, in which patients develop basal cell carcinomas and medulloblastomas, and have skeletal abnormalities, facial dysmorphism, and hyperkeratosis of palms and soles (17). In patients with Gorlin syndrome who receive irradiation, the latency for developing skin cancer is very short, typically 5 years, but may be as short as 1 year (13).

Metastasis affects <0.5% of the patients with BCC, and if it occurs, spreads hematologically to the lymph nodes, lungs, bone, skin, spleen, and brain (11). Some studies have suggested that scalp BCCs are more likely to metastasize due to their increased surrounding vasculature (11). While metastasis is rare, recurrence is common, and it is estimated that 15 to 47% of subjects will have multiple BCCs (13).

Ionizing Radiation

Exposure to ionizing radiation has recently been added to the list of risk factors for BCC. It is estimated that 10% of survivors who received ionizing radiation will develop non-melanomatous skin cancers (4). BCC is more likely than other NMSCs in survivors exposed to ionizing radiation because 70% of proliferating stem cells are in the basal layer of the epidermis, and these stem cells have a higher rate of proliferation than cells in the suprabasal layer, where SCC develop. Thus, BCC is more likely to occur with ionizing radiation as the highly proliferating cells are predominantly affected by radiation (18). Some reports suggest that SCCs occur more frequently with high doses of ionizing radiation, whereas participants receiving low dose radiation have higher rates of

BCCs (6). It has also been postulated that different areas of the skin are more sensitive to radiation, with the neck, face, and back being more sensitive than the scalp, palms, or soles (19). Latency between exposure of radiation and development of skin cancer varies with the dose of radiation, with lower doses leading to skin cancer up to 50 years later, but higher doses having a shorter latency (19).

The first indications of the risk factor of ionizing radiation were based on studies in the atomic bomb survivors. Ron et al collected a cohort of 79,972 subjects who were residents of Hiroshima or Nagasaki during the atomic bomb, were alive without cancer on 1/1/1958, and had calculations done of the estimated doses of radiation (5). Dosimetry analysis accounted for both gamma-ray and neutron exposure, and resulted in estimates in Seiverts (Sv) for each exposed person. One Seivert is approximately equivalent to one Gray (20). The cohort was followed until 12/31/1987, and data on 208 first skin cancers was analyzed. Of these 208 cancers, 80 were BCCs, with significant increased rates as the radiation dose increased (5). In people exposed to less than one Seivert, the rate per 100,000 persons per year was 3.9, but this increased to 20 in subjects with more than one Seivert exposure. The conclusions of the study demonstrated an excess relative risk of 1.9 for a person who was exposed to the bombings at age 30, with a decrease in the risk by 11% for each additional year at exposure (5). Furthermore, the majority of BCCs occurred in non sun-exposed areas, with a relative risk of 10.

Other studies on ionizing radiation risks were done on subjects treated for dermatologic conditions. Until the 1960s, benign dermatologic conditions, including acne, eczema, hemangiomas, hirsutism, warts, tinea capitis, and hypertrophic lymphoid tissue, were treated with ionizing radiation (21). Between 1910 and 1959, the treatment

of choice for tinea capitis was ionizing radiation with 200,000 children worldwide exposed to radiation. The Adamson-Kienbock procedure used 5 overlapping fields of radiation with doses given to cause temporary epilation (22). Average scalp doses were 4.75 Gray, with the range between 3.3 and 6 Gray (23). Typical treatment courses were given over 5 consecutive days (6). Of the 200,000 total children treated, 2224 participants received irradiation at Bellevue Hospital in New York. Of these, there were 128 cases of NMSC, significantly larger than the 38 cases in the population of subjects treated with topical ointments alone. Of interest, Caucasians and subjects with a significant history of sun exposure continued to have a higher risk of NMSC, with an excess absolute risk of 10 (CI 3.2-31) (23).

Ron et al completed a similar study with 10,834 subjects who received radiation for tinea capitis matched with 10,834 population controls and 5392 sibling controls. Of these, the incidence of skin cancer was 1.6 per 10,000 persons per year, with a relative risk of 4.2 (6). Furthermore, there was a linear dose response, which appeared to plateau at the highest doses of 13 Gy (6). They confirmed previous work in atomic bomb survivors that age at exposure was important in risk stratification, with children exposed at less than 5 years having a relative risk of 19 compared with a relative risk of 2 in children over the age of 10. The inverse relationship between age at exposure and risk of BCC is thought to be secondary to either the increased cell proliferation in young children or the increased time the subjects have in order to undergo other exposures that will lead to carcinogenesis (6).

In a study done in Israel of subjects receiving radiation therapy for tinea capitis, multivariate analysis showed both summer sunbathing and radiation induced alopecia led

to significantly higher relative risks of BCCs, controlling for radiation therapy (24). Interestingly, skin cancer cases had higher rates of alopecia than their matched controls, leading the investigators to speculate that the actual radiation doses might have been higher for the cases than the controls (24).

Other studies done on subjects who received radiation therapy for tuberculous lymphadenitis also showed a significantly higher rate of BCCs than would be expected in the general population (25). This risk was higher in subjects receiving greater than 20 Gray as compared to those receiving lower doses of radiation. Furthermore, they demonstrated that subjects with a greater severity of skin changes from radiation (including atrophy, teleangiectasia, pigment changes, fibrosis, ulceration, and hyperkeratosis) had higher rates of skin cancer.

As noted earlier, the age at exposure is important to the risk of development of BCC, in part due to the latency period. The typical latency period is 4 to 40 years, but can be as long as 70 years, after exposure to ionizing radiation at doses used for benign dermatologic conditions (21, 26). As the latency period increases, the cumulative risk of developing BCC increases dramatically. In subjects exposed to radiation 20-24 years earlier, the excess rate of BCC was 79 per 10,000 person-years. This increased to 420 per 10,000 person-years as the latent period increased to 30-35 years (27).

A population based case-control study performed in New Hampshire demonstrated a similar increase in the odds ratio for developing BCC in those subjects who had received radiation therapy with an odds ratio (OR) of 1.88 (28). This study also confirmed that subjects who had received radiotherapy before the age of 20 years and those who had a latency of greater than 40 years had a statistically significant increase in

the rates of BCC. Sites exposed to radiation therapy had a statistically higher OR for developing BCC, but no correlative increase in development of squamous cell carcinomas. There was no statistical difference in rates of BCC development in those with increased sun exposure (28). As hypothesized in previous studies, a dose-dependent effect was suggested in that only subjects receiving fractionated doses of greater than 30 Gy developed BCCs (28). This concurs with other studies that show that radiation induced skin cancer is due to nonlethal mutations of cells caused by repeated doses of small amounts of radiation (21). An in-vitro study of lymphocytes from subjects receiving low dose ionizing radiation (treatment for tinea or other dermatologic disorders), high dose ionizing radiation (treatment for cancer), and excess UV radiation (from high sun exposure) demonstrated that when lymphocytes were rechallenged with xrays, those with the low dose exposure had a statistically lower repair mechanism than the other subject groups and healthy controls (15).

