RISK FACTORS FOR BASAL CELL CARCINOMA, SQUAMOUS CELL CARCINOMA, AND MELANOMA AMONG PATIENTS FROM A CANADIAN DERMATOLOGY CLINIC

by

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Risk Factors for Basal Cell Carcinoma, Squamous Cell Carcinoma, and Melanoma Among Patients From a Canadian Dermatology Clinic

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submitted by Jenny Lee in partial fulfilment of the requirements for

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Abstract

Background: Targeted screening of high-risk individuals is recommended over population screening to identify and manage skin cancer patients. Previous published skin cancer risk prediction models have been developed from a general population with the purpose of identifying those at high risk from the general public. A model developed for use in clinics can potentially aid physicians in their care for patients. Before this model can be developed, risk factors for skin cancer in a clinical setting should be investigated.

Objectives: The overall aim was to investigate the different risk factors for skin cancer and their associations with basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma in a Canadian clinical population.

Methods: For this case-control study, 1003 patients were surveyed from the Skin Care Centre in Vancouver between January 2020 and December 2021. Demographics, personal history, phenotypic characteristics, and ultraviolet exposure measures were collected through an interviewer-administered survey. Odds ratios were estimated from univariate regressions to assess the relationships between different variables and the different skin cancer types (melanoma, BCC, SCC).

Results: Our study population of 1003 included 105 melanoma, 367 BCC, and 148 SCC cases. There were 13 significant variables for melanoma, 17 for BCC, and 15 for SCC. Apart from age, presence of many lentigines was the strongest risk factor for melanoma (odds ratio [OR] 9.44, 95% confidence interval [CI] 4.25-24.0) and BCC (OR 22.8, CI 10.7-56.7). Apart from age, light eyes

(OR 24.5, CI 6.15-164 for green, OR 12.6, CI 3.72-78.4 for blue) showed strongest effects for SCC risk.

Conclusion: We found significant associations between many proposed risk factors and the 3 types of skin cancer. Age, gender, phenotypic characteristics, and history of sunburns were important risk factors for all skin cancer types. At the same time, some of our findings did not support the relationships found in literature, possibly due to our study being based on a clinical population. Future research involving multivariate analyses should be conducted to provide further insight into the associations between risk factors and skin cancer in a Canadian clinical population.

Lay Summary

Skin cancer, being the most common malignancy globally, is associated with significant health and economic burdens for patients and the health care system. Skin cancer risk prediction models can be used to identify high-risk individuals and focus management and preventative measures on these patients, thereby alleviating some of the burden. However, currently available models were developed for use in a general rather than a clinical population. We examined the relationships between different risk factors and the three major types of skin cancer in a Canadian clinical population. Most of our findings were consistent with the literature, with age, gender, phenotypic characteristics, and history of sunburns being important risk factors for all skin cancer types. This study explored a wide range of risk factors for skin cancer and will guide our next step in developing risk prediction models for use in Canadian clinics.

Preface

This thesis was written by Jenny Lee with feedback and edits from Dr. Sunil Kalia (Principal investigator) and supervisory committee members Dr. Harvey Lui and Dr. Tim K. Lee. Dr. Tashmeeta Ahad also provided feedback for chapters 3 to 6. This study was conceived by Dr. Sunil Kalia and designed by Dr. Sunil Kalia and Jenny Lee with input from members of the Photomedicine Institute in UBC (Dr. Harvey Lui, Dr. Tim K. Lee, Dr. Tashmeeta Ahad, Dr. Haishan Zeng, and Dr. Jianhua Zhao). The research for this thesis was predominantly performed by Jenny Lee. Initial point of contact with patients was conducted by Dr. Sunil Kalia, Dr. Harvey Lui, and Dr. Tashmeeta Ahad, after which recruitment was completed by Jenny Lee. Patient interviews were mainly carried out by Jenny Lee, with aid from Dr. Sunil Kalia, Dr. Harvey Lui, and Dr. Tashmeeta Ahad. Patient chart reviews, data cleaning, and data analyses were completed by Jenny Lee with guidance from Dr. Sunil Kalia. Ethics approval for this study was received from the UBC Clinical Research Ethics Board (H19-04028).

Table of Contents

List of Tables

List of Figures

List of Abbreviations

BC	British Columbia
BCC	Basal cell carcinoma
CI	Confidence interval
KC	Keratinocyte carcinoma
NMSC	Nonmelanoma skin cancer
OR	Odds ratio
PUVA	Psoralen + ultraviolet-A
SCC	Squamous cell carcinoma
SD	Standard deviation
UV	Ultraviolet
VCHRI	Vancouver Coastal Health Research Institute

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Chapter 1: Introduction

1.1 Skin Cancer

1.1.1 Skin Cancer Types

Basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma are the three most common types of skin cancer. BCC and SCC are jointly referred to as keratinocyte carcinomas (KCs) based on their common cell of origin.[1,2] Melanoma, the least common but most serious of the three major skin cancer types, arises from uncontrolled growth of pigment-producing melanocytes.[3] BCC is the most common skin cancer, comprising approximately 80% of KC cases, while SCC accounts for the remaining 20%.[2,4] Nonmelanoma skin cancer (NMSC) is also used to refer to BCC and SCC, but the term KC is now favoured over NMSC as the latter can also refer to any other skin cancer that is not melanoma, such as Merkel cell carcinoma, Kaposi's sarcoma or dermatofibrosarcoma protuberans.[1]

1.1.2 Epidemiology

Skin cancer is the most common malignancy globally.[2,5] During 2020 alone, there were over one million new cases of NMSC (excluding BCC) and over three hundred thousand new cases of melanoma worldwide.[6] Specifically in Canada, the incidence of skin cancer almost matches the combined incidences of lung, breast, colorectal, and prostate cancers (the four most common cancers excluding skin cancer).[4] Moreover, at least 40% of all cancer incidences in Canada are KCs. Based on the most recently published figures, there were 76,100 new cases of NMSC in 2014 and 8,700 new cases of melanoma in 2021 in Canada.[4,7] However, these numbers are likely underestimates as most cancer registries do not systematically collect information on KCs.[4,8] Both skin cancer

incidence and mortality rates have been increasing steadily over the past few decades, and despite interventions to curb this rising incidence, these rates are still increasing.[4,9]

The prevalence of skin cancer, not to mention the mortality associated with melanoma (which accounts for 75% of skin cancer deaths), poses significant health and economic burdens for patients as well as the health care system.[10] Early detection of skin cancers is desired due to its effects of improving prognosis and survival, and reducing medical costs for metastatic skin cancer treatment.[11,12] While screening facilitates early diagnosis, its use at the population level for skin cancer is costly. Moreover, it is unclear whether population level screening will effectively reduce disease morbidity and mortality.[13] Targeted screening of high-risk individuals may provide a more effective strategy that enables more efficient use of healthcare resources.[13–15] The first and most important step in this strategy is to identify and understand which risk factors contribute to the development of skin cancer.

1.2 Risk Factors for Skin Cancer According to Literature

Cutaneous carcinogenesis is dependent on the combination of intrinsic and environmental risk factors. Risk factors can largely be divided into four groups: demographics, patient history, phenotypic characteristics, and UV exposure.

1.2.1 Demographics

Age is a well-known risk factor for all types of cancer, including skin cancer. As age increases, so does the incidence of melanoma.[16] Likewise, advancing age is linked with a higher risk of BCC and SCC, with incidence rising exponentially from ages 40 to 80 years.[17,18] Gender also

plays a role in skin cancer risk, with studies consistently showing incidences of melanoma, BCC, and SCC to be higher in men than in women.[18–20]

1.2.2 Patient History

1.2.2.1 Family History of Melanoma

Family history can be an important contributor to disease risk, as it is for melanoma. Based on pooled estimates from a meta-analysis, family history of melanoma was very significantly associated with an increased risk of melanoma.[21] Recent findings from a prospective study also showed an increased risk of melanoma for those with a first-degree relative with melanoma.[22] Moreover, this study reported that those with a first-degree family history of melanoma had increased risks of developing of BCC and SCC.

1.2.2.2 Actinic Keratosis

Actinic keratosis is a very common pre-malignant skin lesion treated by physicians, characterized by rough scaly patches that develop from long-term sun exposure.[23] People with actinic keratosis are at an increased risk of melanoma compared to those without.[21] Presence of actinic keratoses is also associated with a greater risk of both BCC and SCC.[23–25] The relationship between actinic keratosis and SCC is specifically noteworthy, as a large proportion of SCC patients have a history of actinic keratoses.[23]

1.2.2.3 Immunosuppression

Transplant history is associated with an increased risk of melanoma, with meta-analysis results showing organ transplant recipients to have more than twice the risk of melanoma compared to the

general population.[26] People with an organ transplant also have a higher risk of KC compared to the general population.[20,27,28] Transplant recipients most commonly developed SCC of all cancers; risk of SCC was 60-200-fold higher.[20,27] The reported risk for BCC among transplant recipients was more modest, with an organ transplant history being accompanied by a 10-fold increase in BCC risk.[27,28]

Transplant history most often goes hand in hand with the use of immunosuppressants, as these drugs are used to prevent the immune system from reacting to, and subsequently rejecting the transplanted organ.[28] A case-control study found the use of immunosuppressive drugs to be associated with an increased risk of melanoma; risk increased with a greater number of prescriptions.[29] Studies have also found higher risk of KC with longer durations and higher levels of immunosuppressive therapy.[20,27,28]

1.2.2.4 Lifestyle History

A conclusive association between tobacco smoking and skin cancer has not yet been found. A meta-analysis published in 2012 reported lower risk of melanoma for ever smokers in men, while no significant association between smoking and melanoma for women was reported.[30] Pooled estimates based on a more recent meta-analysis showed lower risk of melanoma for current and former smokers compared to non-smokers.[31] For KC overall, a significant relationship with smoking was not found.[32] One meta-analysis reported no significant association between smoking and BCC, while another reported slightly lower risk for ever compared to never smokers in men and slightly higher risk for ever smokers in women.[30,32] Meanwhile, smoking was found to be associated with an increased risk of SCC, with no significant association found specifically for men and an increased risk for ever compared to never smokers found for women.[30,32]

Alcohol consumption is positively associated with melanoma, BCC, and SCC risk. [33,34] A dose-dependent increase in risk for all three skin cancer types was found. However, while this positive association was found in both case-control and cohort studies for melanoma, only cohort studies showed this relationship for BCC and SCC.

1.2.3 Phenotypic Characteristics

1.2.3.1 Eye/Hair Colour and Skin Reaction to Sun Exposure

Eye colour, hair colour as well as a person's burning and/or tanning reaction to UV exposure (Fitzpatrick skin type) are all well-established risk factors for skin cancer. More information on Fitzpatrick skin type can be found in Methods section 2.4.1.1 and Table 2.1. Studies have consistently reported lighter eye colours to be associated with a greater risk for melanoma and KCs, with blue and green typically considered to be lighter colours.[21,25,35,36] Individuals with red and blonde hair compared to dark brown hair have a higher risk of melanoma, BCC, and SCC.[21,25,35,36] A person whose skin tans rather than burns (Fitzpatrick skin types III/IV vs. I) is at an increased risk of melanoma.[21,25,35,36] Similarly, studies have reported BCC and SCC risk to be higher in people with skin that burns and never tans compared to those who tan and never burn.[21,35,36]

1.2.3.2 Pigmented Skin Lesions

The presence/number of nevi and atypical nevi are important risk factors for melanoma. Results from meta-analyses have reported risk of melanoma to increase with greater numbers of nevi.[37,38] Similarly, pooled estimates found that the presence/a greater number of atypical nevi was associated with a higher risk of melanoma.[37,38] Fewer studies have investigated the association

between nevi and KCs. Based on published results, presence of nevi was related to an increased risk of BCC, while no significant relationship was found for SCC.[35,39]

Individuals with a greater number of freckles are at an increased risk of melanoma.[21] Similarly, risk of KC was greater for those with many compared to those with no freckles.[40] When the association was studied separately for BCC and SCC, an increased risk of BCC was found for people with freckles during childhood, while a significant link was not found between freckles and SCC risk.[35,41,42]

Lentigines, characterized as light yellow to dark brown spots found in body locations chronically exposed to the sun, are strong markers of sun damage, occurring more during adulthood and with long-term sun exposure.[43,44] Despite being a presumptive risk factor for skin cancer, there are few studies on the association between lentigines and skin cancer. A recent publication reported an increased risk of skin cancer for those with greater numbers of lentigines on the face.[45] Another recent investigation found risk of melanoma to be higher for those with more lentigines on the back.[46] A positive relationship was also found between presence of lentigines and risk of BCC.[24] Although some studies explored the relationship between SCC and lentigines in the 1990's, no significant association was found.[25,47]

1.2.4 UV Exposure

UV exposure plays a critical role in an individual's risk for skin cancer, and is widely considered to be the most important environmental risk factor. Sun exposure is often characterized into two general patterns, intermittent (periodic and often intense) or chronic (continuous and repetitive), each being associated with different types of skin cancers.

1.2.4.1 Intermittent Sun Exposure

Studies have found BCC and melanoma to be associated with intermittent sun exposure.[48–51] Major forms of intermittent exposure used by researchers are recreational sun exposure (encompassing outdoor sports, water activities, and sunbathing), sunny holidays, and sunburns. [49,51] Recreational activities and vacations in sunny places are significantly related to risk of melanoma.[51] For BCC, while some[49,50] studies reported increased risk for individuals who participated in outdoor recreational activities and sunny holidays, one study[41] found BCC risk to increase with childhood recreational sun exposure and decrease with lifetime recreational exposure. Evidence has not shown SCC to be significantly associated with intermittent sun exposure.[42,48]

Sunburns, and especially severe sunburns, are an important measure of intermittent sun exposure and are linked with an increased risk of all three types of skin cancer. People with sunburns during childhood as well as adulthood have higher risks of melanoma. Based on a meta-analysis, 9 of 15 studies reported that the risk associated with sunburns was higher in childhood than in adulthood, although meta-regression showed this difference to be non-significant.[51] Both childhood and lifetime history of sunburns were associated with an increased risk of BCC and SCC.[41,48,52,53]

1.2.4.2 Chronic Sun Exposure

Chronic sun exposure is often assessed via an individual's history of occupational sun exposure. While intermittent sun exposure has been generally found to be related to melanoma and BCC, chronic or occupational sun exposure has been found to be related to SCC.[50] Pooled estimates show that individuals with a history of occupational sun exposure have an increased risk of SCC compared to those without.[54] Studies have also found however, that occupational sun exposure is

associated with an increased BCC risk.[55] In contrast, a high level of occupational sun exposure was found to be associated with a lower risk of melanoma.[51]

1.2.4.3 Other Sources of UV Radiation

People with a history of recreational tanning bed usage have an increased risk of melanoma, BCC, and SCC, with an even greater risk of KC for those who used tanning beds before the age of 25.[56,57] Apart from tanning beds, UV radiation therapies are another source of artificial UV radiation. Two major types of phototherapy are Psoralen + UVA (PUVA) and UVB treatments, commonly used to treat various skin diseases including psoriasis, eczema, and vitiligo. PUVA is associated with an increased risk of melanoma, especially for those exposed to high doses and for those treated for a long time (over 15 years).[58] Increased risk of BCC and SCC was also found with exposure to PUVA therapy in a dose-dependent manner.[59–61] While there is a clear relationship between PUVA and skin cancer risk, studies have not found a significant association between UVB phototherapy and skin cancer risk.[61]

1.3 Risk Estimated from Clinic vs. General Populations

As earlier mentioned, targeted screening of high-risk individuals may be more effective versus population screening to identify and manage skin cancer patients. In order to identify these individuals, considerable research has been conducted to develop skin cancer risk prediction models.[14,40] These statistical models make use of information on different potential risk factors and their interactions to stratify people into risk categories. Risk estimates from these models can be used to aid physicians in communicating personal risks, providing preventative advice, and identifying

individuals at high-risk for continued surveillance so that cancer can be diagnosed and treated early.[14,62]

The choice of study population (general population vs. hospital/clinic population) can affect results of a risk prediction model. Some studies have reported hospital controls to be more similar to cases as compared to general population controls, with odds ratios estimates using hospital controls being closer to the null value as compared to those based on general population controls.[63,64] On another note, models based on a general population commonly obtain information through self-reported questionnaires. Assessments of important skin lesions such as nevi are also commonly self-reported, as few studies incorporate in-person components to have a physician assess these lesions. While this comes with the advantage of potentially surveying a larger sample in a shorter timeframe, self-reported data is subject to sampling, recall, and response biases.[65–67] Regarding case/control information, most studies do confirm skin cancer diagnoses through methods such as linkage to cancer registries.

Some types of questions, such as those regarding one's history of sunburns will be subject to recall bias regardless of the method used to collect information. However, for information that can be validated, or be more reliable without the use of self-reports, using self-reports may be an issue. For example, in the case of skin cancer status, it is especially important to have this confirmed through pathology reports or some other form of validation as people can often forget or mistake their cancer history. Further, as the primary outcome variable in risk prediction models, skin cancer status misclassification can have significant effects on the overall findings.

Fitzpatrick skin type (Methods section 2.4.1.1 and Table 2.1) is an example of a variable that may be difficult for participants to self-assess. Participants may report their skin type based on their current level of sun exposure and the time of year. For example, those that have recently avoided the

sun may be unsure which skin type to identify with, and may need additional clarifications so that they can make an assessment based on their past years when they did get some sun exposure. As well, pigmented skin lesions such as nevi, atypical nevi, and lentigines can be difficult for the lay person to distinguish as well as quantify. Studies on the validity of self-reports of these lesions are lacking. In fact, not many models include lentigines as a potential risk factor, although this may potentially be a very important and strong predictor of skin cancer. A study may be subject to less bias if a physician were to assess these characteristics, as opposed to collected via subject self-assessments.

1.4 Rationale and Aims

Many skin cancer risk prediction models have been developed from a general population, with the purpose of identifying those at high risk of skin cancer from the general public. We were interested in developing models for use in clinics, as a clinical model has the potential to aid physicians in their decision-making process regarding potential skin cancers. As well, these models may help reduce the burden for dermatology clinics if unnecessary referrals from primary care providers could be prevented. Therefore, we sought to examine the risk factors for skin cancer in a clinical setting. Particularly, our study was based on a large Canadian dermatology clinic. There has been one previous case-control study by Marrett and colleagues in 1992 that developed a melanoma risk prediction model based on a Canadian population.[68] Their model was based on a general rather than a clinic population. Limitations of that study included the exclusion of patients with previous melanoma and the inclusion of few variables for their model. For example, important risk factors for melanoma such as family history of melanoma and measures of sun exposure were not surveyed.

To the best of our knowledge, a melanoma risk prediction model has not yet been developed from a Canadian clinic population. Further, no risk prediction models have been developed in Canada for keratinocyte cancers. In fact, compared to models for melanoma, research on keratinocyte cancer risk prediction models is scarce. Our eventual goal is to develop risk prediction models based on a Canadian clinic population not only for melanoma, but also for keratinocyte cancers.

The overall aim of this thesis was to investigate the different risk factors skin cancer and their associations with BCC, SCC, and melanoma, as a first step to our future goal. Our objectives were to:

1. Summarize the literature on risk factors for melanoma, BCC, and SCC.
2. Characterize our study population.
3. Assess the relationship between different risk factors and risk of melanoma, BCC, and SCC.
4. Identify the strongest risk factors for each skin cancer type, based on univariate analyses.

Chapter 2: Methods

This chapter details the methodology for the thesis, including the study population, participant eligibility, data collection, and statistical analysis.

2.1 Overview of Methods and Ethical Concerns

We used a case-control design to investigate the risk factors for 3 skin cancer types (basal cell carcinoma, squamous cell carcinoma, melanoma) among patients in Vancouver, Canada. There were three phases to the study: data collection form development, data collection, and data analysis (**Figure 2.1**).