Other populations exposed to increased radiation also have been shown to have higher rates of skin cancer. Examples include radiologists, who when matched to physicians of similar age and ethnicity, had a significantly higher rate of skin cancer (29). Further studies have been done in uranium miners, other subjects treated for benign skin dermatoses, and infants treated for thymic enlargement, all of which confirmed increased risks of developing BCCs when compared to similar non-exposed populations (30-32).

Secondary Malignancies

In 1991, Arai defined radiation-related cancer as any cancer with a different histology from the primary cancer, a latency period of 2 years from the radiation therapy,

and a cancer that developed within the radiation field (33). Recent incidence rates show 12,000 children under the age of 20 years are diagnosed with cancer in the United States each year. With a significant decline in mortality over the past 30 years, this results in one of every 900 people between the ages of 15 and 45 being a childhood cancer survivor (34).

Given these large numbers of cancer survivors, the Childhood Cancer Survivor Study (CCSS) was created in 1994 to follow survivors who had survived 5 years from their original cancer diagnosis. Of the 20,276 eligible survivors within the 25 participating centers, 12,455 agreed to full participation in the study with medical record abstraction, and questionnaire return (35). Sixty-eight per cent of the eligible survivors received radiation therapy as a component of their treatment, and the most common diagnoses were leukemia (33%), central nervous system (CNS) cancers (14%) and Hodgkin disease (13%). In the early questionnaires, childhood cancer survivors expressed significant anxiety over development of a secondary malignancy (35).

Of the eligible survivors, in January 2003, 213 patients within the CCSS had at least one documented NMSC, leading to a total of 615 cancers, 97% of which were BCCs (7). Of these, 90% of the cases of NMSC were associated with a history of radiation therapy, and 49% had an original diagnosis of Hodgkin disease (7). The incidence of BCC was 350 per 100,000 person-years in those who had received radiation therapy, as compared to 23 per 100,000 person-years in those who had not. Multivariate analysis showed that patients who were Caucasian, had a family history of skin cancer, had a longer time since diagnosis, and were older at the time of diagnosis continued to have a higher risk of BCC. As demonstrated in the atomic bomb survivors, these BCCs

developed in both sun-exposed and non-sun-exposed areas of the skin. The final results showed that childhood cancer survivors between the ages of 35 and 44 years had a similar incidence of BCC to the general population at age 75 (7).

Chemotherapy/Immunosuppression

Seventy-nine per cent of childhood cancer survivors received treatment with chemotherapy, and therefore it is important to know if immunosuppression from chemotherapy leads to an increased risk of BCC (35). In solid organ transplant recipients receiving long-term immunosuppression with a combination of cyclosporine, azathioprine, steroids and methotrexate, 487 of 702 total cancers in a population of 1558 participants were NMSCs, compared to the expected number of 15 cases (36). The highest excess risk was found in subjects over the age of 50 years who were in their first year of immunosuppression. The authors hypothesized that these subjects would likely have developed skin cancer within the next few years and that the immunosuppression weakened the innate immune system's control over the skin cancer, therefore leading to earlier development of skin cancer (36). Seventy-two per cent of these cases were SCCs, whereas in the general population only 42% of NMSCs are SCCs. A study in Sweden of 5356 organ transplant recipients demonstrated a relative risk of 108.6 in men and 92.8 in women for developing NMSCs, the majority of which are SCCs (37). A similar study in Australia and the United Kingdom studied subjects on immunosuppression for solid organ transplants and also documented an increase in the number of SCCs but not in the number of BCCs (38).

Other research has been done in subjects with AIDS who have higher rates of BCC than the general population (39). The rate of developing all non-AIDS defining cancers, including BCC and SCC, was correlated with duration of HIV infection and a history of opportunistic infections, but not CD4 counts. Furthermore, subjects receiving highly active antiretroviral therapy (HAART) therapy were less likely to develop cancers, leading to speculation that HAART therapy provides some tumor surveillance. This leads to unclear results as to whether immunosuppression is responsible for increased rates of cancers, or whether there is another mechanism (39). Subjects with AIDS have functional deficiencies of la-positive and adenosinetriphosphatase-positive Langerhans' cells, a finding also detected in patients who have received UV irradiation or corticosteroids (40).

It is known that NK cells, helper T cells, and skin antigen presenting cells (Langerhan's cells) are used for tumor surveillance (41). In a study of 61 subjects with a history of biopsy-proven BCC, lower CD4/CD8 ratios were correlated with high sun-exposure. The combination of low sun exposure and a high CD4/CD8 ratio led to a significantly lower risk of subsequent BCC. However, when multivariate analysis was performed, there was no increased predictive value from CD4/CD8 ratios when prior history of BCC and sun exposure were included (41).

Other studies have shown UV radiation induces a decreased helper T cell: suppressor T cell ratio and decreased NK cell activity, thus giving a plausible explanation for why skin cancer occurs after UV radiation. Further investigation of humans revealed that UV irradiation from solariums led to a decrease in Langerhans' cells in the skin which correlated with a decreased delayed hypersensitivity response, therefore limiting

the person's ability to appropriately respond to foreign antigens and tumors (42). Similar responses were noted in humans with 30 minutes of sun exposure for 12 days out of a 2 week period. However, the decrease in delayed hypersensitivity was not as significant as in those in the solarium study, possibly due to the added UV-A exposure from the solarium, in addition to the UV-B exposure from both the sun and the solarium (43). While typically UV-B radiation is responsible for solar-induced carcinogenesis on the skin, studies have shown a similar decrease in Langerhan's cells in the skin from high UV-A exposure (44). While the human studies did not show changes in specific T cells, prior studies in mice exposed to chronic irradiation had shown specific increased suppressor T cell activity specific for tumor antigens with a resultant decreased response to UV-induced tumors (45). Therefore, it is important to assess the role of immunosuppression in childhood cancer survivors and determine if this also plays a role in their increased development of BCCs.

Methods

Hypothesis

The frequency of exposure to each dose range of radiation in cases who developed BCCs is statistically equal to the frequency of exposure to each dose range of radiation in controls, controlling for sun sensitivity, family history, secondary malignancies, and other components of childhood cancer treatment regimens.

Study Design

Childhood Cancer Survivor Study

The Childhood Cancer Survivor Study (CCSS) is a multicenter NIH-funded retrospective cohort study established in 1994 (35). Survivors in the 25 participating institutions were identified based on the following criteria: diagnosis and treatment of cancer (including leukemia, central nervous system malignancy, neuroblastoma, kidney tumors, bone sarcomas, soft tissue sarcoma, Hodgkin disease, and non-Hodgkin lymphoma), diagnosis between January 1, 1970 and December 31, 1986, age less than 21 years at the time of diagnosis, and at least a 5 year survival from the date of diagnosis. To qualify survivors also had to be residents of the United States or Canada and speak English or Spanish.

After identifying the eligible cohort, a questionnaire was sent to the survivors (or next of kin for those known to have died after survival for 5 years). In those survivors in which the questionnaire was completed and consent for medical record evaluation was obtained, medical record abstraction was done via a structured protocol. From the medical records, qualitative information on 49 chemotherapeutic agents and quantitative

information on 26 agents was obtained. Radiation therapy records were photo-copied and all surgical procedures were abstracted and stored. Radiation therapy data was collected through M.D. Anderson Cancer Center's Department of Radiation Physics. A follow-up questionnaire was completed by subjects in 2000, and both surveys are available for review at www.stjude.org/ccss.

Patient Selection

Twenty-thousand, two hundred seventy six subjects fulfilled the eligibility criteria. Of these, 14,370 completed the questionnaire and 12,858 signed permission for medical record abstraction, and were thus eligible for this study. From the baseline survey distributed in 1995, there were 213 survivors with 615 occurrences of non-melanomatous skin cancers (NMSC) (7). Ninety-seven per cent of these were basal cell carcinoma (BCC). Further reports have been made in a subsequent follow-up 1 survey distributed in 2001, totaling 264 cases of NMSC that were considered for this study. NMSC cases were defined by self-report, and pathologic confirmation was attempted, coordinated through the CCSS Pathology Review Center at Columbus Children's Hospital. Collected data included the pathologic type of NMSC, the location of the tumor, any history of multiple occurrences, and the date of diagnosis. Multiple occurrences were defined as survivors who had separate visits for NMSC removal or had more than one NMSC removal from different locations. As cohort eligibility was determine by 5-year survival, only NMSCs that occurred after 5 years were used in this analysis.

Individuals who self-reported a NMSC, either in the baseline or follow-up 1 survey, were sent an ancillary NMSC survey to obtain information on the type, location, and date of diagnosis of the NMSC. This ancillary survey was sent in conjunction with the subsequent follow-up 2 survey, which was distributed in 2003. Data from the ancillary survey and pathology report (if available) were assessed by two reviewers. For discrepancies in the data, the pathology report was considered the true source if the dates differed, but the ancillary NMSC survey was used as the truth if the locations differed. For survivors with different numbers of skin cancers reported on the self-report and the pathology reports, cases were resolved on an individual basis. To ensure validity of cases, all cases were independently reviewed by investigators at MD Anderson and at Emory, and conflicting results were resolved by joint conferences.

Patients: Inclusion/exclusion

All survivors in the initial cohort who met the criteria for development of a NMSC within the follow-up period were included in the initial selection process. Of the 264 cases of NMSC, 39 were excluded because there was no documented BCC, 3 were excluded because there was not enough information to accurately confirm the diagnosis, 4 were excluded because the documented BCC occurred after the last follow-up date, and 3 were excluded because of a history of Gorlin syndrome documented by the pathology report.

Study Design

A nested case-control study was designed using the eligible 215 cases. For this study, cases were pediatric cancer survivors with a diagnosis of a BCC; controls were pediatric cancer survivors without a diagnosis of a BCC at the time of the BCC in the case. Three controls per case were sampled from the original cohort. Matching occurred on age at diagnosis of first cancer (within five years, with groupings as follows: 0-4 years, 5-9 years, 10-14 years, and 15-20 years). Controls were also matched on the time of follow-up, such that controls had to survive at least as long as it took for the case to develop a BCC. The follow-up period was defined in days from cohort entry to the first BCC, death, or completion of the last questionnaire. If cases had multiple BCCs within the time period of the study, the first BCC was chosen for analysis and control selection. Since survivors often are diagnosed with one BCC, have it surgically removed, and then within a short period of time are asked to see a dermatologist for full skin screening, we elected to group the development of BCCs within 2 month periods. Of the 215 samples, 153 had only one BCC in the first two month cluster, 38 had 2 BCCs, 13 had more than 3 BCCs with the maximum number being 8 in the first cluster. This is demonstrated in Figure 1.

Predictor Variables, Outcome Variable

The outcome of interest in this study is the development of a BCC in a childhood cancer survivor. The main predictor variables are the exposure to radiation therapy, in addition to the maximum dose of radiation therapy received (grouped via 0-999 cGy, 1000-2499 cGy, 2500-3499 cGy, 3500-4499 cGy, and > 4500 cGy). For each skin

cancer, data was collected on laterality, the region of the body, the surface of the body. Other variables of interest are basic demographics, including sex, race, initial cancer diagnosis, age at diagnosis, initial treatment course (use of chemotherapy, surgery, and radiation), and whether the survivor is on any current chemotherapy or immunosuppressant medications. Genetic risk factors including any secondary malignancies, family history of both melanoma and non-melanomatous skin cancers, skin color, tanning characteristics, eye color, and hair color were also assessed. Information on sun sensitivity was obtained from the follow-up 2 survey. The survey asked if the survivor had ever suntanned, ever artificially tanned, and how many sunburns on various parts of their body they had received over their lifetime. Finally, information on medical behavior was included from this survey. This included the number of visits to physicians, whether the survivor had ever had a skin exam, and whether they had skin removal or a history of skin cancer. This set of variables provided sufficient information to assess the risk of various doses of radiation to the development of a BCC, in addition to providing information on possible interactions between other risk factors such as sun sensitivity.

Sample Size

After eliminating cases based on the above criteria, the final sample size included 215 cases and 645 controls for a total of 860 observations.

Analysis

Chi-square tests were used to compare the frequency of different risk factors among cases and controls. Statistically significant differences were determined at the

α=0.05 level. Univariate analysis was done on the variables of interest to determine the statistically significant variables predictive of an increased risk of basal cell carcinoma. The Breslow-Day test of homogeneity was performed across different strata of variables. Multivariate conditional logistic regressions were then performed. Using SAS 9.2, there was no apparent collinearity between the predictor variables. However, due to clinical concerns for collinearity, race, eye color, and hair color were eliminated from the model, leaving tanning characteristics and skin color to represent sun sensitivity. The data set included information from different timepoints. The follow-up 2 survey, sent in 2003, provided the information for many of the sun sensitivity and sun protection questions. From our sample population, 145 survivors did not complete the follow-up 2 questionnaire, and therefore did not provide this information. Therefore, the first model was done only including variables that were considered clinically significant and were not part of the follow-up 2 questionnaire. This included the initial diagnosis, the maximum dose of radiation received, a history of secondary malignancy, and a family history of non-melanomatous skin cancer. For the second model, dummy variables were created for the missing observations from the follow-up 2 questionnaire to allow sun sensitivity observations to be included. Thus, added variables were tanning characteristics, skin color, and history of sunburns, both as a child and after the age of 21 years. To assess possible interactions, interaction terms between radiation and tanning characteristics, radiation and history of sunburns, radiation and secondary malignancy, radiation and skin color, and radiation and family history of non-melanomatous skin cancers were added to the model and assessed for statistical significance as a term and as they added to the model. Finally, the dose response of varying doses of radiation were

compared to determine if there was a plateau effect, controlling for other clinically significant variables.