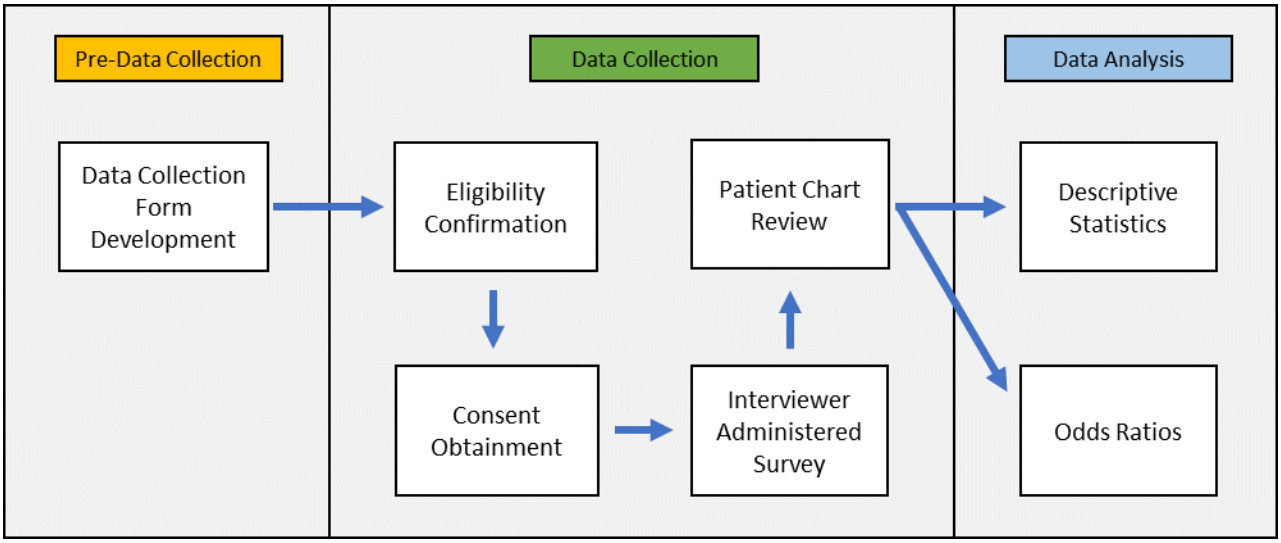

Figure 2.1 Overview of methods.

This study has been reviewed and approved by the University of British Columbia Clinical Research Ethics Board (H19-04028). Informed written consent was obtained from all study participants.

2.2 Study Population and Eligibility

The study population was recruited from the Skin Care Centre, a dermatology clinic in Vancouver General Hospital, British Columbia, Canada. Patients were eligible for the study provided they were 1) referred for or concerned about potential skin cancer, 2) greater than 18 years old, and 3) English speaking. A total of 1003 participants were surveyed between January 2020 and December 2021.

2.3 Development of Data Collection Form

A literature review followed by consultations of a group of skin experts (6 dermatologists/skin cancer researchers at the Photomedicine Institute, Vancouver Coastal Health Research Institute) was conducted to identify risk factors for basal cell carcinoma, squamous cell carcinoma, and melanoma. These risk factors were used to develop a data collection form (**Appendix A.1**). There was an iterative process in developing this form: multiple cycles of feedback and revisions from the group of skin experts were completed before it was finalized.

2.3.1 Components

The data collection form includes the following variables: demographics (age, gender), personal and medical history (personal history of skin cancer, family history of skin cancer, actinic keratosis history, transplant history, immunosuppression medications, medical history, skin cancer diagnosis day of the visit, smoking status, drinking status), phenotypic characteristics (eye colour, hair colour, Fitzpatrick skin type, number of total and atypical nevi, freckle density, lentigo density), and UV exposure (childhood sunburns, adult sunburns, number of tanning bed sessions, radiation treatment exposure, lifetime occupational and recreational sun exposure, residence history, vacations

to sunny destinations). Specifics on how each variable was assessed are detailed in the following section (**2.4.1 Variable Assessments**).

2.4 Data Collection: Interviews Using the Data Collection Form

As detailed in section 2.3, a data collection form was created; this was employed to survey participants.

2.4.1 Variable Assessments

Demographics

Patients' age (years) and gender (Male/Female) were recorded based on the information on their clinic charts. In addition to age, the year and month of birth was recorded.

Participant History

Personal history of skin cancer (Yes/No/Unsure; If yes, specify date/type), family history of skin cancer (Yes/No/Unsure; If yes, specify date/type), actinic keratosis history (Yes/No/Unsure; If yes, specify date/type), transplant history (Yes/No; If yes, specify date/type), immunosuppressant history (Yes/No; If yes, specify date/type), and other medications/medical history (specify) were acquired from patient interviews and later reinforced from chart reviews. Smoking (Never/Former/Current) and drinking (Never/Former/Current) status were recorded based on patients' interview answers.

Phenotypic Characteristics

Eye colour (Light/Medium/Dark/Other(specify)) was recorded based on participants' responses. Short of mid-way into the study, more detailed eye colour was specified in consideration of future comparisons with other studies that take a more specific record of eye colour. Light eye colour was specified further as blue, green, or grey; medium as hazel or light brown. Dark eye colour only included dark brown. Natural hair colour at age 20 (Black/Dark Brown/Light Brown/Blonde/Red) was recorded based on participants' interview answers.

Fitzpatrick skin type is a widely used system in dermatology, developed by Thomas Fitzpatrick to classify patients based on their skin burning and tanning reactions to sun exposure (**Table 2.1**).[69] Participants' Fitzpatrick skin type was assessed by asking "How does your skin react when you go in the sun for an hour around noon at the start of the summer, without sun protection?", "Does your skin tend to burn/tan?". The frequency of burning was quantified as rarely, usually, sometimes, always to coincide with the original Fitzpatrick classification. Tanning was classified into never, with difficulty, average, with ease. When necessary, additional prompting with variations of the former questions were asked. For instance, individuals who currently limited their sun exposure, were then asked, "When you used to go outside more often, did your skin burn or tan?" was carried out. As well, for participants with brown or black skin, skin colour was considered for classification into Fitzpatrick skin types V and VI.

Pigmented lesion variables (nevi, atypical nevi, freckles, lentigines) were assessed by clinicians during the interview process, which is detailed in **2.4.2 Interview Process**. Density of nevi greater than 2mm, as well as density of lentigines, were recorded : none/few/some/many according to a diagram adapted from literature (**Appendix A.2 Nevi density diagram**).[68,70] The whole body was assessed for nevi, unless participants were not comfortable for a whole body examination, in

which case the back and exposed areas of the body were examined (face, neck, arms). The number of atypical nevi/nevi larger than 5mm (from the entire body when possible) were recorded as well (0 /1-2 / 3-5 / 6+). Freckle density was also documented as none/few/some/many according to a diagram adapted from literature (**Appendix A.3 Freckle density diagram**).[70]

Table 2.1 Fitzpatrick skin type classification system.

Skin Type	**Skin Burning and Tanning Responses to Sunlight**
I	Always burns, never tans
II	Usually burns, tans with difficulty
III	Sometimes burns, tans about average
IV	Rarely burns, tans with ease
V	Brown skin colour (unexposed skin); Rarely burns, tans very easily
VI	Black skin colour (unexposed skin); Never burns, tans very easily

Ultraviolet Exposure

The number of severe sunburns each as a child under 18 years old and as an adult 18 years and older were recorded as: 0, 1-2, 3-5, 6-10, 10-20, >20.. Severe sunburns were described as those that involved peeling, blisters, or pain for 2 or more days. A count of participants' lifetime tanning bed sessions was categorized as: 0, 1-10, 11-50, 51-100, 101-499, 500+. Exposure to radiation treatment was assessed by asking whether patients had radiation treatments such as ultraviolet A (UVA), ultraviolet B (UVB), and psoralen and ultraviolet A (PUVA) for conditions including

eczema, acne, and skin diseases. Patients' answers were reinforced by checking their chart records. Lifetime occupational as well as recreational sun exposure (five-point Likert scale) was accounted for by asking "Compared to other people, how would you rate your lifetime recreational and occupational sun exposure?". More details on the type(s) of recreational sun exposure that participants were involved in were documented (Sun tanning/Outdoor sports/Water activities/Gardening/Walking). A list of all places (country and ages lived) that participants resided in for more than 6 months was also collected. Finally, the frequency of sunny holidays taken was assessed by asking "How often do you take vacations to sunny destinations between October and April?" and/or "How many sunny holidays have you taken in your life between October and April?". Responses were recorded as 1 of 4 categories: none, few = up to once every 10 years, some = up to once every 5 years, and many = yearly or more.

2.4.2 Interview Process

Convenience sampling was used to recruit participants that met the eligibility criteria described in **2.2 Study Population and Eligibility**. All participants were recruited during their visit to see a dermatologist at the Skin Care Centre. Once an eligible subject was identified, the patient's physician asked whether the patient would be interested in participating in a research study. If the patient agreed, a member of the study team (J.L.) approached the patient, provided an overview of the study, answered questions regarding participation, and obtained informed consent. Participants were not provided with any remuneration.

After consent was acquired, the data collection form (**Appendix A.1**) was completed in two parts: an interviewer-administered survey and a clinician assessment. For the interviewer-administered survey, a member of the study team (J.L., T.A., S.K.) led patients through the data

collection form and recorded data onto a paper copy. Specifics of the questions asked are detailed above in **2.3.1 Components** and **2.4.1.1 Variable Assessments**. The remaining part of the survey involved a clinical assessment, which the patient's physicians (S.K., T.A., H.L.) completed during their time with the patient. Data from the assessment (nevi, atypical nevi, freckles, lentigines, and skin cancer diagnosis day of the visit) was recorded onto the same paper copy of the form used in the interviewer-administered survey.

2.5 Data Collection: Chart Reviews

After completing the survey, patient charts were reviewed to validate and supplement medical information, including skin cancer history, actinic keratosis history, medications, history of ultraviolet radiation treatment, and other medical history. Skin cancer history was predominantly extracted from surgical pathology reports. In cases where pathology reports were not available, referral letters from the patient's family doctor, letters to the family doctor, and/or patient assessment notes were used. The other pieces of medical information were also extracted from letters and notes.

Some patients had biopsies day of the visit. As such, "skin cancer diagnosis day of the visit" could not be determined. For these patients, their biopsy results were followed up later in time, during which "skin cancer diagnosis day of the visit" was recorded based on the surgical pathology report received.

2.6 Data Storage

Data were stored as hard copies as well as in electronic form. Data were initially recorded, as mentioned above, on paper data collection sheets. These sheets are stored in locked cabinets in locked rooms of Vancouver Coastal Health Research Institute (VCHRI) facilities. Hard copy data

were manually entered onto Excel spreadsheets for electronic storage and analysis. Electronic data are stored through an encrypted, password protected network and accessed through a secure computer. All recorded data were de-identified to protect the identity of participants: a unique identification number was assigned to each participant, and used on the data collection sheets as well as electronic data files.

2.7 Outcome (Dependent) Variable

The outcomes of interest in this study pertain to skin cancer status (skin cancer, keratinocyte carcinoma, basal cell carcinoma, squamous cell carcinoma, and melanoma). These were analyzed as binary variables (cases/controls), and definitions for cases and controls per skin cancer outcome can be found in **2.8 Case and Control Definitions**. The status of each skin cancer type was obtained from 2 survey items: personal history of skin cancer and skin cancer diagnosis day of the clinic visit. While 3 categories were used to assess personal history of skin cancer (Yes/No/Unsure), participants with an unsure history were removed from univariate analyses so that the outcome could be assessed as a binary variable. Skin cancer diagnosis day of the clinic visit (Yes/No; If yes, specify date/type) was assessed by the attending physicians during their check-up with the patient.

2.8 Case and Control Definitions

Our study population includes a range of patients: those that don't have a history of skin cancer, those that have had 1 type of skin cancer, and those that have had more than 1 type of skin cancer. The case and control definitions used in this thesis are detailed in **Table 2.2**.

Table 2.2 Case and control definitions used for the study.

Outcome under Analysis	Case	Control
Skin Cancer	Patients that have a history of basal cell carcinoma, squamous cell carcinoma, **or** melanoma	Patients that don't have a history of any type of skin cancer (basal cell carcinoma, squamous cell carcinoma, melanoma)
Keratinocyte Carcinoma	Patients that have a history of basal cell **or** squamous cell carcinoma	
Basal Cell Carcinoma	Patients that have a history of basal cell carcinoma	
Squamous Cell Carcinoma	Patients that have a history of squamous cell carcinoma	
Melanoma	Patients that have a history of melanoma	

2.9 Statistical Analysis

We performed descriptive and univariate analyses for all variables collected except for previous skin cancer history and places of residence, which were left for future analyses. All statistical analyses were conducted using R statistical software (Version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics (means, medians, frequencies, percentages) were calculated where applicable for each variable, and for each outcome. These statistics, along with the age distributions and percentage frequency distributions (for all categorical variables) created, were examined to compare cases with controls for each outcome.

2.9.1 Univariate Analysis

Univariate binary logistic regression models were developed to assess the associations between potential risk factors and the different types of skin cancers. The odds ratios and their corresponding 95% confidence intervals from the model outputs were reported. Global two-sided p-values (significant at $p < 0.05$) for each variable were also reported.

Binary logistic regression models assume that continuous variables are linearly associated with the log-odds of the outcome variable. For our one continuous variable, age, we checked this assumption using the widely used Box-Tidwell test. In the presence of non-linearity, we used binary logistic regressions with splines to examine the association between age and outcome. We used 4 knots for the splines, placed at the default locations as set by the rms package in R statistical software (5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles of the age distribution). Splines are commonly used to address non-linear effects in regression models, as they can capture the non-linearity while avoiding the disadvantages that come with categorization of continuous variables (reduced precision and power, false assumption of a linear relationship, arbitrary cut-off points leading to loss of information and overfitting of model).[71,72]

Several variables had zero counts in one or more of their categories, and as such led to errors due to separation issues when conducting logistic regressions. Two methods were used to account for this issue. For tanning bed history, Fitzpatrick skin type, and nevus density, categories were combined to resolve the problem stemming from zero counts. For tanning bed history, 101-499 sessions was combined with 500+ sessions. For Fitzpatrick skin type, types IV and V were combined. For nevus density, “none” was combined with “few”, and “some” was combined with “many”. For specific eye colour and atypical nevi, Firth’s bias reduced logistic regression was

performed instead of combining categories as 1) the zero count was only in 1 category level, and 2) we were interested in seeing the effects of the category levels that would otherwise have been combined. Firth's method was also used to analyze transplant history, as there were only two categories (combining would not have been possible).

2.9.2 Missing Data and Excluded Data

Frequencies and percentages of missing data were reported for each variable as "unknown" in tables. Our figures of distributions exclude the unknown category, although for specific eye colour and specific hair colour, the unknown category is included as there was missing data for a large portion of participants. Observations with missing data for variables were excluded from the respective univariate regression analyses and corresponding odds ratio calculations, except for family history of melanoma as noted below.

Some of our participants were unsure their status of melanoma, BCC and SCC. These participants were removed from all analyses. In addition, some of our variables (family history of melanoma, actinic keratosis history, childhood and adulthood sunburns) also have records of being unsure. For the distribution analyses, we've included the unsure category for family history of melanoma, but excluded the category for the other variables. We included the unsure category for family history of melanoma as there were quite a few patients who were unsure of their family histories, and we were interested in examining if the "yes" and "unsure" responses were linked to different associations with skin cancer. There was 1 unknown record for family history of melanoma, which was combined with the unsure records for the univariate regression analyses.

Chapter 3: Study Population Characteristics and Demographics

This chapter presents an overview of the study population and an analysis of demographic variables.

3.1 Study Population Characteristics

We surveyed a total of 1003 patients, of which 489 were skin cancer cases and 514 were controls. The mean age of the study population was 62 years (standard deviation [SD]: 16, range: 18-93), and there was a relatively even distribution of gender (51% male, 49% female). Most participants were Fitzpatrick skin types II/III (75%) and had light colour eyes (56%). BCC (367 cases) was the most common skin cancer found in patients, followed by SCC (148 cases) then melanoma (105 cases). Some participants had more than 1 type of skin cancer, as can be seen from **Figure 3.1**.

Compared to controls, both the mean and the median age were higher for cases (across all skin cancer types). There was a greater proportion of males in cases, and it was more common for cases to have lighter eye and hair colours compared to controls. Cases were more likely than controls to have more photosensitive skin (Fitzpatrick skin types I/II), while controls were more likely than cases to have less photosensitive skin (Fitzpatrick skin types (IV/V). We found an obvious difference between cases and controls in terms of lentigo density, with cases more likely to have a greater number of lentigines. History of childhood and adulthood sunburns also differed between cases and controls, with cases more likely to have greater numbers of sunburns. Distributions of the surveyed risk factors for our total population as well as for each outcome type are reported in tables throughout chapters 3 to 6 (**Tables 3.1, 4.1, 4.3, 4.5, 4.7, 4.19, 5.1, 5.3, 5.5, 5.7, 5.9, 5.11, 5.13, 6.1, 6.3, 6.5, 6.7, 6.9, 6.11, 6.13**).

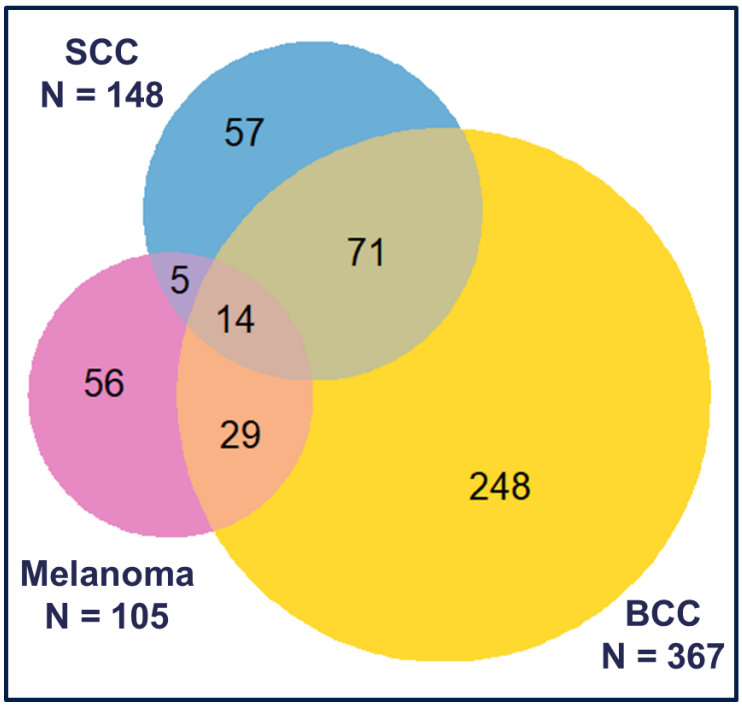

Figure 3.1 Distribution of melanoma, BCC, and SCC cases in the study population.

3.2 Univariate Regressions

Univariate binary logistic regressions were performed to assess the associations between each risk factor and outcome status (skin cancer, keratinocyte carcinoma, melanoma, BCC, SCC). The odds ratios and 95% confidence intervals from these regressions are shown in tables throughout chapters 3 to 6 (**Tables 3.2, 4.2, 4.4, 4.6, 4.8, 4.10, 5.2, 5.4, 5.6, 5.8, 5.10, 5.12, 5.14, 6.2, 6.4, 6.6, 6.8, 6.10, 6.12, 6.14**).