Results

Initial demographics of the sample population are shown in Table 1. A diagnosis of Hodgkin disease and radiation during initial therapy were significantly higher in cases than controls. There were also significantly more cases describing their race as white, although the overall sample population was predominantly white. Although the numbers were small, a diagnosis of soft tissue sarcoma and bone cancers were more prevalent in the control population, possibly reflecting the different distribution and dosing of radiation therapy in these patients. There appeared to be no statistical difference between cases and controls with their initial treatment with chemotherapy, or any current immunosuppressants, demonstrating that in this sample population, neither chemotherapy nor immunosuppression appeared to have a significant role in BCC development.

Genetic risk factors are compared in Table 2. Cases were more likely to report a secondary malignancy, and had higher rates of family members with non-melanomatous skin cancers. Variables including skin color, tanning characteristics, eye color, and hair color were all part of the follow-up 2 questionnaire, distributed in 2003. One hundred forty-five of the sample population did not complete the follow-up 2 questionnaire, explaining the large numbers of missing observations as documented. Of those who completed the questionnaire, controls more frequently had brown skin and black hair, possibly representing protection against the sun's carcinogenic rays. Similarly, cases more commonly reported their tendency to burn when exposure to sun.

Table 3 explores the relationship between prior sun exposure and development of BCCs. These questions composed part of the follow-up 2 questionnaire, and once again,

145 patients did not complete this questionnaire; and some survivors chose to not answer specific questions. Accounting for the missing observations, there was no apparent difference between cases and controls in their exposure to suntans, exposure to artificial tanning, or their history of sunburns both before and after the age of 21 years.

Prior medical behavior of the sample population is explored in Table 4. Cases were more likely to have sought medical care in the two years prior to the survey, and were more likely to have full skin exams. From this information, it is possible that more of the controls would have been diagnosed with BCCs had they sought adequate medical care prior to completion of the questionnaires, representing possible selection bias in the study.

As it appears that radiation therapy is one of the major risk factors for subsequent development of BCCs in our study, the percentage of BCCs that occurred within the field of radiation were calculated. Over half of the BCCs developed in the field of radiation, and 74% of cases of BCC occurred either within the field or close to the field of radiation as shown in Table 5. Nineteen cases did not have enough information to calculate this statistic, and were divided amongst those without documentation of the tumor site (2 cases), without documentation of the radiation site (12 cases) or without documentation for either (5 cases).

Tables 6-9 demonstrate the results of univariate analysis in our study population. As suggested in Table 1, Hodgkin disease, radiation therapy, and Caucasian race were statistically associated with development of BCCs. The risk of developing a BCC based on the dose of radiation was particularly interesting. The odds ratio increased from 1000-2400 cGy up to 3500-4499 cGy, with a relative risk of 8.43 (95% CI = 4.64 - 15.32). The

highest doses of radiation (>4500 cGy) had a lower relative risk of 3.58 (95% CI = 1.81 – 7.11), possibly indicating a plateau of risk as the radiation dose became higher.

There was an increased risk of developing BCC in survivors with a history of secondary malignancies or with a family history of non-melanomatous skin cancers. Furthermore, survivors who reported their skin color as pale, white, or very light had a relative risk close to 2 (95% CI = 1.25 – 3.13) for development of BCC. This suggests that there is some role of sun exposure in the development of BCCs, even in our sample population of childhood cancer survivors. Further suggestion of a possible role of sun exposure was documented by the relative risk of 2.04 (95% CI = 1.12 – 3.73) in survivors who reported always burning when exposed to sun. Eye color did not lead to an increased risk of BCC, and brown hair was found to have a higher risk, possibly due to the large number of cases who reported having brown hair.

Previous sun exposure or sunburns were not statistically associated with an increased risk of development of BCC among our survivor population. Thus, it appears that while sun exposure may play a role, the role of radiation overwhelms any role of sun exposure in childhood cancer survivors. In Table 9, people who did not seek medical care appeared to be protected against development of BCC, emphasizing the importance of medical care in childhood cancer survivors. Especially as many BCCs occur in non-sun exposed areas in patients exposed to radiation therapy, it is important to not only seek medical care but have full skin exams in order to ensure that the BCCs are being detected and treated in a timely fashion. The relative risk of 13.74 (95% CI = 8.67 – 21.76) in survivors who received full skin exams suggests that survivors not undergoing this

surveillance may have BCCs that are missed until they develop elsewhere or become larger and more noticeable.

One of the interests in this study was the possible interaction between sun exposure and ionizing radiation exposure in the study population. To test for possible interaction, the Breslow-Day test of homogeneity was used. Using this test, there was no interaction affecting the relationship between radiation exposure and the development of a BCC (data not shown). To further explore possible risk factors and interaction, multivariate analysis was performed. As many of the risk factors were possibly collinear, a collinearity matrix was utilized. Using this, there was no collinearity between sex, race, skin color, eye color, hair color, and tanning characteristics (data not shown). Despite this statistical analysis, it is apparent that there is some collinearity between these variables. To better account for this in the multivariate analysis, race, hair color, and eye color were eliminated, leaving tanning characteristics and skin color to provide a person's risk for developing BCC based on sun exposure and overall pigmentation.

Conditional logistic regression was first performed using the variables not included in the follow-up 2 questionnaire. With multivariate analysis, Hodgkin disease, increasing doses of radiation, and a family history of non-melanomatous skin cancer were all independently associated with an increased risk of development of BCCs. Hodgkin disease provided an increased risk of 2.27 (95% CI = 1.11 – 4.65) whereas a family history of non-melanomatous skin cancer had an odds ratio of 2.34 (95% CI = 1.29 – 4.35).

A second conditional logistic regression was performed as shown in Table 11. This included the variables in the follow-up 2 questionnaire to allow for determination of

the risk added by sun exposure. To account for the large numbers of missing observations, dummy variables were made with the missing group as a separate level. Including this information in the model, Hodgkin disease continued to provide an increased risk with an odds ratio of 2.89 (95% CI = 1.35 – 6.21). Furthermore, the risks associated with increasing doses of radiation persisted. Family history also continued to provide a significant risk of 2.45 (95% CI = 1.31 – 4.6). Finally, light brown skin color demonstrated some effect of sun exposure even when accounting for radiation therapy. This led to an increased risk of 2 (95% CI = 1.12 – 3.57), demonstrating that skin pigmentation as a marker of sun exposure was not as influential as radiation therapy, initial diagnosis, or family history.

To further analyze possible interactions between sun sensitivity and radiation exposure, interaction terms were added to the multivariate model. We explored the interaction of radiation and tanning characteristics, radiation and a history of sunburns, radiation and a secondary malignancy, radiation and skin color, and radiation and family history. None of these interaction terms were statistically significant, and including them did not improve the Homer-Lemeshow goodness of fit test of the models (data not shown). Therefore, it was determined that there was no significant interaction in this survivor population.

Finally, to further explore the effect of radiation doses on the risk of development of BCC, different levels of radiation doses were included in the model, as documented above. As shown in Figure 2, there is an increased risk associated with increasing doses of radiation. However, this drops significantly at the highest level of radiation, >4500 cGy. Thus there appears to be a plateau of the effect of radiation at the highest doses.

Discussion

This study is a retrospective nested case-control study of childhood cancer survivors and their risk of development of BCCs. Using our unique population, we were able to explore not only the effect of ionizing radiation on the risk of development of BCCs, but also to explore the possible role of sun sensitivity and the potential interaction between sun sensitivity and radiation therapy.

As demonstrated in previous studies (7), radiation therapy and Hodgkin disease continue to provide the largest risks of developing BCCs. Therefore, it is imperative in this population to counsel survivors to seek medical care, and use appropriate skin protection to try and decrease other risks associated with development of skin cancer. Our study suggests that survivors who do not seek medical care and do not have full skin exams have a much lower risk of being diagnosed with a BCC. This suggests that the survivors who did not seek medical care possibly could have BCCs that are not being diagnosed and therefore stresses the importance of regular physical exams with physicians in childhood cancer survivors. Many studies have shown that a large percentage of childhood cancer survivors are not aware of their initial diagnosis or their initial treatment, and this potentially leads to a lack of concern over seeking further medical care (46).

Another risk factor that continued to provide increased risk in multivariate analysis was a family medical history of non-melanomatous skin cancers. Therefore, family history should be a part of counseling survivors for future care and should be involved in risk stratification for development of BCCs. It will be important in future

guidelines for survivors, families and healthcare providers to document the importance of regular medical care and understand their risk factors to provide adequate preventive guidelines for future care.

Interestingly, light brown skin color provided an increased risk of development of BCCs. However, exploring other risks associated with increased sun exposure, including lifetime sunburns and the likelihood of burning when exposed to the sun did not appear to provide significant risk when accounting for radiation, initial diagnosis, and family history. This suggests that the role of radiation possibly overwhelms any increased risk associated with sun exposure. Furthermore, it has been postulated that the interaction of high radiation doses and increased sun sensitivity would affect the risk of development of BCCs (24). Both in univariate and multivariate analyses, there appeared to be no statistically significant interaction between sun exposure, family history, secondary malignancies, skin color, lifetime sunburns and a history of radiation therapy.

Previous studies of subjects who were immunosuppressed for various reasons demonstrated an increased risk of BCCs (36-40). Other studies documented changes in T cells and antigen presenting cells in patients exposed to chronic low doses of solar radiation (41, 42). However, in our study, there was no association between past treatment with chemotherapy and an increased risk of BCC development. Furthermore, there did not appear to be an association between current immunosuppression and increased carcinogenesis. This needs to be further explored, as there were few cases or controls who reported current immunosuppression or chemotherapy, therefore limiting the analysis.

Finally, one of the most interesting parts of this study was evaluating the risk of radiation across different doses of radiation. It appeared that at levels of radiation >4500 cGy, the risk actually decreased. Previous studies of leukemia risk have shown that at the highest doses of radiation, the risk of leukemia was decreased as the bone marrow cells were destroyed, and thus less likely to undergo oncogenesis at a later date (47). One can speculate that a similar occurrence is associated with high doses of radiation to the skin. Therefore, at the highest doses, it is possible that the basal layer of skin cells are destroyed so significantly that they are not at as high a risk of oncogenesis as with more intermediate doses. It will be important to further study this risk relationship in future sample populations.

There are limitations of this study that must be addressed in interpreting the results. First, this is a retrospective study and a large percentage of the data is based on survivor questionnaires. As is well known in other studies involving patient questionnaires, there is a recall bias inherent in the study. We have attempted to verify many of the pertinent risk factors in this study, including the actual radiation doses, the pathologic confirmation of the BCC, and the treatment records from the survivor's initial diagnosis. However, the questions, especially from the follow-up 2 questionnaire, including the sun sensitivity questions, are only based on survivor recall. It is possible that survivors misrepresented or misremembered the number of sunburns they had in their lifetime, their likelihood to burn, and the number of visits to the physician. Furthermore, as stated above, there were many subjects who did not complete the follow-up 2 questionnaire. This resulted in a decrease of 145 observations, dropping our total sample for those questions to 715. While this is still a large number of observations, and

there does not appear to be any bias in who answered the follow-up 2 questionnaire, it is possible that there was bias in reporting with these data points.

However, within the limitations of a retrospective questionnaire based study, this study has many aspects that improve the statistical analysis. It is a nested case control study, and therefore all known cases of basal cell carcinoma were sampled, decreasing the selection bias. Furthermore, by conducting a matched analysis, we attempted to further decrease the sampling bias inherent in retrospective case-control studies. In addition, as stated above, many of the answers to the questionnaires were supplemented by medical record abstraction that was verified by multiple independent reviewers. This further strengthens the data collected in this study. Given the known risks associated with radiation therapy, and the long latency period between radiation treatment and development of BCCs, it will likely be very difficult to conduct a prospective study analyzing these risks, and therefore retrospective studies such as this will provide physicians with the best information to counsel childhood cancer survivors in the future.

From this study, it is apparent that radiation provides a significant risk in the future development of basal cell carcinomas. As previously shown, childhood cancer survivors are at higher risk of developing BCCs, and these BCCs typically occur at a much younger age than those due to sun exposure in the general population. Other risk factors that appear to further increase the risk are family history, skin color, and Hodgkin disease. Future studies will further delineate the specific dose of radiation to the basal cell carcinoma, providing even further information on dose-dependent risk. The combination of that information and this study will be used to provide guidelines for health care providers to better counsel survivors in the future.

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Figure 1: Clustering of tumor cases within first two month period