Apart from age, the strongest significant risk factor for both skin cancer and keratinocyte carcinoma was presence of many lentigines (OR 13.3 for skin cancer, 19.8 for KC). Light eye colour (OR for green eyes: 8.57 for skin cancer, 10.7 for KC), having a history of actinic keratosis (OR 7.25 for skin cancer, 10.3 for KC), Fitzpatrick skin type I (OR 6.91 for skin cancer, 7.25 for KC), and red hair (OR 6.33 for skin cancer, 6.84 for KC) were also strongly risk factors. Other statistically significant variables for both skin cancer and keratinocyte carcinoma included gender, smoking status, nevus density, atypical nevi, freckle density, history of childhood sunburns, history of adulthood sunburns, UV radiation treatment history, recreational sun exposure history, and lifetime frequency of sunny holidays. In addition, immunosuppressant history was significantly associated with keratinocyte carcinoma.

There were 13 statistically significant variables for melanoma: age, gender, actinic keratosis history, transplant history, drinking status, eye colour, hair colour, Fitzpatrick skin type, nevus density, lentigo density, history of childhood sunburns, history of adulthood sunburns, and occupational sun exposure history. Having a family history of melanoma was also significantly related to melanoma, though the variable as a whole did not reach significance. BCC was significantly associated with 17 risk factors: age, gender, actinic keratosis history, immunosuppressant history, smoking status, eye colour, hair colour, Fitzpatrick skin type, nevus

density, atypical nevi, freckle density, lentigo density, history of childhood sunburns, history of adulthood sunburns, UV radiation treatment history, recreational sun exposure history, and sunny holiday history. For SCC, 15 risk factors were statistically significant: age, gender, actinic keratosis history, immunosuppressant history, eye colour, hair colour, Fitzpatrick skin type, nevus density, atypical nevi, lentigo density, history of childhood sunburns, history of adulthood sunburns, tanning bed history, UV radiation treatment history, and recreational sun exposure history.

3.3 Demographics

3.3.1 Age

Age distributions show that the distributions of cases have a smaller range and are centered at a greater age compared to the distributions of controls (**Figure 3.2**). Both the mean and the median age were higher in cases than controls for all types of skin cancer (**Table 3.1**). SCC had the greatest difference in mean age between cases (75 years, SD: 10) and controls (55 years, SD: 17). BCC cases had a mean age of 69 years (SD: 12). The discrepancy was much smaller for melanoma than for all other outcomes, as melanoma cases had a mean age of 64 (SD = 15) years.

Before building univariate regressions to assess the relationship between age and outcome status, the log-linear assumption for logistic regression was checked through the Box-Tidwell test. For melanoma, SCC, and skin cancer, the tests showed non-significance ($p > 0.05$) for the interaction term for age and the natural logarithm of age, indicating that age satisfied the linearity assumption for logistic regression (**Table 3.3**). However, the interaction term for age and the natural logarithm of age was statistically significant for BCC and keratinocyte carcinoma, indicating presence of non-linearity in the association between age and the log-odds of BCC and keratinocyte carcinoma.

To account for the non-linearity, we used restricted cubic splines with 4 knots to fit age as a continuous variable in our binary logistic regression models for BCC and keratinocyte carcinoma. Non-linearity in this relationship was also confirmed from the plots of log-odds against age obtained from the models, where the log-odds increase until age 55-60, plateaus, then increases again from around age 70 (**Figure 3.3**). We found a significant association between age and both risk of BCC as well as keratinocyte carcinoma (**Table 3.3**). While it is more difficult to interpret results of a model with splines as opposed to a general binary logistic model, calculated odds ratios between 3 age ranges for both BCC and keratinocyte carcinoma are shown in **Table 3.4**. For both outcomes we see

there is a very strong and significant increase in odds between ages 18 and 60, a non-significant increase in odds between ages 60 and 70, and a significant increase in odds between ages 70 and 93.

Based on our results from a simple binary logistic regression, age was significantly associated with skin cancer overall, melanoma, as well as SCC. Each yearly increase in age was associated with an increase of 6 % in the odds of skin cancer, 4% in the odds of melanoma, and 13% in the odds of SCC (**Table 3.2**).

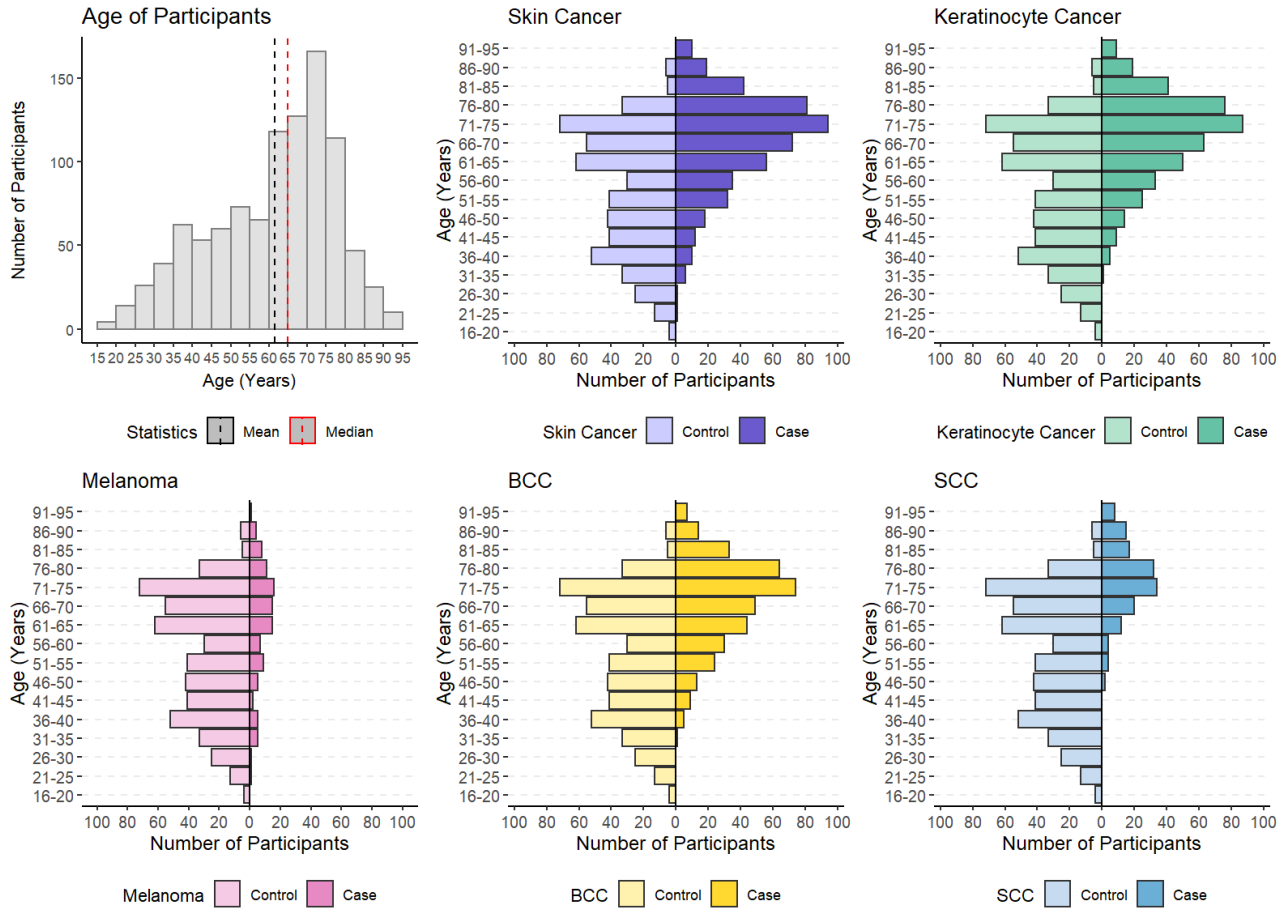

Figure 3.2 Age distributions by outcome.

Table 3.1 Distributions of age and gender.

	Total N = 1,003	Control N = 514	Skin Cancer N = 489	Keratinocyte Carcinoma N = 432	Melanoma N = 105	BCC N = 367	SCC N = 148
Age (years)							
Mean (SD)	62 (16)	55 (17)	68 (13)	70 (12)	64 (15)	69 (12)	75 (10)
Median (IQR)	65 (50, 74)	57 (41, 69)	71 (62, 77)	71 (63, 78)	66 (54, 75)	71 (62, 77)	75 (70, 81)
Range	18, 93	18, 90	25, 93	34, 93	25, 91	34, 93	47, 93
Gender, n (%)							
F	492 (49%)	276 (54%)	216 (44%)	184 (43%)	45 (43%)	158 (43%)	54 (36%)
M	511 (51%)	238 (46%)	273 (56%)	248 (57%)	60 (57%)	209 (57%)	94 (64%)

Table 3.2 Univariate binary logistic regression analyses of age and gender.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Age (years)	1.06 (1.05-1.07)	**<0.001**	NA[b]		1.04 (1.02-1.05)	**<0.001**	NA[b]		1.13 (1.10-1.15)	**<0.001**
Gender		**0.003**		**<0.001**		**0.043**		**0.002**		**<0.001**
F	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
M	1.47 (1.14-1.88)		1.56 (1.21-2.02)		1.55 (1.01-2.37)		1.53 (1.17-2.01)		2.02 (1.39-2.96)	

[a] OR = Odds Ratio, CI = Confidence Interval
[b] Refer to Table 3.4 for odds ratios calculated for KC and BCC using cubic spline models
p-values significant at ≤0.05 are **bolded**

Table 3.3 Box-Tidwell test: statistical significance of the interaction terms between age and the natural log of age.

	Skin Cancer	Keratinocyte Carcinoma	Melanoma	BCC	SCC
P-value for Age:log(Age)	0.090	0.007*	0.284	0.007*	0.096
*Significant at p ≤0.05					

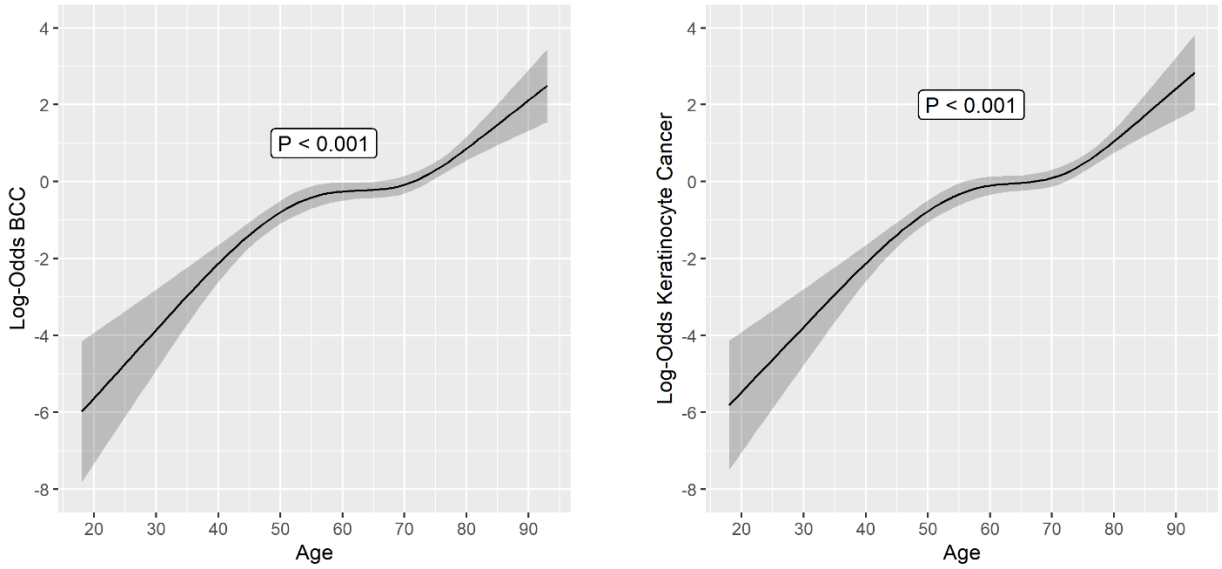

Figure 3.3 Association between age and risk of BCC/Keratinocyte Carcinoma. The solid black lines show the log-odds, and the grey bands show the corresponding 95% confidence intervals from restricted cubic spline models with 4 knots (3 degrees of freedom).

Table 3.4 Odds ratios between 3 sets of ages for BCC and Keratinocyte Carcinoma based on restricted cubic spline models with 4 knots.

	BCC		Keratinocyte	
Age	**Odds Ratio**	**95% CI[a]**	**Odds Ratio**	**95% CI[a]**
60 vs. 18	305	43.1-2163	299	48.8-1836
70 vs. 60	1.20	0.91-1.57	1.22	0.92-1.62
93 vs. 70	13.17	4.53-38.3	15.6	5.21-46.5
[a] CI = Confidence Interval				

3.3.2 Gender

Although for the overall study population, there were roughly equal numbers of males and females (51% vs. 49%), cases were more likely to be males compared to controls for all skin cancer types (**Table 3.1**). SCC cases had the highest proportion of males (63.5%), while cases for other outcomes had proportions around 56-57% (**Figure 3.4**). For controls, the proportion of males was smaller than that of females (46% vs. 54%).

Gender was significantly associated with all types of skin cancer (**Table 3.2**). Being male was most strongly associated with an increased risk of SCC (OR 2.02, CI 1.39-2.96). Males also had a greater risk of having skin cancer (OR 1.47, CI 1.14-1.88), keratinocyte carcinoma (OR 1.56, CI 1.21-2.02), melanoma (OR 1.55, CI 1.01-2.37), and BCC (OR 1.53, CI 1.17-2.01).

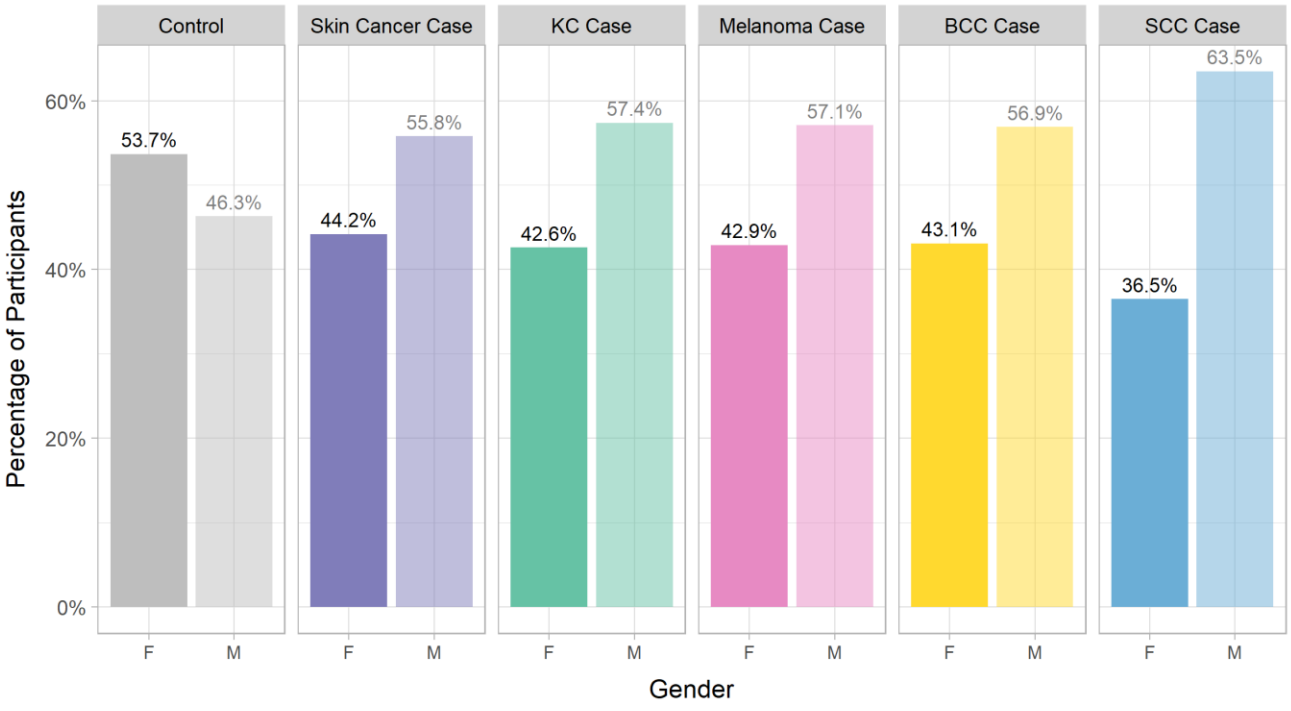

Figure 3.4 Gender distributions by outcome.

Chapter 4: Participant History

This chapter presents an analysis of variables related to participant history, including family history of melanoma, actinic keratosis history, receiving a transplant, taking immunosuppressant medications, smoking and drinking history.

4.1 Family History of Melanoma

A greater proportion of melanoma cases compared to controls had a family history of melanoma (18% vs. 11%) (**Table 4.1**). Overall, the variable family history of melanoma was not significantly associated with melanoma, perhaps because the association between an unsure family history and melanoma was not significant. Individually, having a family history of melanoma compared to not having a family history of melanoma was significantly associated with an increased risk of melanoma (OR 1.84, CI 1.02-3.23) (**Table 4.2**). While participants that were unsure about their family history of melanoma also had an increased risk of melanoma, this association was not significant (OR 1.59, CI 0.83-2.91).

We saw the opposite trend for keratinocyte carcinomas as well as skin cancer overall, as a greater proportion of controls compared to cases had a family history of melanoma. However, we did not see a significant association between having a family history of melanoma and keratinocyte carcinoma (OR 0.79, CI 0.51-1.21), or skin cancer (OR 0.84, CI 0.56-1.26) (**Table 4.2**).

Table 4.1 Distributions of family history of melanoma.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Family History of Melanoma							
No	781 (78%)	401 (78%)	380 (78%)	335 (78%)	70 (67%)	279 (76%)	117 (79%)
Yes	106 (11%)	59 (11%)	47 (9.6%)	39 (9.0%)	19 (18%)	35 (9.5%)	9 (6.1%)
Unsure	115 (11%)	54 (11%)	61 (12%)	57 (13%)	15 (14%)	52 (14%)	21 (14%)
Unknown	1 (<0.1%)	0 (0%)	1 (0.2%)	1 (0.2%)	1 (1.0%)	1 (0.3%)	1 (0.7%)

[1] n (%)

Table 4.2 Univariate binary logistic regression analyses of family history of melanoma.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Family History of Melanoma		0.43		0.24		0.070		0.20		0.083
No	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Yes	0.84 (0.56-1.26)		0.79 (0.51-1.21)		1.84 (1.02-3.23)		0.85 (0.54-1.32)		0.52 (0.24-1.04)	
Unsure	1.19 (0.81-1.77)		1.26 (0.85-1.89)		1.59 (0.83-2.91)		1.38 (0.92-2.09)		1.33 (0.76-2.27)	

[a] OR = Odds Ratio, CI = Confidence Interval
p-values significant at ≤0.05 are **bolded**

4.2 Actinic Keratosis History

In general, more participants in our study population had a history of actinic keratosis (60%) than not (40%) (**Table 4.3**). In contrast, it was more common for our controls to not have a history of actinic keratosis (61%) than have a history (39%). **Figure 4.1** shows that a greater percentage of cases had a history of actinic keratosis compared to controls, for all skin cancer types. A greater proportion of melanoma cases (70%) had a history of actinic keratosis, compared to our total participants. For both keratinocyte carcinomas, we saw that the majority of cases (~90%) had a history of actinic keratosis.

Having a history of actinic keratosis was significantly associated with an increased risk of all types of skin cancer (**Table 4.4**). This effect was greatest for SCC (OR 19.6, CI 10.8-39.3), followed by BCC (OR 9.94, CI 7.08-14.2), then melanoma (OR 3.59, CI 2.30-5.70). Accordingly, there was also a significant positive relationship between actinic keratosis history and skin cancer overall (OR 7.25, CI 5.43-5.95) and keratinocyte carcinoma overall (OR 10.3, CI 7.47-14.5).

Table 4.3 Distributions of actinic keratosis history.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Actinic Keratosis History							
No	400 (40%)	313 (61%)	87 (18%)	57 (13%)	32 (30%)	50 (14%)	11 (7.4%)
Yes	600 (60%)	199 (39%)	401 (82%)	374 (87%)	73 (70%)	316 (86%)	137 (93%)
Unsure	3 (0.3%)	2 (0.4%)	1 (0.2%)	1 (0.2%)	0 (0%)	1 (0.3%)	0 (0%)

[1] n (%)

Table 4.4 Univariate binary logistic regression analyses of actinic keratosis history.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Actinic Keratosis History		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
No	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Yes	7.25 (5.43-9.75)		10.3 (7.47-14.5)		3.59 (2.30-5.70)		9.94 (7.08-14.2)		19.6 (10.8-39.3)	

[a] OR = Odds Ratio, CI = Confidence Interval
p-values significant at ≤0.05 are **bolded**

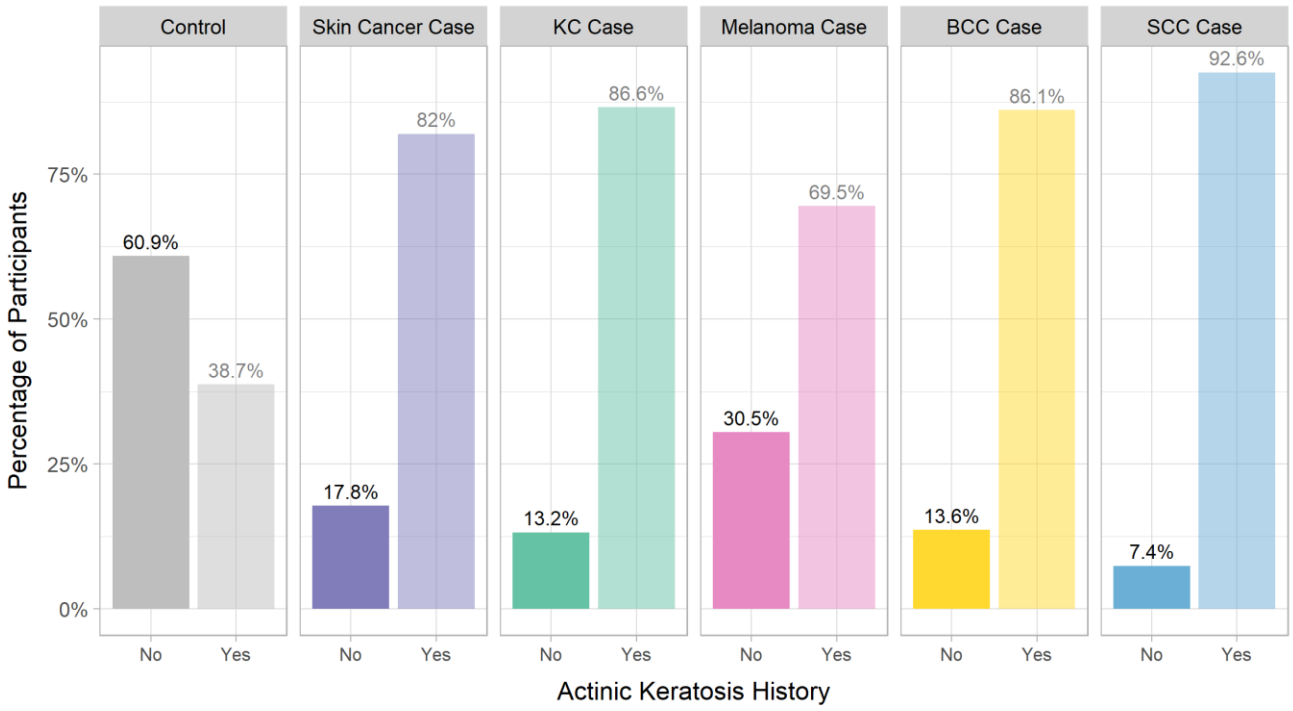

Figure 4.1 Distribution of actinic keratosis history by outcome.

4.3 Immunosuppression

4.3.1 Transplants

Having a history of transplants was rare in our study population (4.1%) (**Table 4.5**). While this finding was constant across all our outcomes for both cases and controls, there were some minute differences (**Figure 4.2**). A slightly lower percentage of BCC cases (3.5%) compared to our controls (4.5%) had a transplant history. None of our melanoma cases were transplant recipients. A greater percentage of SCC cases (6.1%) compared to controls had a transplant history. Transplant history had a significant inverse relationship with melanoma (OR 0.10, CI 0-0.72) (**Table 4.6**). We did not find a significant association between history of transplants and all other outcomes.

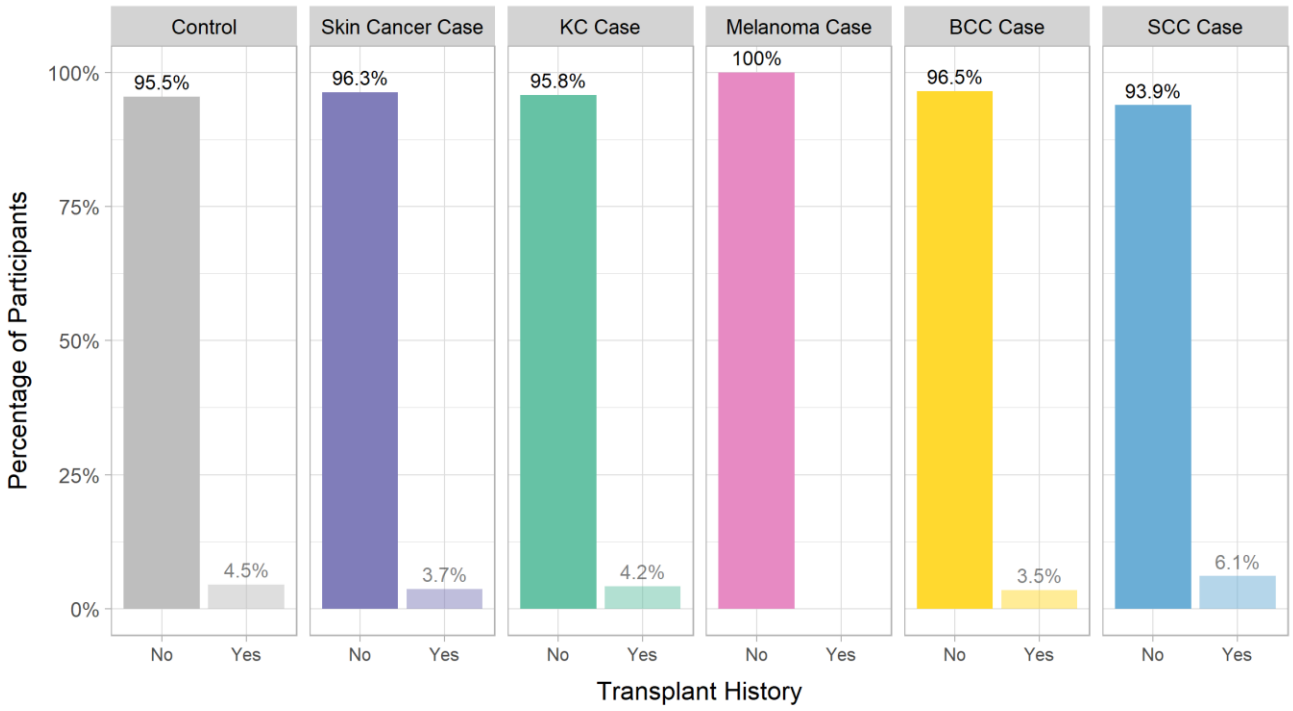

Figure 4.2 Distribution of transplant history by outcome.

4.3.2 Immunosuppressants

Most of our study population did not have a history of using immunosuppressives, with only 12% having used them (**Table 4.5**). As with transplant history, the distributions of immunosuppressant history did not deviate largely from this observation, but there were still some differences between outcomes (**Figure 4.3**). For both keratinocyte carcinomas, a higher proportion of cases compared to controls had a history of using immunosuppressants. The discrepancy was greatest for SCC, as 18.9% of cases had used immunosuppressives before, while 10.1% of our controls had a history of immunosuppressants. There was a smaller discrepancy for BCC cases, as 14.7% had used immunosuppressants. We saw an opposite trend for melanoma, as 8.6% of cases and had a history of immunosuppressants.

Table 4.5 Distributions of transplant and immunosuppressant histories.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Transplant History							
No	962 (96%)	491 (96%)	471 (96%)	414 (96%)	105 (100%)	354 (96%)	139 (94%)
Yes	41 (4.1%)	23 (4.5%)	18 (3.7%)	18 (4.2%)	0 (0%)	13 (3.5%)	9 (6.1%)
Immunosuppressant History							
No	882 (88%)	462 (90%)	420 (86%)	366 (85%)	96 (91%)	313 (85%)	120 (81%)
Yes	121 (12%)	52 (10%)	69 (14%)	66 (15%)	9 (8.6%)	54 (15%)	28 (19%)

[1] n (%)

Table 4.6 Univariate binary logistic regression analyses of transplant and immunosuppressant histories.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Transplant History		0.53		0.82		**0.016[b]**		0.49		0.43
No	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Yes	0.82 (0.43-1.53)		0.93 (0.49-1.74)		0.10 (0-0.72)[b]		0.78 (0.38-1.55)		1.38 (0.59-2.96)	
Immunosuppressant History		0.052		**0.017**		0.62		**0.040**		**0.006**
No	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Yes	1.46 (1.00-2.15)		1.60 (1.09-2.37)		0.83 (0.37-1.67)		1.53 (1.02-2.31)		2.07 (1.24-3.40)	

[a] OR = Odds Ratio, CI = Confidence Interval
[b] Values obtained from Firth's bias-reduced logistic regression
p-values significant at ≤0.05 are **bolded**

We found an increased risk of BCC (OR 1.53, CI 1.02-2.31), SCC (OR 2.07, CI 1.24-3.40), and keratinocyte carcinoma overall (OR 1.60, CI 1.09-2.37) for participants with a history of using immunosuppressants (**Table 4.6**). While a greater risk was similarly found for skin cancer overall (OR 1.46, CI 1.00-2.15), this observation was not statistically significant (p=0.052). There was no statistically significant association between history of immunosuppressants and melanoma.

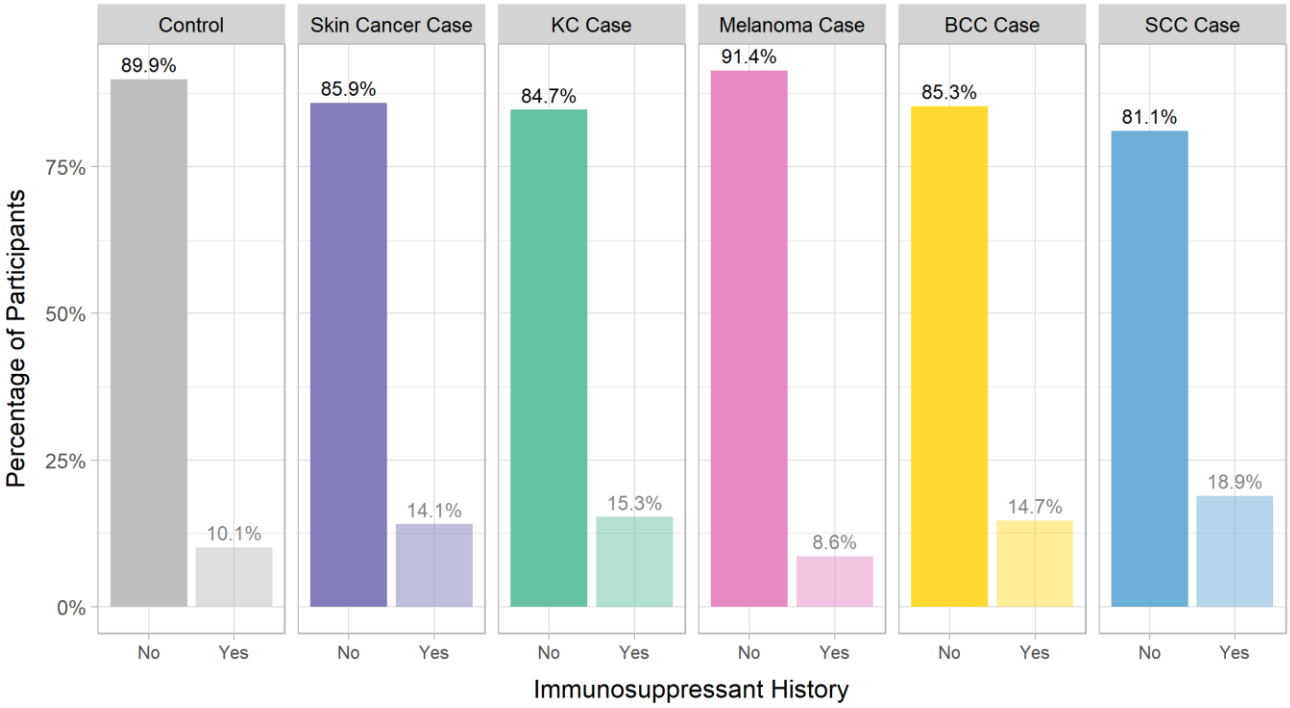

Figure 4.3 Distribution of immunosuppressant history by outcome.

4.4 Drinking and Smoking History

4.4.1 Drinking

The majority (82%) of our study participants were current drinkers, while 11% were former, and 7.2% were never drinkers (**Table 4.7**). The distribution in drinking status was similar between BCC cases and controls (**Figure 4.4**). For SCC, a slightly greater proportion of cases compared to

controls were former drinkers (13% vs. 10%), while a slightly smaller proportion of cases compared to controls were current drinkers (78% vs. 82%). While melanoma cases and controls had similar percentages of former drinkers, more cases compared to controls were current drinkers (87% vs 82%) and more controls compared to cases were never drinkers (8% vs. 2%).

We found a statistically significant association between drinking and risk of melanoma. Risk of melanoma was higher for both current (OR 4.45, CI 1.34-27.6) and former drinkers (OR 4.64, CI 1.18-30.9) compared to never drinkers (**Table 4.8**). Drinking was not found to be significantly associated with any of the other outcomes.

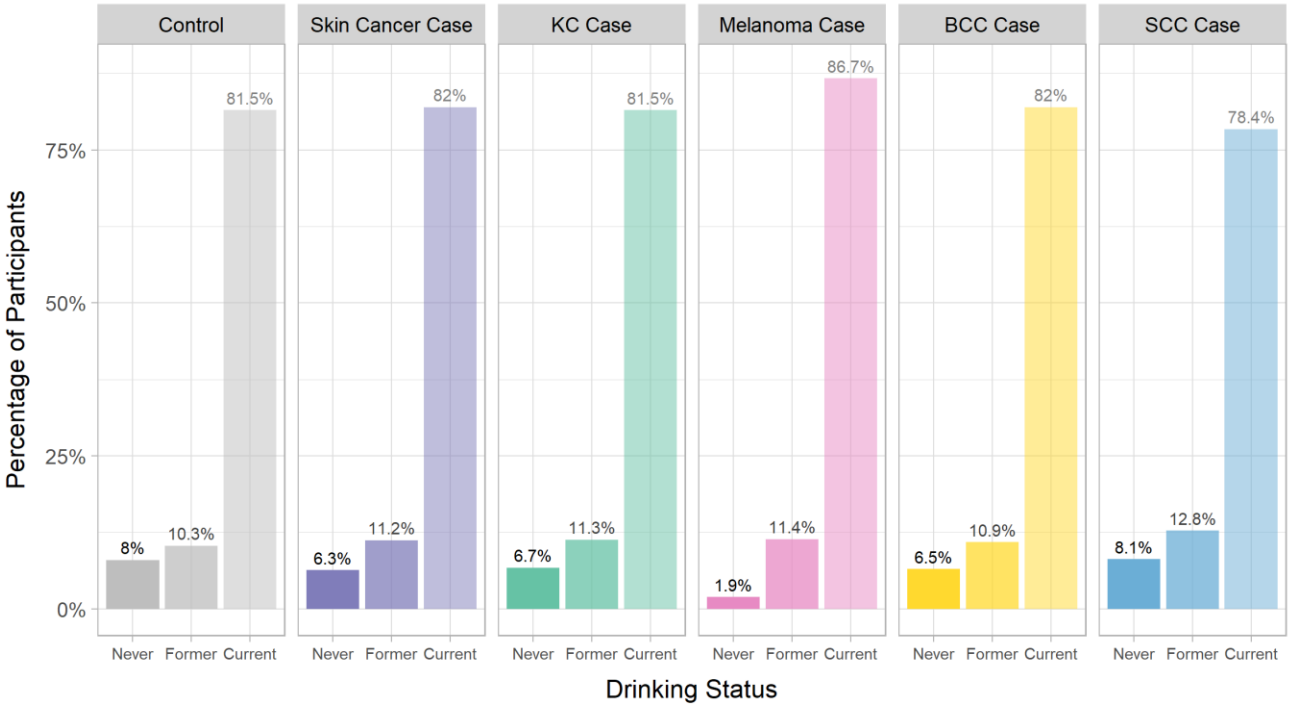

Figure 4.4 Distribution of drinking history by outcome.

Table 4.7 Distributions of drinking status.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Drinking Status							
Never	72 (7.2%)	41 (8.0%)	31 (6.3%)	29 (6.7%)	2 (1.9%)	24 (6.5%)	12 (8.1%)
Former	108 (11%)	53 (10%)	55 (11%)	49 (11%)	12 (11%)	40 (11%)	19 (13%)
Current	820 (82%)	419 (82%)	401 (82%)	352 (81%)	91 (87%)	301 (82%)	116 (78%)
Unknown	3 (0.3%)	1 (0.2%)	2 (0.4%)	2 (0.5%)	0 (0%)	2 (0.5%)	1 (0.7%)

[1] n (%)

Table 4.8 Univariate binary logistic regression analyses of drinking status.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Drinking Status		0.56		0.69		**0.038**		0.71		0.67
Never	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Former	1.37 (0.75-2.51)		1.31 (0.71-2.43)		4.64 (1.18-30.9)		1.29 (0.68-2.49)		1.22 (0.54-2.87)	
Current	1.27 (0.78-2.07)		1.19 (0.73-1.97)		4.45 (1.34-27.6)		1.23 (0.73-2.10)		0.95 (0.50-1.93)	

[a] OR = Odds Ratio, CI = Confidence Interval
p-values significant at ≤0.05 are **bolded**

4.4.2 Smoking

More than half (58%) of our study population were never smokers; 40% were former smokers, and only 2.2% were current smokers (**Table 4.9**). For the two keratinocyte carcinomas, a smaller proportion of cases compared to controls were never smokers, while a greater proportion of cases compared to controls were former smokers (**Figure 4.5**). The proportions of current smokers were similar for keratinocyte cases and controls. For melanoma, similar trends were seen for never and former smokers as were seen for KCs, but there was a slightly greater percentage of cases compared to controls for current smokers (4.8% vs. 1.8%).

Smoking was not significantly associated with risk of melanoma or SCC. Smoking was significantly associated with BCC, with former smokers having a higher risk of BCC (OR 1.42, CI 1.08-1.88) (**Table 4.10**). There was a statistically significant relationship between smoking and skin cancer as well as keratinocyte carcinoma, although a closer look into the categories shows that only former smokers had a greater risk of skin cancer (OR 1.41, CI 1.10-1.83) and keratinocyte carcinoma (OR 1.45, CI 1.12-1.89). We did not find a statistically significant association between current smokers and any of the outcomes.