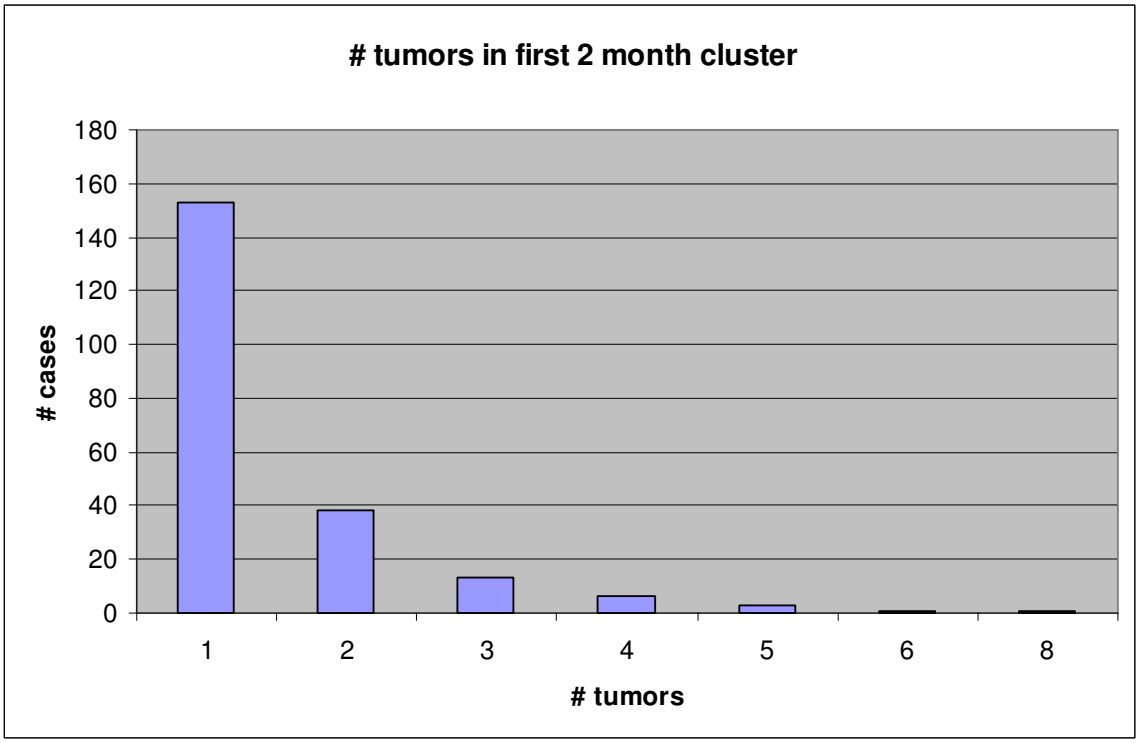


Table 1: Basic demographic information comparing cases and controls

Variable	Cases (%)	Controls (%)	Chi-sq	P value
Sex			1.04	0.31
Males	113 (52.56)	313 (48.53)		
Females	102 (47.44)	332 (51.47)		
Race			9.89	0.002
White	210 (97.67)	589 (91.32)		
Other	5 (2.33)	56 (8.68)		
Diagnosis			61.14	<0.0001
Leukemia	52 (24.19)	163 (25.27)	0.10	0.75
CNS tumor	21 (9.77)	62 (9.61)	0.004	0.95
Hodgkin disease	105 (48.84)	159 (24.65)	44.34	<0.0001
Non Hodgkin lymphoma	15 (6.98)	58 (8.99)	0.84	0.36
Kidney tumor	4 (1.86)	27 (4.19)	*	0.14*
Neuroblastoma	0	20 (3.10)	*	0.007*
Soft tissue sarcoma	11 (5.12)	75 (11.63)	7.60	0.006
Bone sarcoma	7 (3.26)	81 (12.56)	15.19	<0.0001
Age at diagnosis			0	1
0-4 years	35 (16.28)	105 (16.28)		
5-9 years	29 (13.49)	87 (13.49)		
10-14 years	52 (24.19)	156 (24.19)		
15-20 years	99 (46.05)	297 (46.05)		
Treatment				
Chemotherapy			0.08	0.78
Yes	137 (67.82)	416 (68.87)		
No	65 (32.18)	188 (31.13)		
Missing	13	41		
Surgery			0.11	0.74
Yes	172 (86)	525 (86.92)		
No	28 (14)	79 (13.08)		
Missing	15	41		
Radiation			49.66	<0.0001
Yes	191 (94.55)	424 (70.20)		
No	11 (5.45)	180 (29.80)		
Radiation Doses			73.57	<0.0001
0 cGy	11 (5.53)	180 (30.15)	48.48	<0.0001
1-999 cGy	3 (1.51)	9 (1.51)	*	1*
1000-2499 cGy	54 (27.14)	148 (24.79)	0.42	0.52
2500-3499 cGy	17 (8.54)	40 (6.70)	0.76	0.38
3500-4499 cGy	82 (41.21)	118 (19.77)	35.58	<0.0001
4500-5499 cGy	18 (9.05)	52 (8.71)	0.02	0.89
>5500 cGy	8 (4.02)	36 (6.03)	1.15	0.28
Incident dose	4 (2.01)	2 (0.34)	*	0.04*
Dose unknown	2 (1.01)	12 (2.01)	*	0.54*
Missing	16	48		
Current Chemo or Immunosuppression			0.24	0.63
Yes	5 (2.48)	19 (3.15)		
No	197 (97.52)	584 (96.85)		
Missing	13	42		

***** indicates use of Fisher exact test; p value calculated at alpha=0.05.

Table 2: Genetic risk factors comparing cases and controls

Variable	Cases (%)	Controls (%)	Chi-sq	P value
Any secondary malignancy			5.18	0.02
Yes	36 (16.74)	70 (10.85)		
No	179 (83.26)	575 (89.15)		
Family history - melanoma			*	0.39*
Yes	6 (2.80)	11 (1.71)		
No	208 (97.20)	634 (98.29)		
Family history - NMSC			10.32	0.001
Yes	25 (11.68)	34 (5.27)		
No	189 (88.32)	611 (94.73)		
Skin color			12.41	0.006
Pale/white skin	100 (49.26)	212 (41.90)	3.19	0.07
Very light skin	72 (35.47)	157 (31.03)	1.31	0.25
Tan/brown skin	31 (15.27)	130 (25.69)	8.96	0.003
Brown/black skin	0	7 (1.38)	*	0.20*
Missing	12	139		
Tanning characteristics			13.94	0.003
Never tan, always burn	55 (27.23)	89 (17.66)	8.13	0.004
Sometimes tan	72 (35.64)	155 (30.75)	1.58	0.21
Usually tan	55 (27.23)	194 (38.49)	8.01	0.005
Always tan	20 (9.90)	66 (13.10)	1.38	0.24
Missing	13	141		
Eye color			0.33	0.85
Blue eyes	76 (37.81)	180 (35.50)	0.33	0.56
Hazel/green eyes	62 (30.85)	163 (32.15)	0.11	0.74
Brown eyes	63 (31.34)	164 (32.35)	0.07	0.80
Missing	14	138		
Hair color			5.76	0.12
Blond hair	22 (10.89)	51 (10.12)	0.09	0.76
Red hair	20 (9.90)	44 (8.73)	0.24	0.62
Brown hair	126 (62.38)	282 (55.95)	2.44	0.12
Black hair	34 (16.83)	127 (25.20)	5.73	0.02
Missing	13	141		

***** indicates use of Fisher exact test; p value calculated at alpha=0.05.

Table 3: Rates of previous sun exposure in cases compared with controls

Variable	Cases (%)	Controls (%)	Chi-sq	P value
Ever suntan			3.03	0.08
Yes	171 (85.07)	454 (89.72)		
No	30 (14.93)	52 (10.28)		
Missing	14	139		
Ever artifically tan			1.10	0.29
Yes	58 (28.86)	166 (32.94)		
No	143 (71.14)	338 (67.06)		
Missing	14	141		
< 21 years old				
Sunburn back			2.01	0.57
Yes	172 (88.21)	428 (86.99)		
No	23 (11.79)	64 (13.01)		
Missing	20	153		
Sunburn limbs			3.63	0.30
Yes	142 (74.35)	334 (69.87)		
No	49 (25.65)	144 (30.13)		
Missing	24	167		
Sunburn face			3.33	0.34
Yes	167 (85.20)	389 (80.04)		
No	29 (14.80)	97 (19.96)		
Missing	19	159		
Sunburn body			2.65	0.45
Yes	95 (50.26)	220 (46.71)		
No	94 (49.74)	251 (53.29)		
Missing	26	174		
>21 years old				
Sunburn back			1.24	0.74
Yes	118 (64.84)	318 (67.66)		
No	64 (35.16)	152 (32.34)		
Missing	33	175		
Sunburn limbs			0.25	0.97
Yes	85 (47.49)	219 (47.51)		
No	94 (52.51)	242 (52.49)		
Missing	36	184		
Sunburn face			4.56	0.21
Yes	110 (60.11)	294 (63.93)		
No	73 (39.89)	171 (36.77)		
Missing	32	180		
Sunburn body			1.86	0.60
Yes	54 (30.00)	121 (27.13)		
No	126 (70.00)	325 (72.87)		
Missing	35	199		

Table 4: Medical behavior of cases and controls

Variable	Cases (%)	Controls (%)	Chi-sq	P value
Healthcare in last 2 years			9.19	0.002
Yes	202 (94.39)	560 (86.82)		
No	12 (5.61)	85 (13.18)		
Missing	1			
Visits to physicians			14.20	0.03
≤ 2 visits	24 (11.94)	132 (23.28)		
> 2 visits	177 (88.06)	435 (76.72)		
Missing	14	78		
Healthcare on follow-up			4.36	0.04
Yes	195 (96.06)	469 (91.60)		
No	8 (3.94)	43 (8.40)		
Missing	12	133		
History of skin exam			162.84	<0.0001
Yes	175 (87.50)	161 (33.75)		
No	25 (12.50)	316 (66.25)		
Missing	15	168		
History of skin removal			221.54	<0.0001
Yes	199 (99.00)	188 (37.23)		
No	2 (1.00)	317 (62.77)		
Missing	14	140		
History of skin cancer			234.54	<0.0001
Yes	115 (56.93)	29 (5.71)		
No	87 (43.07)	479 (94.29)		
Missing	13	137		

Table 5: Location of BCC compared to radiation field

BCC	N (%)
In field	121 (56.28)
Close to field	38 (17.67)
Out of field	26 (12.09)
No tumor site	2 (0.93)
No site for radiation	12 (5.58)
Neither tumor or radiation site	5 (2.33)
No radiation	11 (5.12)

Table 6: Univariate analysis of basic demographic risk factors

Variable	Odds Ratio	95% CI
Sex		
Males	1.18	0.86 - 1.60
Females	1	
Race		
White	3.99	1.58 - 10.10
Other	1	
Diagnosis		
Leukemia	1	
Bone sarcoma	0.27	0.12 - 0.62
Soft tissue sarcoma	0.46	0.23 - 0.93
Kidney tumor	0.46	0.16 - 1.39
Non Hodgkin lymphoma	0.81	0.42 - 1.55
CNS tumor	1.06	0.59 - 1.91
Hodgkin disease	2.07	1.39 - 3.08
Neuroblastoma	*	*
Treatment		
Chemotherapy		
Yes	0.95	0.68 - 1.34
No	1	
Surgery		
Yes	0.92	0.58 - 1.47
No	1	
Radiation		
Yes	7.37	3.92 - 13.87
No	1	
Radiation Doses		
0 Gy + incident doses	1	
1-999 cGy	4.04	0.99 - 16.54
1000-2499 cGy	4.43	2.40 - 8.16
2500-3499 cGy	5.16	2.38 - 11.18
3500-4499 cGy	8.43	4.64 - 15.32
>4500 cGy	3.58	1.81 - 7.11
Current Chemo or Immunosuppression		
Yes	0.78	0.29 - 2.12
No	1	

***** There were no cases with neuroblastoma.

Table 7: Univariate analysis of genetic risk factors

Variable	OR	95% CI
Any secondary malignancy		
Yes	1.65	1.07 - 2.55
No	1	
Family history - melanoma		
Yes	1.66	0.61 - 4.55
No	1	
Family history - NMSC		
Yes	2.38	1.38 - 4.09
No	1	
Skin color		
Pale/white skin	1.98	1.25 - 3.13
Very light skin	1.92	1.19 - 3.11
Tan/brown skin	1	
Brown/black skin	*	*
Tanning characteristics		
Never tan, always burn	2.04	1.12 - 3.73
Sometimes tan	1.53	0.86 - 2.72
Usually tan	0.94	0.52 - 1.68
Always tan	1	
Eye color		
Blue eyes	1.10	0.74 - 1.63
Hazel/green eyes	0.99	0.66 - 1.50
Brown eyes	1	
Hair color		
Red hair	1.6979	0.8863 - 3.2526
Brown hair	1.669	1.0826 - 2.5729
Blond hair	1.6113	0.8607 - 3.0164
Black hair	1	

* There were no cases who reported brown/black skin color.

Table 8: Univariate analysis of previous sun exposure

Variable	OR	95% CI
Ever suntan		
Yes	0.65	0.40 - 1.06
No	1	
Ever artifically tan		
Yes	0.83	0.58 - 1.18
No	1	
< 21 years old		
Sunburn back		
Yes	1	
No	0.89	0.54 - 1.49
Sunburn limbs		
Yes	1	
No	0.80	0.55 - 1.17
Sunburn face		
Yes	1	
No	0.70	0.44 - 1.10
Sunburn body		
Yes	1	
No	0.87	0.62 - 1.22
>21 years old		
Sunburn back		
Yes	1	
No	1.13	0.79 - 1.63
Sunburn limbs		
Yes	1	
No	1.00	0.71 - 1.41
Sunburn face		
Yes	1	
No	1.14	0.80 - 1.62
Sunburn body		
Yes	1	
No	0.87	0.59 - 1.27

Table 9: Univariate analysis of previous medical behavior

Variable	OR	95% CI
No healthcare in last 2 years		
Yes	0.39	0.21 - 0.73
No	1	
Visits to physicians		
≤ 2 visits	0.45	0.28 - 0.71
> 2 visits	1	
No healthcare on follow-up		
Yes	0.45	0.21 - 0.97
No	1	
History of skin exam		
Yes	13.74	8.67 - 21.76
No	1	
History of skin removal		
Yes	167.77	41.19 - 683.42
No	1	

Table 10: Multivariate model of predictors of development of BCCs considering cancer-related risk factors