Table 4.9 Distributions of smoking status.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Smoking Status							
Never	580 (58%)	319 (62%)	261 (53%)	229 (53%)	60 (57%)	196 (53%)	79 (53%)
Former	397 (40%)	184 (36%)	213 (44%)	192 (44%)	40 (38%)	161 (44%)	66 (45%)
Current	22 (2.2%)	9 (1.8%)	13 (2.7%)	9 (2.1%)	5 (4.8%)	8 (2.2%)	2 (1.4%)
Unknown	4 (0.4%)	2 (0.4%)	2 (0.4%)	2 (0.5%)	0 (0%)	2 (0.5%)	1 (0.7%)

[1] n (%)

Table 4.10 Univariate binary logistic regression analyses of smoking status.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Smoking Status		**0.018**		**0.020**		0.19		**0.039**		0.15
Never	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Former	1.41 (1.10-1.83)		1.45 (1.12-1.89)		1.16 (0.74-1.79)		1.42 (1.08-1.88)		1.45 (1.00-2.10)	
Current	1.77 (0.75-4.34)		1.39 (0.54-3.62)		2.95 (0.88-8.86)		1.45 (0.53-3.84)		0.90 (0.14-3.57)	

[a] OR = Odds Ratio, CI = Confidence Interval
p-values significant at ≤0.05 are **bolded**

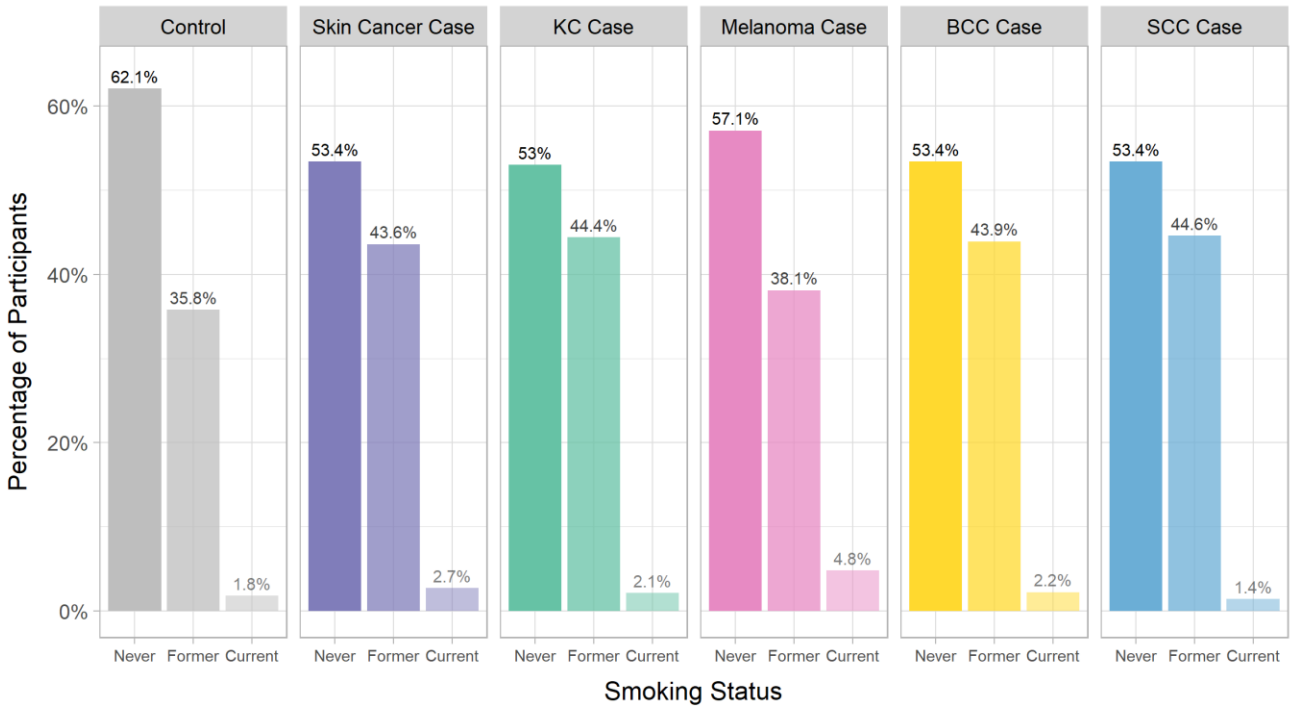

Figure 4.5 Distribution of smoking history by outcome.

Chapter 5: Phenotypic Characteristics

This chapter presents an analysis of phenotypic characteristics, including eye colour, hair colour, Fitzpatrick skin type, nevus density, atypical nevi, freckle density, and lentigo density.

5.1 Eye Colour

In our study population, light eye colour (56%) was most common, followed by medium (29%) and then dark (14%) (**Table 5.1**). This finding stays consistent across all outcomes, but a comparison of cases to controls shows this trend becoming more skewed towards lighter eye colours for cases, and towards darker eye colours for controls (**Figure 5.1**). This trend was most pronounced for SCC, as a greater proportion of cases compared to controls had light-coloured eyes (68% vs. 49%), and a smaller proportion of cases compared to controls had dark-coloured eyes (2.7% vs. 21%). The differences between melanoma cases and controls were not as pronounced: 9% and 3% more cases than controls had light and medium eye colours respectively, while 12% more cases than controls had dark eye colours.

We found eye colour to be significantly associated with all types of skin cancer (**Table 5.2**). The odds of melanoma, BCC, and SCC were greater for participants with medium compared to dark eye colour, and were even greater for participants with light eye colour. Light eye colour was most strongly associated with risk of SCC (OR 11.0, CI 4.46-36.5), as was medium eye colour (OR 7.75, CI 3.02-26.3).

Short of midway through our data collection, we started collecting data on more specific eye colour than the dark/medium/light we initially recorded, to facilitate easier comparison with other studies in the future. Data for specific eye colour was missing for 378 participants (**Table 5.1**). Comparing across colours we classified as medium, hazel eyes were more common than light brown

eyes (**Figure 5.2**). Among the light eye colours, blue was the predominant colour, followed by green then grey.

As seen for eye colour, there was a statistically significant association between specific eye colour and BCC, SCC, keratinocyte carcinoma, as well as skin cancer (**Table 5.2**). For BCC, keratinocyte carcinoma and skin cancer overall, we found a trend towards greater risk with lighter eye colours. Compared to dark brown eyes, light brown, followed by hazel, blue, grey, then green eyes had an increasingly greater odds of BCC, keratinocyte, and skin cancer. While eye colour was also found to be significantly associated with SCC risk, the trend of increasing odds was different, as odds of SCC were increasingly greater in the following order: hazel, light brown, blue, grey, then green. The relationship between specific eye colour and melanoma risk was just short of reaching significance (p=0.053). Among the individual colours, green and blue eyes were significantly linked with an increased risk of melanoma.

Table 5.1 Distributions of eye colour.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Eye Colour							
Dark	144 (14%)	110 (21%)	34 (7.0%)	26 (6.0%)	9 (8.6%)	25 (6.8%)	4 (2.7%)
Medium	291 (29%)	149 (29%)	142 (29%)	125 (29%)	34 (32%)	102 (28%)	42 (28%)
Light	564 (56%)	253 (49%)	311 (64%)	280 (65%)	61 (58%)	239 (65%)	101 (68%)
Unknown	4 (0.4%)	2 (0.4%)	2 (0.4%)	1 (0.2%)	1 (1.0%)	1 (0.3%)	1 (0.7%)
Specific Eye Colour							
Dark Brown	97 (9.7%)	79 (15%)	18 (3.7%)	13 (3.0%)	5 (4.8%)	13 (3.5%)	2 (1.4%)
Light Brown	42 (4.2%)	26 (5.1%)	16 (3.3%)	13 (3.0%)	5 (4.8%)	6 (1.6%)	8 (5.4%)
Hazel	139 (14%)	72 (14%)	67 (14%)	59 (14%)	13 (12%)	53 (14%)	15 (10%)
Blue	272 (27%)	129 (25%)	143 (29%)	129 (30%)	31 (30%)	111 (30%)	41 (28%)
Green	62 (6.2%)	21 (4.1%)	41 (8.4%)	37 (8.6%)	7 (6.7%)	34 (9.3%)	13 (8.8%)
Grey	13 (1.3%)	6 (1.2%)	7 (1.4%)	7 (1.6%)	0 (0%)	6 (1.6%)	2 (1.4%)
Unknown	378 (38%)	181 (35%)	197 (40%)	174 (40%)	44 (42%)	144 (39%)	67 (45%)

[1] n (%)

Table 5.2 Univariate binary logistic regression analyses of eye colour.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Eye Colour		**<0.001**		**<0.001**		**0.005**		**<0.001**		**<0.001**
Dark	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Medium	3.08 (1.99-4.88)		3.55 (2.20-5.88)		2.79 (1.34-6.40)		3.01 (1.85-5.06)		7.75 (3.02-26.3)	
Light	3.98 (2.64-6.12)		4.68 (3.00-7.55)		2.95 (1.48-6.55)		4.16 (2.64-6.77)		11.0 (4.46-36.5)	
Specific Eye Colour		**<0.001**		**<0.001**		0.053[b]		**<0.001**		**<0.001**
Dark Brown	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Light Brown	2.70 (1.20-6.08)		3.04 (1.25-7.46)		3.00 (0.83-10.9)[b]		1.40 (0.45-3.94)		12.2 (2.83-84.0)	
Hazel	4.08 (2.26-7.69)		4.98 (2.59-10.2)		2.69 (0.99-8.29)[b]		4.47 (2.31-9.19)		8.23 (2.22-53.4)	
Blue	4.87 (2.82-8.78)		6.08 (3.32-11.9)		3.52 (1.46-10.1)[b]		5.23 (2.84-10.3)		12.6 (3.72-78.4)	
Green	8.57 (4.19-18.3)		10.7 (4.96-24.5)		5.04 (1.53-17.6)[b]		9.84 (4.53-22.6)		24.5 (6.15-164)	
Grey	5.12 (1.53-17.7)		7.09 (2.06-25.5)		1.11 (0.01-11.8)[b]		6.08 (1.67-22.4)		13.2 (1.39-128)	

[a] OR = Odds Ratio, CI = Confidence Interval
p-values significant at ≤0.05 are **bolded**

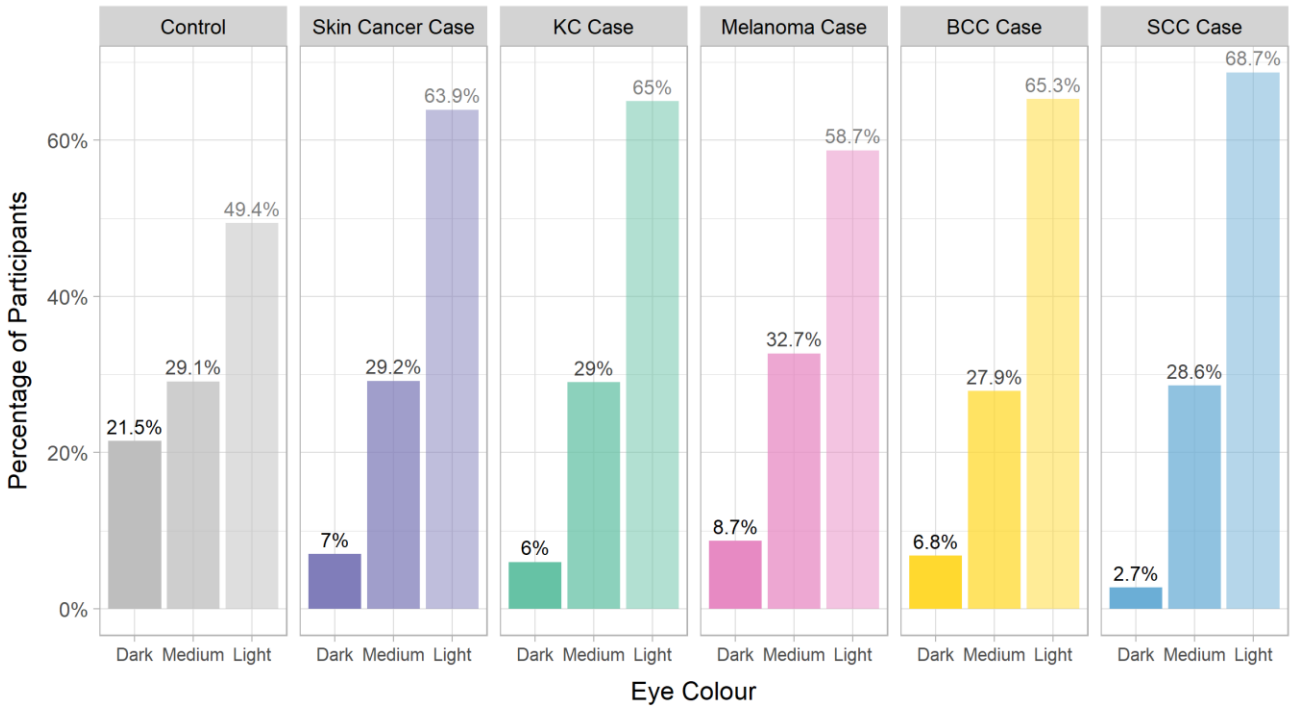

Figure 5.1 Distribution of eye colour by outcome.

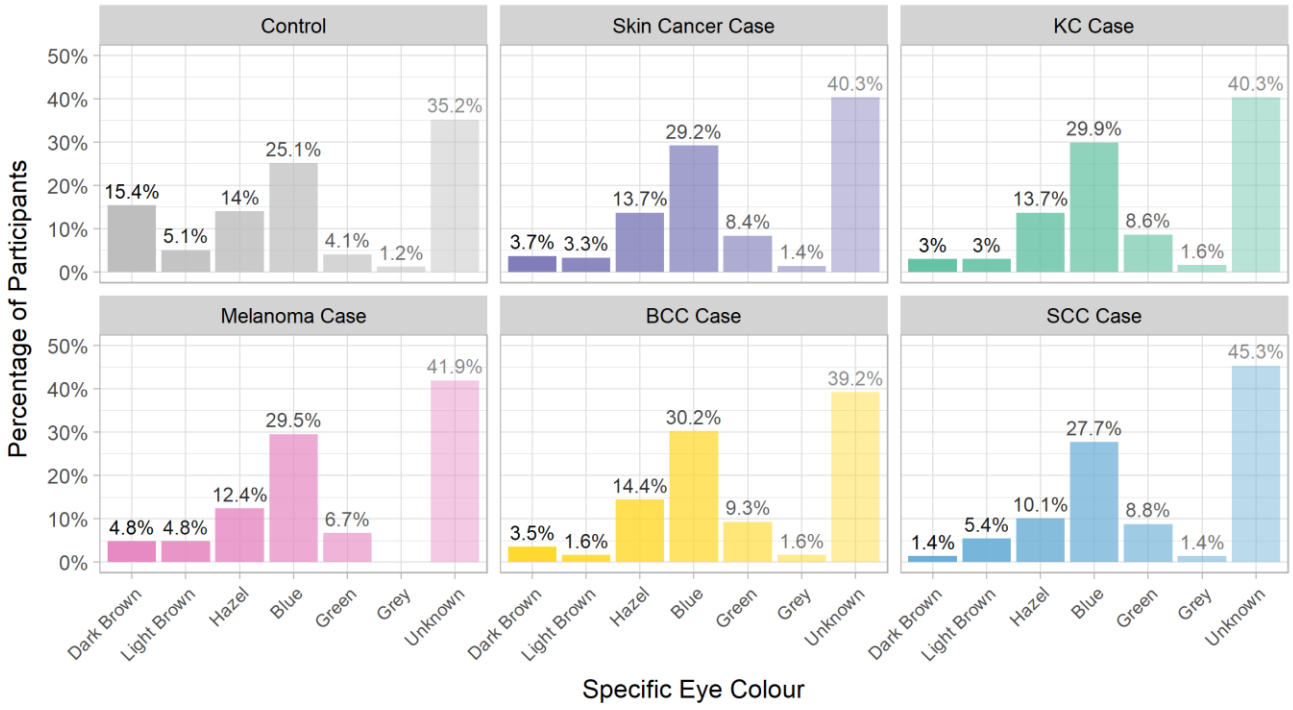

Figure 5.2 Distribution of specific eye colour by outcome.

5.2 Hair Colour

Most of our study population had light brown/blonde hair (51%) and black/dark brown hair (40%), while red hair was less common (9%) (Table 3.1). This finding stays consistent across all outcomes, but a comparison of cases to controls shows a trend more skewed towards lighter/red hair colours for cases, and towards darker colours for controls (**Figure 5.3**). A greater percentage of BCC and SCC cases had red and light brown/blonde hair compared to controls. In contrast, a greater proportion of controls had black/dark brown hair compared to BCC and SCC cases. We also see that black/dark brown hair is more common in controls than melanoma cases (46% vs. 35%), and red hair is more common in melanoma cases than controls (14% vs. 6%), but the proportion of light brown/blonde hair is similar for cases and controls (51% vs. 48%).

As with specific eye colour, we started recording information on more specific hair colour midway through our data collection. Data for specific hair colour was missing for 297 participants (**Table 5.3**). Generally, dark brown hair was most common, followed by light brown, blonde, red, then black. Again, comparing between cases and controls, we found a trend skewed towards blonde and red hair colours for cases, and towards dark brown and black colours for controls (**Figure 5.4**).

Hair colour was significantly associated with all skin cancer types (**Table 5.4**). Light brown/blonde compared to black hair was associated with 1.45 and 1.83 times the odds of BCC and SCC respectively, while red hair was associated with nearly 3 times the odds of BCC and SCC. While red hair significantly increased risk of melanoma (OR 3.07, CI 1.49-6.18), light brown/blond hair was not significantly associated with melanoma risk.

Specific hair colour had a significant association with all types of skin cancer (**Table 5.4**). With black hair as reference, light brown, blonde, and red hair showed a significantly increased risk of BCC as well as SCC, while dark brown did not show a significant association. Risk of melanoma

was significantly associated with specific hair colour, with the odds increasing progressively towards lighter and red hair colours. However, this increase in odds was significant for only red hair.

Table 5.3 Distributions of hair colour.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Hair Colour							
Black/Dark Brown	400 (40%)	235 (46%)	165 (34%)	144 (33%)	37 (35%)	126 (34%)	45 (30%)
Light Brown/Blonde	510 (51%)	246 (48%)	264 (54%)	233 (54%)	53 (50%)	191 (52%)	86 (58%)
Red	90 (9.0%)	31 (6.0%)	59 (12%)	54 (12%)	15 (14%)	49 (13%)	16 (11%)
Unknown	3 (0.3%)	2 (0.4%)	1 (0.2%)	1 (0.2%)	0 (0%)	1 (0.3%)	1 (0.7%)
Specific Hair Colour							
Black	61 (6.1%)	44 (8.6%)	17 (3.5%)	15 (3.5%)	4 (3.8%)	14 (3.8%)	4 (2.7%)
Dark Brown	232 (23%)	134 (26%)	98 (20%)	84 (19%)	19 (18%)	73 (20%)	29 (20%)
Light Brown	204 (20%)	105 (20%)	99 (20%)	91 (21%)	19 (18%)	72 (20%)	33 (22%)
Blonde	147 (15%)	73 (14%)	74 (15%)	65 (15%)	15 (14%)	55 (15%)	25 (17%)
Red	62 (6.2%)	18 (3.5%)	44 (9.0%)	42 (9.7%)	10 (9.5%)	37 (10%)	14 (9.5%)
Unknown	297 (30%)	140 (27%)	157 (32%)	135 (31%)	38 (36%)	116 (32%)	43 (29%)

[1] n (%)

Table 5.4 Univariate binary logistic regression analyses of hair colour.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Hair Colour		**<0.001**		**<0.001**		**0.011**		**<0.001**		**0.002**
Black/Dark Brown	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Light Brown/Blonde	1.53 (1.17-1.99)		1.55 (1.18-2.04)		1.37 (0.87-2.17)		1.45 (1.09-1.93)		1.83 (1.23-2.75)	
Red	2.71 (1.69-4.42)		2.84 (1.76-4.67)		3.07 (1.49-6.18)		2.95 (1.80-4.90)		2.70 (1.34-5.29)	
Specific Hair Colour		**<0.001**		**<0.001**		**0.035**		**<0.001**		**0.002**
Black	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Dark Brown	1.89 (1.04-3.59)		1.84 (0.98-3.60)		1.56 (0.55-5.60)		1.71 (0.90-3.43)		2.38 (0.88-8.35)	
Light Brown	2.44 (1.33-4.65)		2.54 (1.35-5.00)		1.99 (0.70-7.16)		2.16 (1.12-4.34)		3.46 (1.28-12.1)	
Blonde	2.62 (1.39-5.11)		2.61 (1.35-5.26)		2.26 (0.76-8.32)		2.37 (1.20-4.88)		3.77 (1.35-13.4)	
Red	6.33 (2.95-14.2)		6.84 (3.13-15.7)		6.11 (1.80-24.7)		6.46 (2.90-15.2)		8.56 (2.67-33.5)	

[a] OR = Odds Ratio, CI = Confidence Interval
p-values significant at ≤0.05 are **bolded**

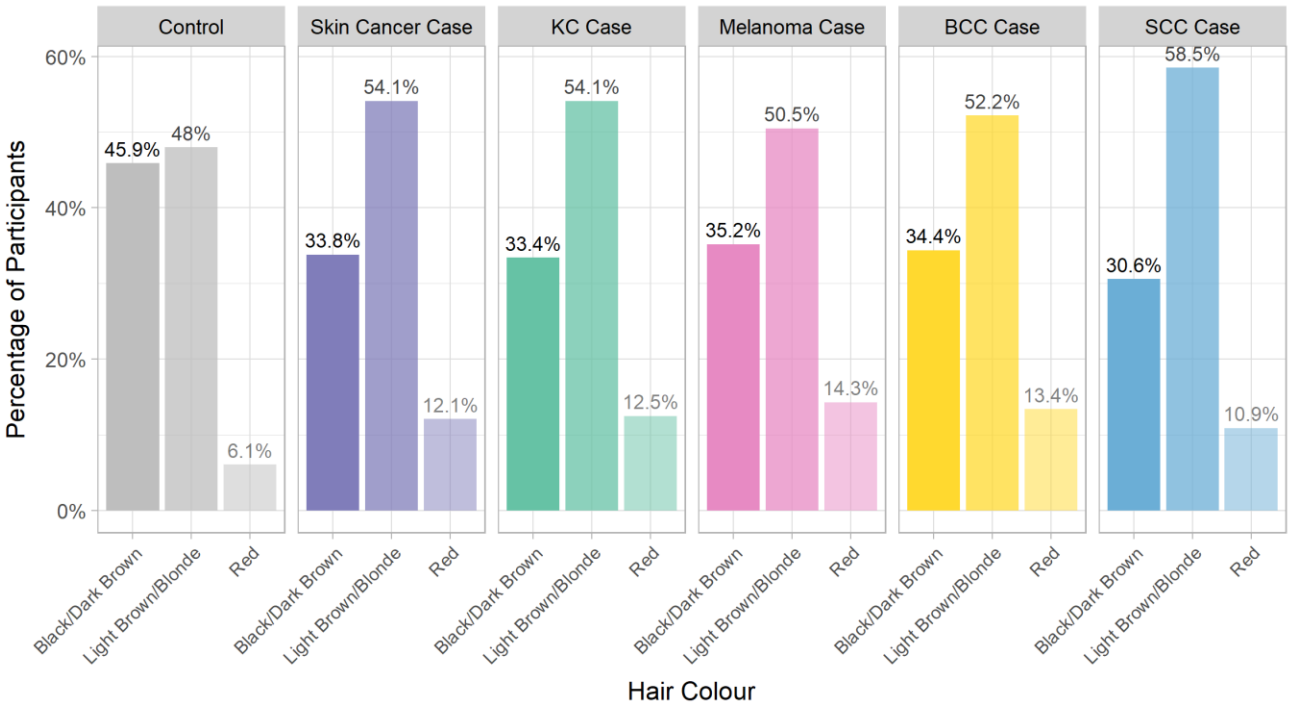

Figure 5.3 Distribution of hair colour by outcome.

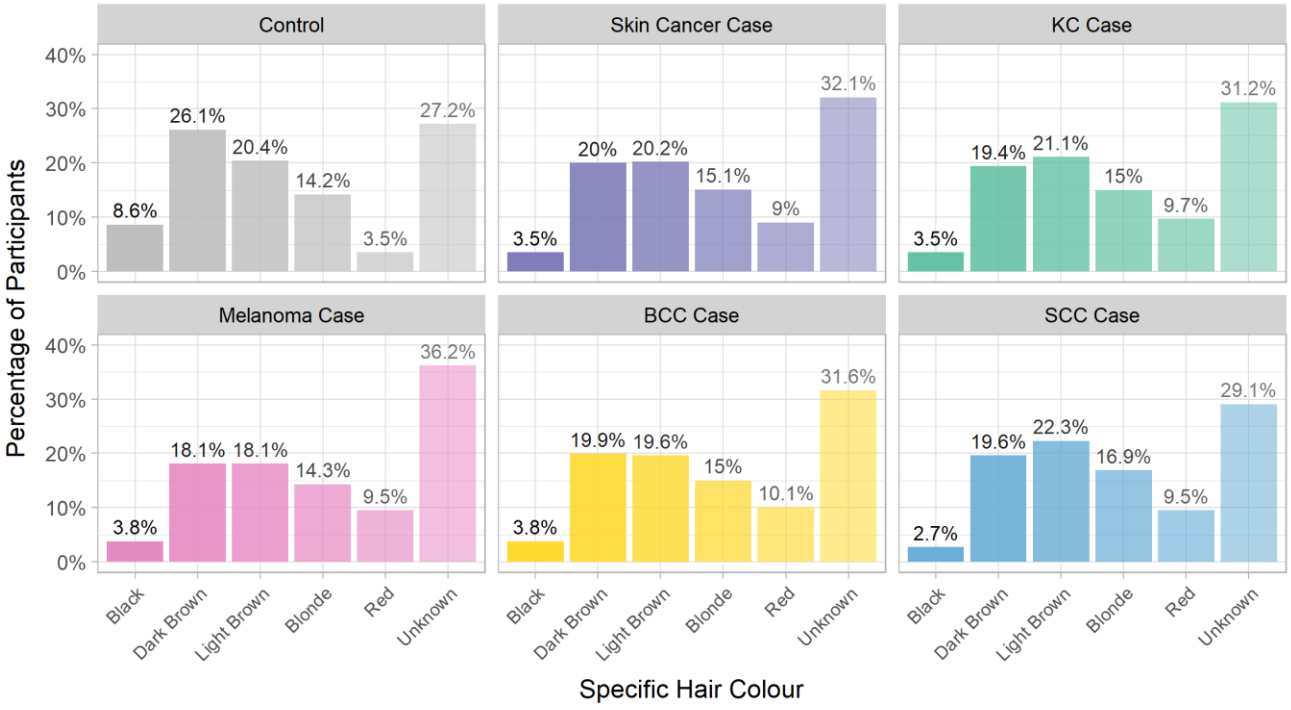

Figure 5.4 Distribution of specific hair colour by outcome.

5.3 Fitzpatrick Skin Type

Our study participants had Fitzpatrick skin types I to V, with skin types II (39%) and II (35%) being most common (**Table 5.5**). Compared to our entire study population, we found cases to be more skewed towards having skin types I and II (more sun sensitive skin types), and controls more skewed towards having skin types III, IV, and V. Skin type V was found only among our controls (**Figure 5.5**). As such, we combined types IV and V when running the univariate regressions. We found Fitzpatrick skin type to be significantly associated with an increased risk for all outcomes, with risk progressively increasing towards the more sun sensitive skin types (**Table 5.6**). Fitzpatrick skin type I, compared to IV/V was most strongly related to an increased risk of SCC (OR 13.7, CI 5.15-47.9).

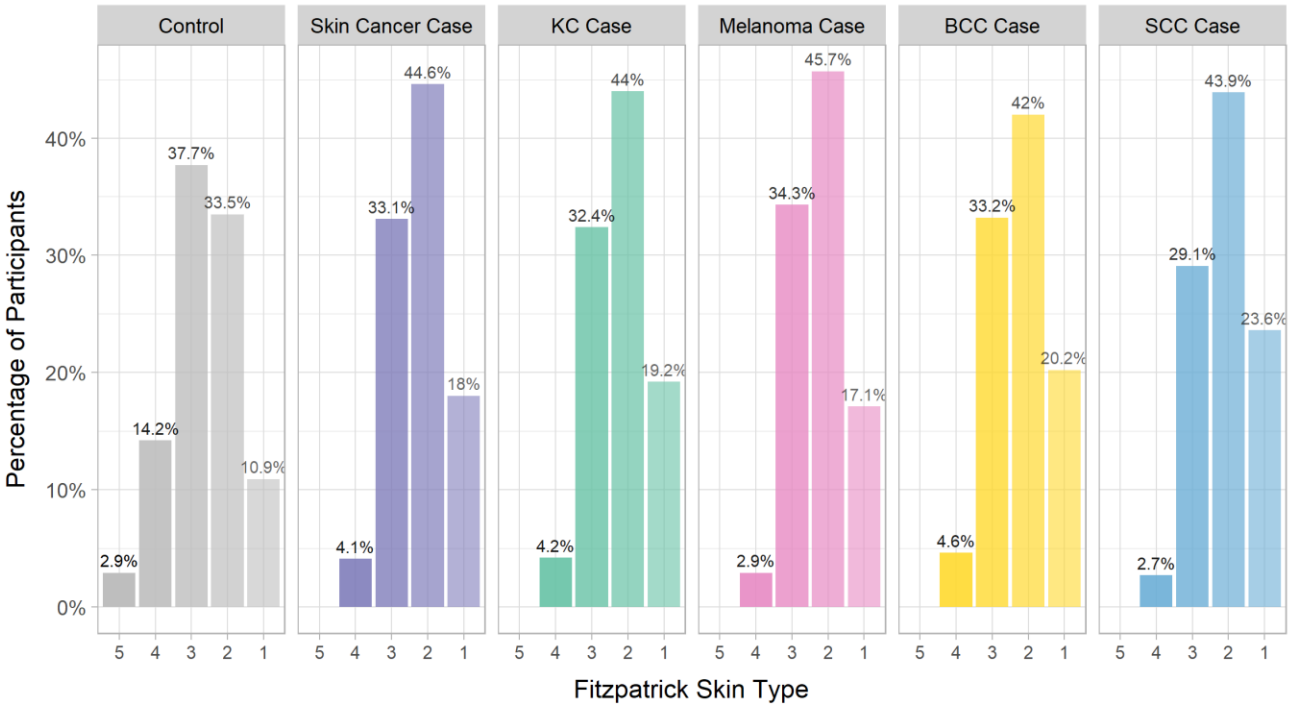

Figure 5.5 Distribution of Fitzpatrick skin type by outcome.

Table 5.5 Distributions of Fitzpatrick skin type.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Fitzpatrick Skin Type							
V	15 (1.5%)	15 (2.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
IV	93 (9.3%)	73 (14%)	20 (4.1%)	18 (4.2%)	3 (2.9%)	17 (4.6%)	4 (2.7%)
III	356 (35%)	194 (38%)	162 (33%)	140 (32%)	36 (34%)	122 (33%)	43 (29%)
II	390 (39%)	172 (33%)	218 (45%)	190 (44%)	48 (46%)	154 (42%)	65 (44%)
I	144 (14%)	56 (11%)	88 (18%)	83 (19%)	18 (17%)	74 (20%)	35 (24%)
Unknown	5 (0.5%)	4 (0.8%)	1 (0.2%)	1 (0.2%)	0 (0%)	0 (0%)	1 (0.7%)
IV/V*	108 (10.8%)	88 (16.9%)	20 (4.1%)	18 (4.2%)	3 (2.9%)	17 (4.6%)	4 (2.7%)

[1] n (%)

*numbers for combined categories are reported for reference as categories were combined for univariate regressions

Table 5.6 Univariate binary logistic regression analyses of Fitzpatrick skin type.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Fitzpatrick Skin Type		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
IV/V	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
III	3.67 (2.21-6.38)		3.53 (2.08-6.29)		5.44 (1.90-23.0)		3.26 (1.89-5.90)		4.88 (1.90-16.6)	
III	5.58 (3.36-9.66)		5.40 (3.19-9.60)		8.19 (2.89-34.3)		4.63 (2.70-8.38)		8.31 (3.30-28.0)	
I	6.91 (3.90-12.7)		7.25 (4.01-13.6)		9.43 (3.02-41.6)		6.84 (3.73-13.1)		13.7 (5.15-47.9)	

[a] OR = Odds Ratio, CI = Confidence Interval

p-values significant at ≤0.05 are **bolded**

5.4 Clinical Assessments

5.4.1 Nevi

The majority of our study participants had few nevi (72%), followed by some (17%), many (8.2%), then no nevi (2.1%) (**Table 5.7**). We found that melanoma cases had more nevi compared to controls, as the distribution of cases was skewed towards having some and many nevi, while controls were skewed towards having none and few nevi compared to the study population (**Figure 5.6**). The opposite was found for the keratinocyte carcinomas: we found some and many nevi to be more common for controls compared to cases, and few nevi to be more common for cases compared to controls.

Since there were some zero counts in our data, we combined the none with the few category, and the some with the many category for the univariate regression analyses. We found that participants with some/many nevi had a significantly increased risk of melanoma compared to participants with none/few nevi (OR 2.05, CI 1.33-3.14) (**Table 5.8**). There was also a significant association between nevus density and both keratinocyte carcinomas, but interestingly some/many nevi compared to none/few nevi had a lower risk of BCC and SCC.

Table 5.7 Distributions of nevus density.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Nevus Density							
None	21 (2.1%)	12 (2.3%)	9 (1.8%)	9 (2.1%)	0 (0%)	7 (1.9%)	4 (2.7%)
Few	726 (72%)	346 (67%)	380 (78%)	356 (82%)	56 (53%)	298 (81%)	131 (89%)
Some	168 (17%)	89 (17%)	79 (16%)	61 (14%)	34 (32%)	57 (16%)	12 (8.1%)
Many	82 (8.2%)	64 (12%)	18 (3.7%)	3 (0.7%)	15 (14%)	3 (0.8%)	0 (0%)
Unknown	6 (0.6%)	3 (0.6%)	3 (0.6%)	3 (0.7%)	0 (0%)	2 (0.5%)	1 (0.7%)
None/Few*	747 (74.1%)	357 (9%)	389 (79.8%)	365 (84.1%)	56 (53%)	305 (82.9%)	135 (91.7%)
Some/Many*	250 (25.2%)	153 (29%)	97 (19.7%)	64 (14.7%)	49 (46%)	60 (16.8%)	12 (8.1%)

[1] n (%)

*numbers for combined categories are reported for reference as categories were combined for univariate regressions

Table 5.8 Univariate binary logistic regression analyses of nevus density.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Nevus Density		**<0.001**		**<0.001**		**0.001**		**<0.001**		**<0.001**
None/Few	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Some/Many	0.58 (0.43-0.78)		0.41 (0.29-0.57)		2.05 (1.33-3.14)		0.46 (0.33-0.64)		0.21 (0.11-0.37)	

[a] OR = Odds Ratio, CI = Confidence Interval

[b] Values obtained from Firth's bias-reduced logistic regression

p-values significant at ≤0.05 are **bolded**

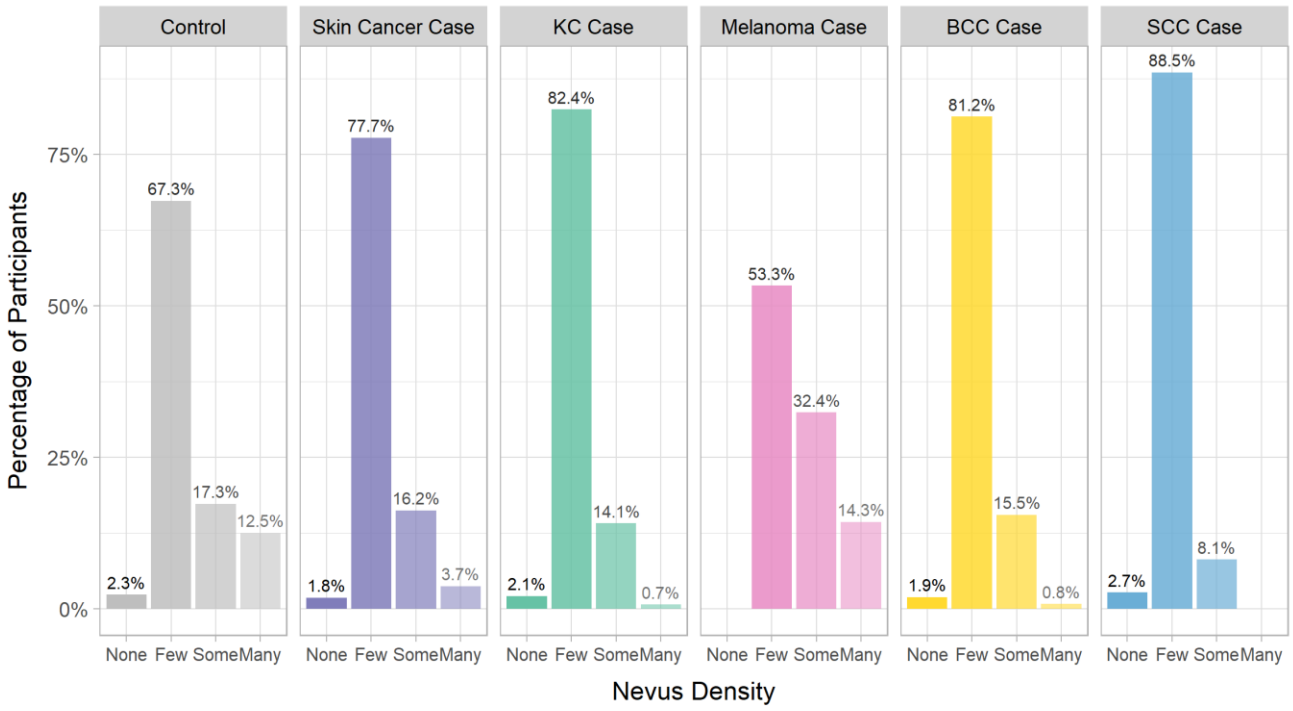

Figure 5.6 Distribution of nevus density by outcome.

5.4.2 Atypical Nevi

Our study population predominantly had no atypical nevi (87%), and presence of 3-5 (0.9%) as well as 6+ atypical nevi (1.1%) was very rare (**Table 5.9**). As expected, melanoma cases more commonly had greater numbers of atypical nevi compared to controls (**Figure 5.7**). In contrast, controls more commonly had greater numbers of atypical nevi compared to BCC and SCC cases.

Presence of atypical nevi was not significantly associated with an increased risk of melanoma (**Table 5.10**). Although having 1-2 and 6+ atypical nevi showed increased risks of melanoma, these associations did not reach significance. There was also a significant relationship between presence of atypical nevi and BCC/SCC risk; the risk of KCs increasingly decreased with greater numbers of atypical nevi.