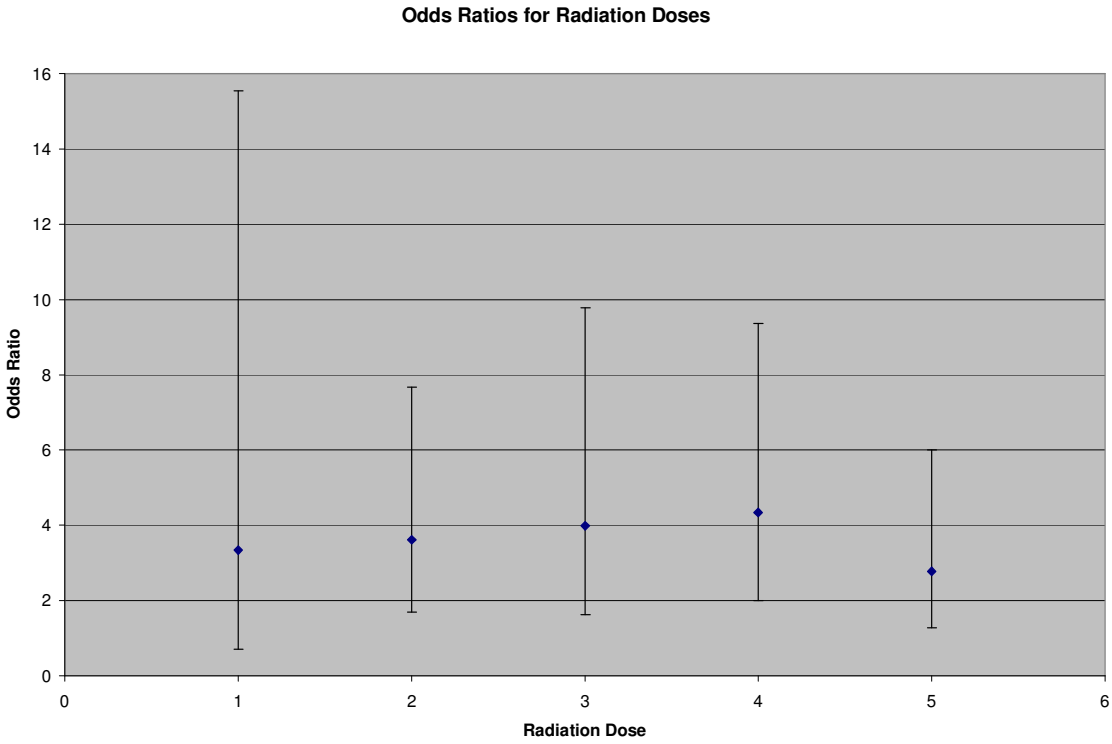
Variable	Parameter Estimate	Standard Error	Chi-Square	P-value	Odds Ratio	95% CI
Diagnosis						
Leukemia					1.00	
CNS tumors	0.27	0.43	0.4	0.53	1.32	0.56-3.08
Hodgkin disease	0.82	0.37	5.01	0.03	2.27	1.11-4.65
Non Hodgkin lymphoma	0.21	0.39	0.29	0.59	1.24	0.57-2.68
Kidney tumor	-1.12	0.65	2.93	0.09	0.33	0.09-1.18
Neuroblastoma	-14.68	590.13	0.0006	0.98	0	0
Soft tissue sarcoma	-0.38	0.48	0.63	0.43	0.69	0.27-1.75
Bone sarcoma	-0.28	0.51	0.3	0.58	0.76	0.28-2.05
Radiation Dose						
0 cGy, incident dose					1.00	
1-999 cGy	1.27	0.76	2.77	0.1	3.55	0.8-15.76
1000-2499 cGy	1.21	0.37	10.85	0.001	3.36	1.63-6.91
2500-3499 cGy	1.24	0.44	8.05	0.005	3.45	1.47–8.13
3500-4499 cGy	1.52	0.37	16.55	<0.001	4.56	2.2-9.47
>4500 cGy	1.1	0.38	8.54	0.004	3.01	1.44-6.29
Any secondary malignancy	0.16	0.25	0.42	0.52	1.18	0.72-1.94
Family history - NMSC	0.86	0.31	7.67	0.006	2.37	1.29-4.35

Table 11: Multivariate model of predictors of development of BCCs, restricted to survivors who completed Follow-up 2 survey

Variable	Parameter Estimate	Standard Error	Chi-Square	P-value	Odds Ratio	95% CI
Diagnosis						
Leukemia					1.00	
CNS tumor	0.35	0.45	0.62	0.43	1.43	0.59-3.45
Hodgkin disease	1.06	0.39	7.39	0.007	2.89	1.35-6.21
Non Hodgkin	0.39	0.42	0.88	0.35	1.48	0.65-3.34
Kidney tumor	-1.15	0.68	2.9	0.09	0.32	0.08-1.12
Neuroblastoma	-14.45	586.29	0.0006	0.98	0	0
Soft tissue sarcoma	-0.23	0.49	0.22	0.64	0.79	0.3-2.09
Bone sarcoma	-0.1	0.52	0.04	0.85	0.91	0.33-2.51
Radiation Dose						
0 cGy, incident dose					1.00	
1-999 cGy	1.2	0.79	2.35	0.13	3.34	0.72-15.55
1000-2499 cGy	1.28	0.38	11.17	0.0008	3.61	1.7-7.67
2500-3499 cGy	1.38	0.46	9.17	0.0025	3.99	1.63-9.78
3500-4499 cGy	1.47	0.39	13.93	0.0002	4.34	2-9.37
>4500 cGy	1.02	0.4	6.65	0.01	2.77	1.28-6.01
Any secondary malignancy	0.21	0.27	0.62	0.43	1.24	0.73-2.09
Family history – NMSC	0.9	0.32	7.79	0.005	2.45	1.31-4.6
Tanning Characteristics						
Always tan					1.00	
Never tan	0.75	0.4	3.56	0.06	2.11	0.97-4.58
Sometimes tan	0.36	0.38	0.89	0.34	1.43	0.68-3
Usually tan	0.16	0.37	0.19	0.66	1.18	0.57-2.42
Missing	-0.31	1.15	0.08	0.78	0.73	0.08-6.9
Skin Color						
Black/Brown					1.00	
Pale/White	0.35	0.3	1.39	0.24	1.42	0.79-2.55
Light Brown	0.69	0.3	5.45	0.02	2	1.12-3.57
Missing	-2.08	1.31	2.52	0.11	0.13	0.01-1.63
Sunburn <21 years						
No					1.00	
Yes	-0.04	0.38	0.01	0.92	0.96	0.45-2.04
Missing	1.23	0.82	2.28	0.13	3.43	0.69-16.9
Sunburn >21 years						
No					1.00	
Yes	-0.1	0.25	0.17	0.68	0.9	0.56-1.46
Missing	0.25	0.41	0.37	0.55	1.28	0.57-2.89

* indicate values not calculated due to extreme data

Figure 2: Odds ratios estimating relative risk of different doses of radiation



Radiation doses: 1: 1-999 cGy, 2: 1000-2499 cGy, 3: 2500-3499 cGy, 4: 3500-4499 cGy, 5: >4500 cGy