Table 5.9 Distributions of atypical nevi.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Atypical Nevi (#)							
0	872 (87%)	433 (84%)	439 (90%)	399 (92%)	81 (77%)	336 (92%)	138 (93%)
1-2	104 (10%)	64 (12%)	40 (8.2%)	28 (6.5%)	19 (18%)	27 (7.4%)	8 (5.4%)
3-5	9 (0.9%)	7 (1.4%)	2 (0.4%)	1 (0.2%)	1 (1.0%)	1 (0.3%)	1 (0.7%)
6+	11 (1.1%)	7 (1.4%)	4 (0.8%)	0 (0%)	4 (3.8%)	0 (0%)	0 (0%)
Unknown	7 (0.7%)	3 (0.6%)	4 (0.8%)	4 (0.9%)	0 (0%)	3 (0.8%)	1 (0.7%)

[1] n (%)

Table 5.10 Univariate binary logistic regression analyses of atypical nevi.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Atypical Nevi (#)		**0.033**		**<0.001[b]**		0.18		**0.002[b]**		**0.038[b]**
0	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
1-2	0.62 (0.40-0.93)		0.48 (0.30-0.75)[b]		1.59 (0.88-2.75)		0.55 (0.34-0.87)[b]		0.41 (0.18-0.82)[b]	
3-5	0.28 (0.04-1.17)		0.22 (0.02-1.00)[b]		0.76 (0.04-4.37)		0.03 (0.01-1.19)[b]		0.63 (0.07-2.90)[b]	
6+	0.56 (0.15-1.88)		0.07 (0-0.60)[b]		3.05 (0.79-10.4)		0.09 (0-0.71)[b]		0.21 (0-1.73)[b]	

[a] OR = Odds Ratio, CI = Confidence Interval
[b] Values obtained from Firth's bias-reduced logistic regression
p-values significant at ≤0.05 are **bolded**

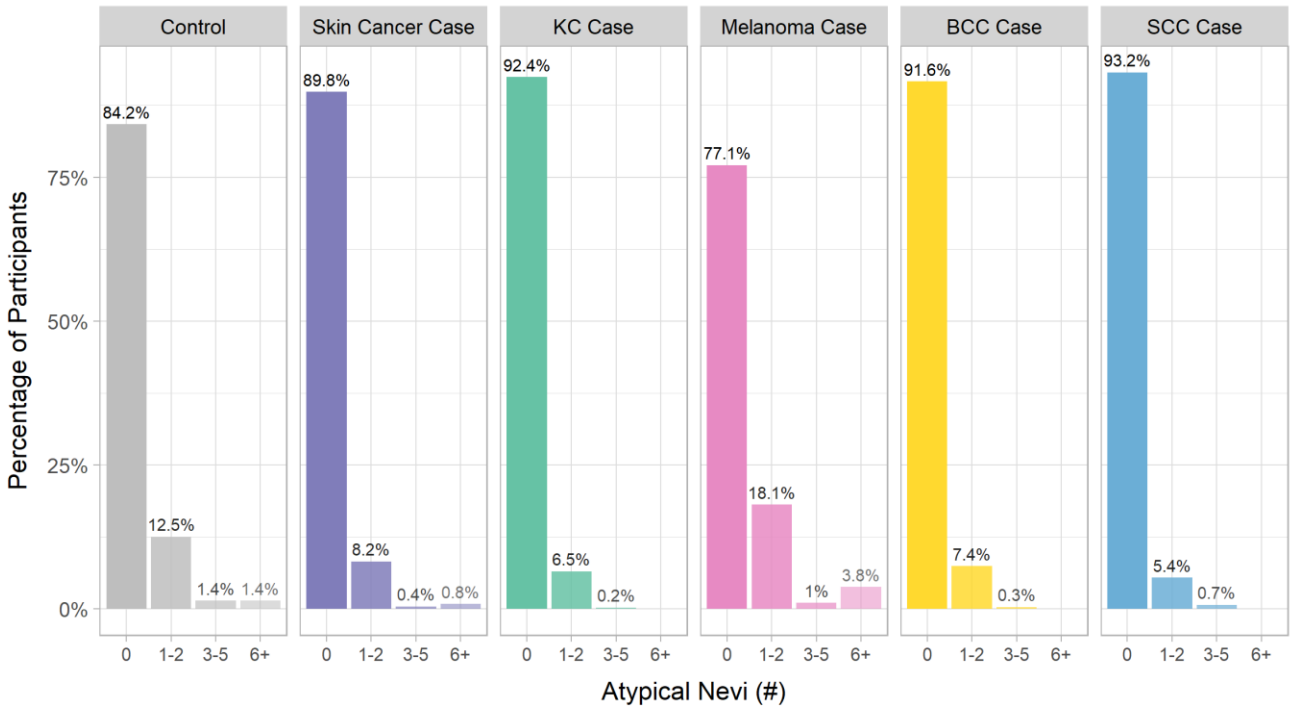

Figure 5.7 Distribution of atypical nevi by outcome.

5.4.3 Freckles

Most of our study population had none (54%) or few (23%) freckles; presence of some (13%) and many (9.6%) freckles was less common (**Table 5.11**). Across all skin cancer types, we found that the distribution of cases was skewed towards having more freckles, while the distribution of controls was skewed towards having less freckles compared to the study population (**Figure 5.8**).

Freckle density overall was significantly associated with BCC risk; although presence of many freckles failed to reach significance, presence of few and some freckles significantly increased risk of BCC (**Table 5.12**). We did not find a significant relationship between freckle density and SCC or melanoma risk. However, we found that risk of skin cancer increased progressively with greater numbers of freckles.

Table 5.11 Distributions of freckle density.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Freckle Density							
None	545 (54%)	304 (59%)	241 (49%)	214 (50%)	48 (46%)	178 (49%)	74 (50%)
Few	227 (23%)	106 (21%)	121 (25%)	105 (24%)	30 (29%)	94 (26%)	32 (22%)
Some	128 (13%)	58 (11%)	70 (14%)	63 (15%)	15 (14%)	53 (14%)	19 (13%)
Many	96 (9.6%)	43 (8.4%)	53 (11%)	47 (11%)	11 (10%)	40 (11%)	21 (14%)
Unknown	7 (0.7%)	3 (0.6%)	4 (0.8%)	3 (0.7%)	1 (1.0%)	2 (0.5%)	2 (1.4%)

[1] n (%)

Table 5.12 Univariate binary logistic regression analyses of freckle density.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Freckle Density		**0.021**		**0.030**		0.10		**0.019**		0.13
None	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Few	1.44 (1.06-1.97)		1.41 (1.02-1.94)		1.79 (1.07-2.96)		1.51 (1.08-2.11)		1.24 (0.77-1.97)	
Some	1.52 (1.03-2.25)		1.54 (1.04-2.30)		1.64 (0.84-3.06)		1.56 (1.03-2.37)		1.35 (0.74-2.36)	
Many	1.55 (1.01-2.41)		1.55 (0.99-2.44)		1.62 (0.75-3.27)		1.59 (0.99-2.54)		2.01 (1.11-3.55)	

[a] OR = Odds Ratio, CI = Confidence Interval
p-values significant at ≤0.05 are **bolded**

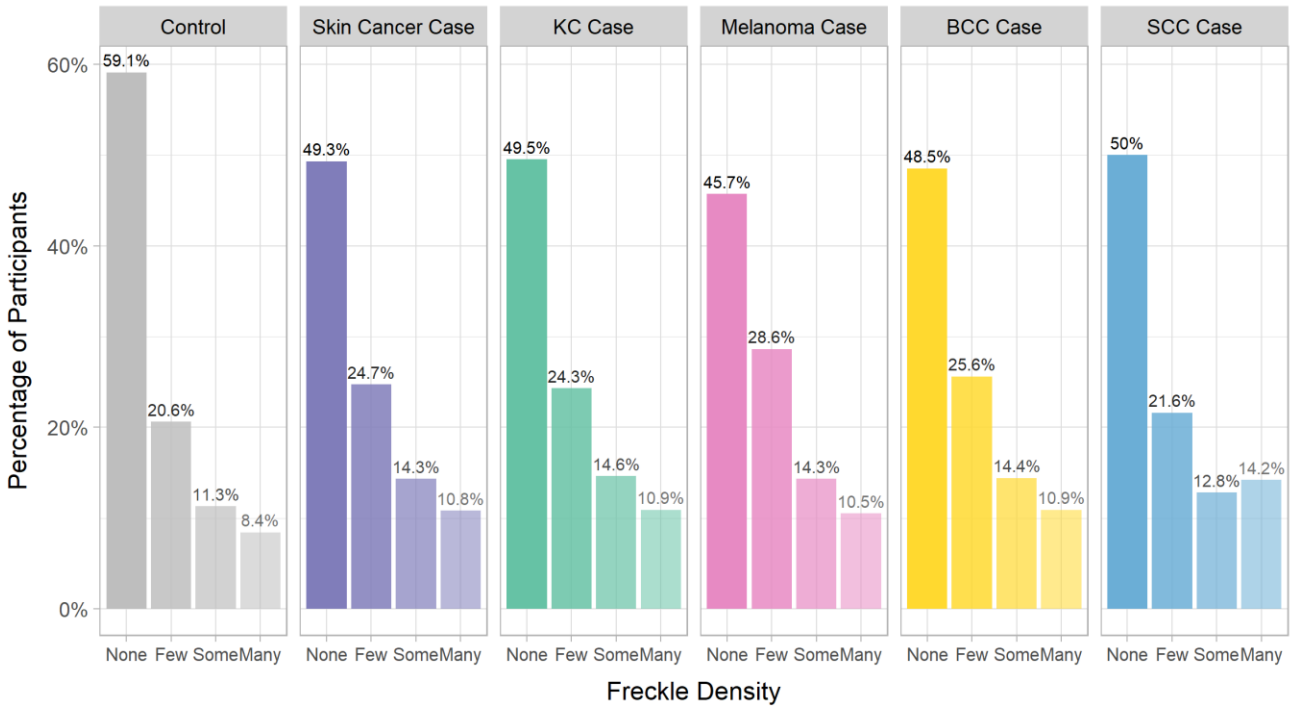

Figure 5.8 Distribution of freckle density by outcome.

5.4.4 Lentigines

Presence of few (29%) and some lentigines (36%) was most common for our study participants, followed by many (22%) then no lentigines (12%) (**Table 5.13**). As seen for freckles, we found a trend (across all skin cancer types) where the distribution of cases was skewed towards having more lentigines, while the distribution of controls was skewed towards having less lentigines compared to the overall study population (**Figure 5.9**).

Presence of lentigines was significantly associated with all skin cancer types (**Table 5.14**). Presence of lentigines showed greatest risk for BCC, as participants with many lentigines had 22.8 times the odds of BCC compared to participants with no lentigines. Risk of SCC similarly increased with greater numbers of lentigines. While presence of lentigines also significantly increased

melanoma risk, the increased odds from presence of few lentigines was not significant. Having many lentigines quite strongly increased risk of melanoma (OR 9.44, CI 4.25-24.0).

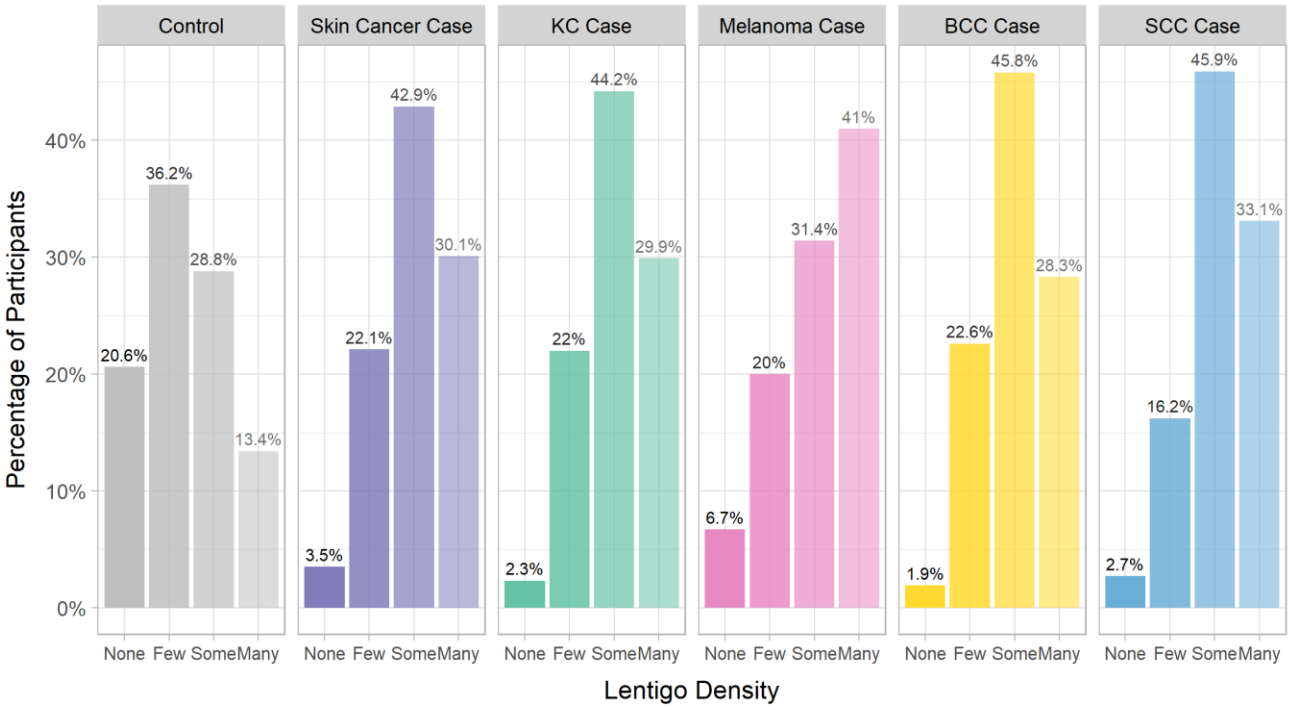

Figure 5.9 Distribution of lentigo density by outcome.

Table 5.13 Distributions of lentigo density.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Lentigo Density							
None	123 (12%)	106 (21%)	17 (3.5%)	10 (2.3%)	7 (6.7%)	7 (1.9%)	4 (2.7%)
Few	294 (29%)	186 (36%)	108 (22%)	95 (22%)	21 (20%)	83 (23%)	24 (16%)
Some	358 (36%)	148 (29%)	210 (43%)	191 (44%)	33 (31%)	168 (46%)	68 (46%)
Many	216 (22%)	69 (13%)	147 (30%)	129 (30%)	43 (41%)	104 (28%)	49 (33%)
Unknown	12 (1.2%)	5 (1.0%)	7 (1.4%)	7 (1.6%)	1 (1.0%)	5 (1.4%)	3 (2.0%)

[1] n (%)

Table 5.14 Univariate binary logistic regression analyses of lentigo density.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Lentigo Density		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
None	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Few	3.62 (2.11-6.55)		5.41 (2.83-11.5)		1.71 (0.74-4.46)		6.76 (3.22-16.6)		3.42 (1.28-11.9)	
Some	8.85 (5.21-15.9)		13.7 (7.24-28.8)		3.38 (1.52-8.58)		17.2 (8.30-41.8)		12.2 (4.85-40.9)	
Many	13.3 (7.56-24.6)		19.8 (10.2-42.7)		9.44 (4.25-24.0)		22.8 (10.7-56.7)		18.8 (7.27-64.4)	

[a] OR = Odds Ratio, CI = Confidence Interval
p-values significant at ≤0.05 are **bolded**

Chapter 6: UV Exposure

This chapter presents an analysis of variables related to UV exposure, including childhood and adulthood sunburn history, history of tanning bed usage, UV radiation history, lifetime occupational and recreational sun exposure history, and lifetime frequency of sunny holidays.

6.1 Sunburn History

For all skin cancer types, we found that cases compared to controls were more likely to have greater numbers of childhood and adulthood sunburns (**Table 6.1**). This finding is especially apparent with the distribution figures for childhood sunburns, where 11+ sunburns was clearly more common for cases than controls, and 0 sunburns was more common for controls compared to cases (**Figure 6.1**). Likewise, 11+ adulthood sunburns was more common in cases and 0 adulthood sunburns was more common in controls (Figure 6.2).

Both childhood and adulthood sunburns were significantly associated with all skin cancer types (**Table 6.2**). Looking into the specific categories, we found that only participants with 11+ sunburns (for both childhood and adulthood) had significantly increased risks of BCC. For melanoma and SCC, the increased risks were significant only for participants with 11+ childhood and >20 adulthood sunburns.

Table 6.1 Distributions of childhood and adulthood sunburns.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
History of childhood sunburns							
0	169 (17%)	107 (21%)	62 (13%)	57 (13%)	12 (11%)	49 (13%)	21 (14%)
1-2	131 (13%)	74 (14%)	57 (12%)	48 (11%)	14 (13%)	41 (11%)	15 (10%)
3-5	170 (17%)	96 (19%)	74 (15%)	66 (15%)	12 (11%)	56 (15%)	21 (14%)
6-10	142 (14%)	80 (16%)	62 (13%)	54 (12%)	14 (13%)	48 (13%)	14 (9.5%)
11-20	177 (18%)	76 (15%)	101 (21%)	86 (20%)	22 (21%)	74 (20%)	29 (20%)
>20	208 (21%)	77 (15%)	131 (27%)	119 (28%)	31 (30%)	98 (27%)	46 (31%)
Unsure	1 (<0.1%)	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown	5 (0.5%)	3 (0.6%)	2 (0.4%)	2 (0.5%)	0 (0%)	1 (0.3%)	2 (1.4%)
History of adulthood sunburns							
0	215 (21%)	123 (24%)	92 (19%)	81 (19%)	23 (22%)	66 (18%)	30 (20%)
1-2	212 (21%)	129 (25%)	83 (17%)	70 (16%)	20 (19%)	61 (17%)	22 (15%)
3-5	195 (19%)	93 (18%)	102 (21%)	90 (21%)	21 (20%)	72 (20%)	31 (21%)
6-10	138 (14%)	73 (14%)	65 (13%)	60 (14%)	9 (8.6%)	54 (15%)	13 (8.8%)
11-20	109 (11%)	49 (9.5%)	60 (12%)	54 (12%)	11 (10%)	51 (14%)	16 (11%)
>20	130 (13%)	43 (8.4%)	87 (18%)	77 (18%)	21 (20%)	63 (17%)	36 (24%)
Unsure	1 (<0.1%)	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown	3 (0.3%)	3 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

[1] n (%)

Table 6.2 Univariate binary logistic regression analyses of childhood and adulthood sunburns.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
History of childhood sunburns		**<0.001**		**<0.001**		**0.002**		**<0.001**		**<0.001**
0	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
1-2	1.33 (0.83-2.12)		1.22 (0.75-1.98)		1.69 (0.74-3.91)		1.21 (0.73-2.01)		1.03 (0.49-2.12)	
3-5	1.33 (0.86-2.06)		1.29 (0.82-2.03)		1.11 (0.47-2.62)		1.27 (0.79-2.05)		1.11 (0.57-2.17)	
6-10	1.34 (0.85-2.11)		1.27 (0.79-2.03)		1.56 (0.68-3.61)		1.31 (0.80-2.15)		0.89 (0.42-1.85)	
11-20	2.29 (1.49-3.55)		2.12 (1.36-3.33)		2.58 (1.22-5.69)		2.13 (1.34-3.40)		1.94 (1.04-3.70)	
>20	2.94 (1.93-4.49)		2.90 (1.89-4.48)		3.59 (1.77-7.69)		2.78 (1.78-4.39)		3.04 (1.70-5.60)	
History of adulthood sunburns		**<0.001**		**<0.001**		**0.018**		**<0.001**		**<0.001**
0	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
1-2	0.86 (0.58-1.27)		0.82 (0.55-1.23)		0.83 (0.43-1.59)		0.88 (0.57-1.35)		0.70 (0.38-1.27)	
3-5	1.47 (0.99-2.17)		1.47 (0.98-2.20)		1.21 (0.63-2.32)		1.44 (0.94-2.22)		1.37 (0.77-2.42)	
6-10	1.19 (0.77-1.83)		1.25 (0.80-1.94)		0.66 (0.28-1.46)		1.38 (0.87-2.19)		0.73 (0.35-1.46)	
11-20	1.64 (1.03-2.61)		1.67 (1.04-2.70)		1.20 (0.53-2.60)		1.94 (1.19-3.18)		1.34 (0.66-2.65)	
>20	2.71 (1.73-4.29)		2.72 (1.71-4.36)		2.61 (1.31-5.20)		2.73 (1.68-4.48)		3.43 (1.90-6.27)	

[a] OR = Odds Ratio, CI = Confidence Interval
p-values significant at ≤0.05 are **bolded**

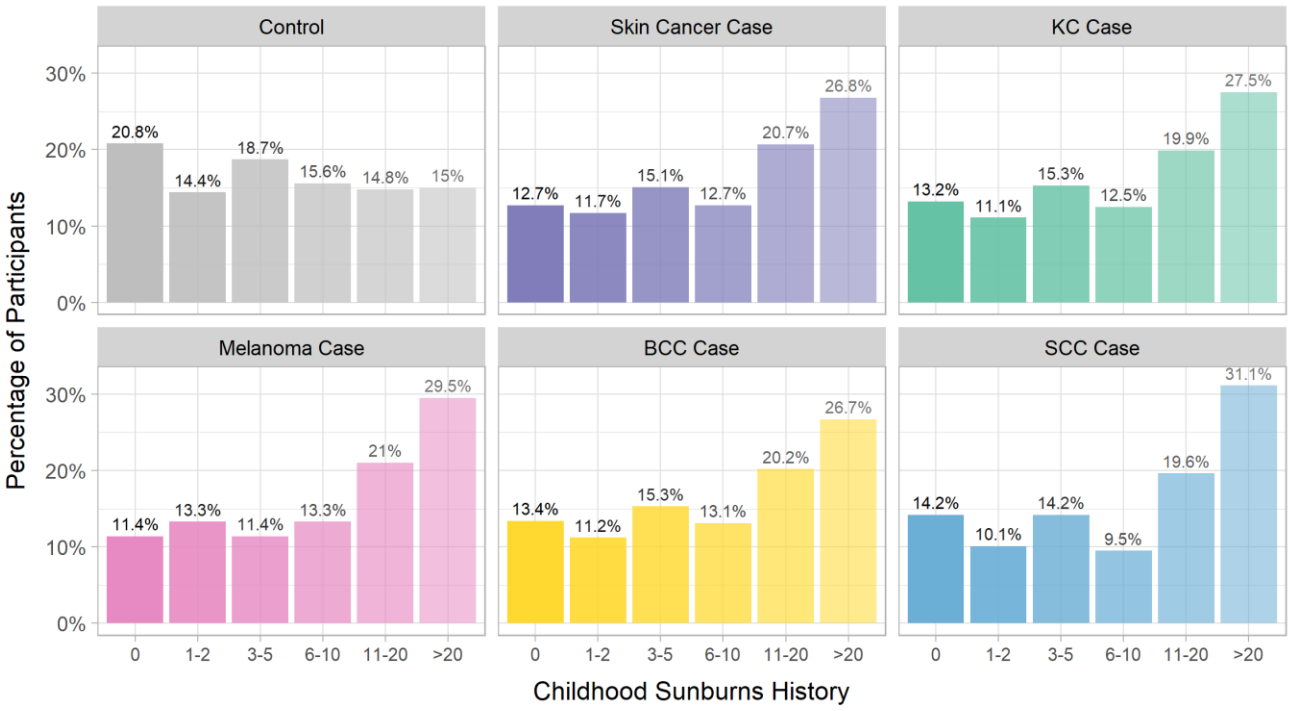

Figure 6.1 Distribution of childhood sunburns by outcome.

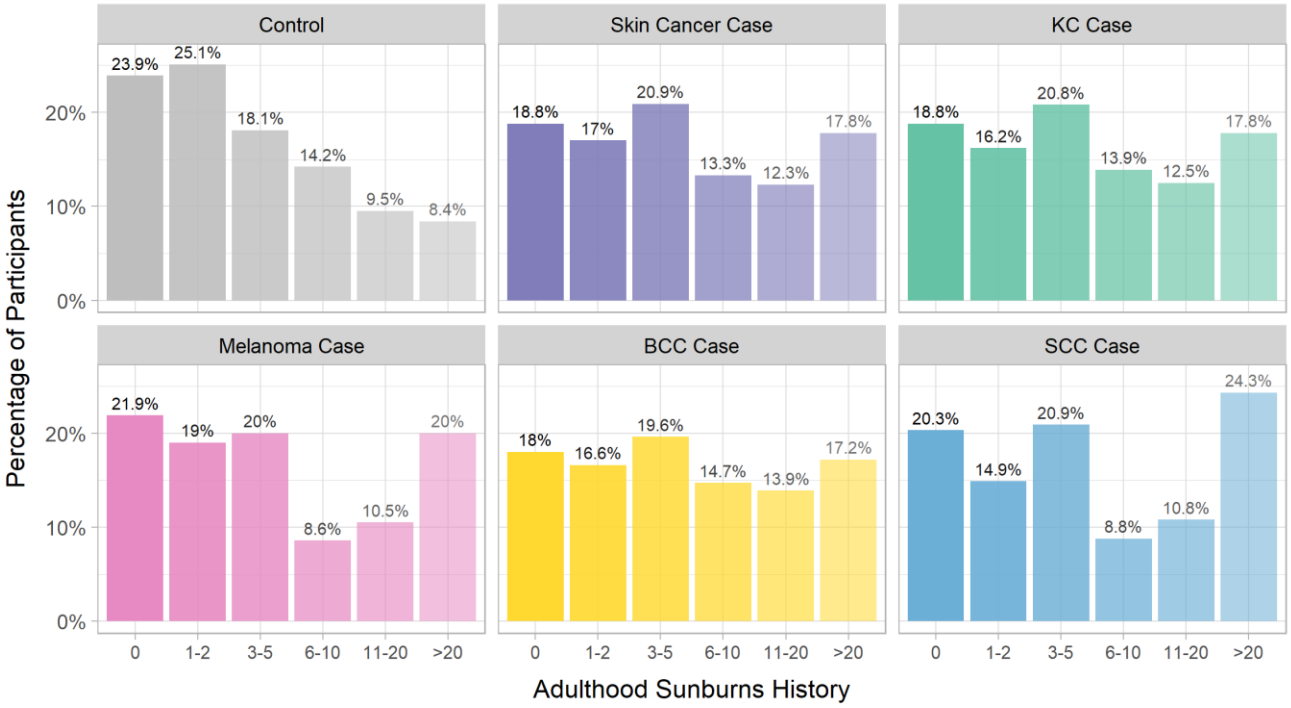

Figure 6.2 Distribution of adulthood sunburns by outcome.

6.2 Tanning Bed Usage

Most of our study population (65%) did not have a history of tanning bed usage, and there was a trend towards a smaller proportion of participants with an increasing number of sessions (**Table 6.3**). We did not find an obvious discrepancy between cases and controls in terms of tanning bed history apart from SCC cases and controls, where cases were more likely to have a smaller frequency of tanning bed usage (**Figure 6.3**). Accordingly, we found that participants with 1-50 tanning bed sessions had a significantly lower risk of SCC compared to participants with no history of tanning beds (**Table 6.4**). No significance was found for the association between a history of 51+ tanning bed sessions and SCC risk. History of tanning bed usage was not found to be significantly related to risk of BCC or melanoma.

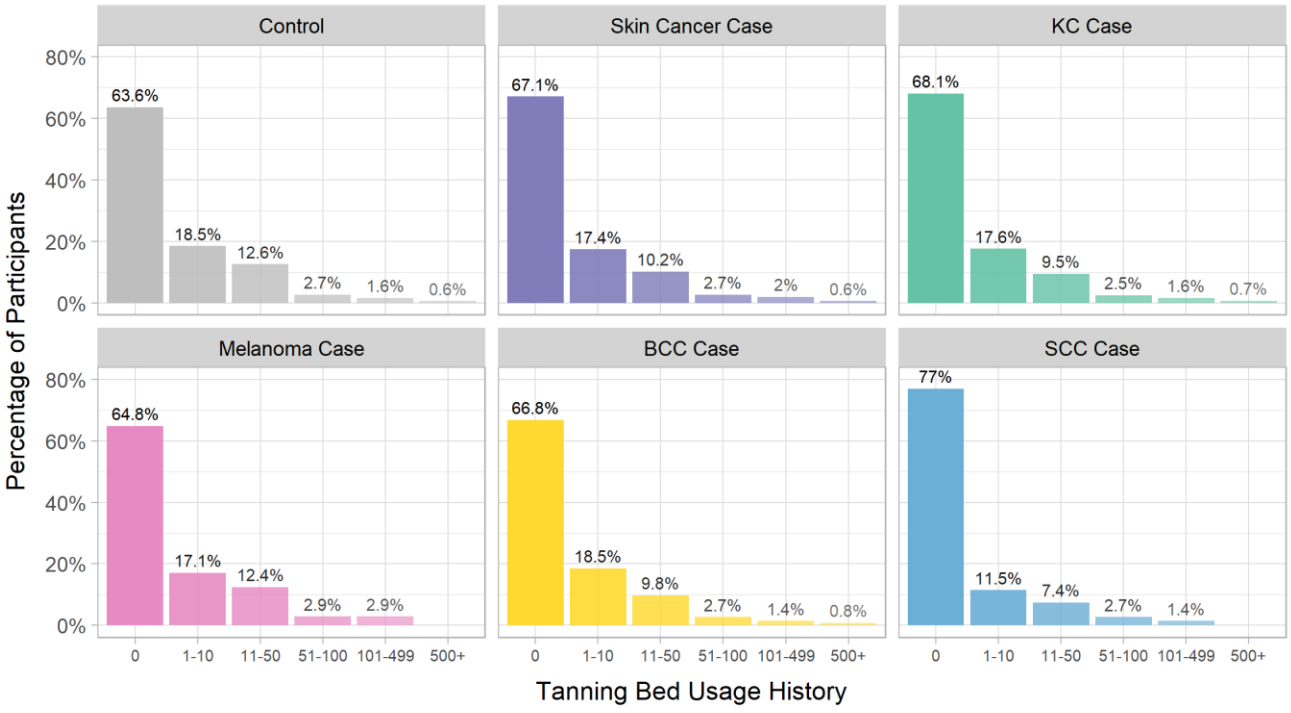

Figure 6.3 Distribution of tanning beds by outcome.

Table 6.3 Distributions of tanning bed history.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	KC N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Tanning Bed History (# of Sessions)							
0	655 (65%)	327 (64%)	328 (67%)	294 (68%)	68 (65%)	245 (67%)	114 (77%)
1-10	180 (18%)	95 (18%)	85 (17%)	76 (18%)	18 (17%)	68 (19%)	17 (11%)
11-50	115 (11%)	65 (13%)	50 (10%)	41 (9.5%)	13 (12%)	36 (9.8%)	11 (7.4%)
51-100	27 (2.7%)	14 (2.7%)	13 (2.7%)	11 (2.5%)	3 (2.9%)	10 (2.7%)	4 (2.7%)
101-499	18 (1.8%)	8 (1.6%)	10 (2.0%)	7 (1.6%)	3 (2.9%)	5 (1.4%)	2 (1.4%)
500+	6 (0.6%)	3 (0.6%)	3 (0.6%)	3 (0.7%)	0 (0%)	3 (0.8%)	0 (0%)
Unknown	2 (0.2%)	2 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
101+	24 (2.4%)	11 (2.2%)	13 (2.6%)	10 (2.3%)	3 (2.9%)	8 (2.2%)	2 (1.4%)

[1] n (%)

*numbers for combined categories are reported for reference as categories were combined for univariate regressions

Table 6.4 Univariate binary logistic regression analyses of tanning bed history.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Tanning Bed History (# of Sessions)		0.70		0.56		0.99		0.76		**0.040**
0	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
1-10	0.89 (0.64-1.24)		0.89 (0.63-1.25)		0.91 (0.50-1.58)		0.96 (0.67-1.36)		0.51 (0.29-0.88)	
11-50	0.77 (0.51-1.14)		0.70 (0.46-1.07)		0.96 (0.48-1.79)		0.74 (0.47-1.14)		0.49 (0.24-0.92)	
51-100	0.93 (0.42-2.01)		0.87 (0.38-1.95)		1.03 (0.23-3.26)		0.95 (0.40-2.17)		0.82 (0.23-2.34)	
101+	1.18 (0.52-2.72)		1.01 (0.42-2.43)		1.31 (0.29-4.33)		0.97 (0.37-2.43)		0.52 (0.08-1.98)	

[a] OR = Odds Ratio, CI = Confidence Interval

p-values significant at ≤0.05 are **bolded**

6.3 UV Radiation Treatment

Only 6.9% of our study participants had a history of UV radiation treatment (**Table 6.5**). Across all outcomes, cases more commonly had a history of UV radiation treatment compared to controls (**Figure 6.4**). For BCC and SCC, more than twice as many cases as controls had a history of UV radiation treatment. UV radiation treatment history was significantly associated with both BCC (OR 2.32, CI 1.36-4.04) and SCC risk (OR 2.76, CI 1.42-5.30) (**Table 6.6**). However, a significant relationship was not found with melanoma risk (OR 2.02, CI 0.86-4.36).

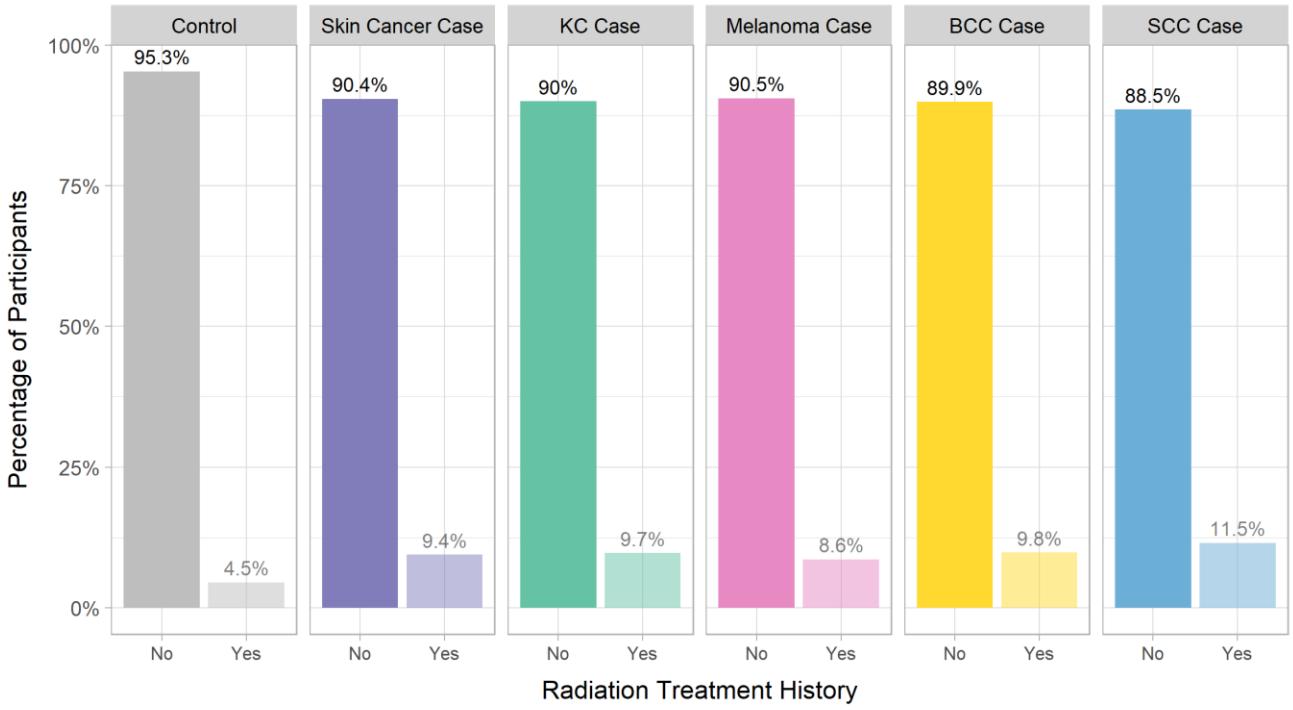

Figure 6.4 Distribution of ultraviolet radiation treatment history by outcome.

Table 6.5 Distributions of UV radiation treatment history.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
UV Radiation Treatment History							
No	932 (93%)	490 (95%)	442 (90%)	389 (90%)	95 (90%)	330 (90%)	131 (89%)
Yes	69 (6.9%)	23 (4.5%)	46 (9.4%)	42 (9.7%)	9 (8.6%)	36 (9.8%)	17 (11%)
Unknown	2 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (1.0%)	1 (0.3%)	0 (0%)

[1] n (%)

Table 6.6 Univariate binary logistic regression analyses of UV radiation treatment history.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
UV Radiation Treatment History		**0.002**		**0.001**		0.10		**0.002**		**0.003**
No	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Yes	2.22 (1.34-3.78)		2.30 (1.37-3.95)		2.02 (0.86-4.36)		2.32 (1.36-4.04)		2.76 (1.42-5.30)	

[a] OR = Odds Ratio, CI = Confidence Interval
p-values significant at ≤0.05 are **bolded**

6.4 Lifetime Occupational Sun Exposure

A large portion of our study population (54%) reported very low lifetime occupational sun exposure, and the proportions of participants became increasingly smaller with greater histories of lifetime occupational sun exposure (**Table 6.7**). For melanoma, cases were more likely than controls to have a greater lifetime sun exposure history, with high and very high exposures more common for cases and very low exposures more common for controls (**Figure 6.5**). Similar trends were seen for BCC and SCC, though with smaller effects.

Occupational sun exposure was significantly associated with melanoma, with low (OR 1.73, CI 1.09-2.75) and high (OR 3.31, CI 1.27-8.08) exposures showing significantly increased risks compared to very low exposure (**Table 6.8**). We did not find occupational sun exposure as a whole to be significantly related to risk of BCC or SCC. However, patients with high lifetime occupational sun exposures had greater risks of BCC (OR 2.21, CI 1.12-4.47) compared to those with very low occupational sun exposures.

Table 6.7 Distributions of occupational sun exposure history.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Occupational Sun Exposure History							
Very Low	539 (54%)	292 (57%)	247 (51%)	221 (51%)	47 (45%)	185 (50%)	74 (50%)
Low	301 (30%)	147 (29%)	154 (31%)	133 (31%)	41 (39%)	116 (32%)	43 (29%)
Moderate	99 (9.9%)	53 (10%)	46 (9.4%)	41 (9.5%)	7 (6.7%)	34 (9.3%)	15 (10%)
High	41 (4.1%)	15 (2.9%)	26 (5.3%)	23 (5.3%)	8 (7.6%)	21 (5.7%)	9 (6.1%)
Very High	19 (1.9%)	6 (1.2%)	13 (2.7%)	11 (2.5%)	2 (1.9%)	9 (2.5%)	5 (3.4%)
Unknown	4 (0.4%)	1 (0.2%)	3 (0.6%)	3 (0.7%)	0 (0%)	2 (0.5%)	2 (1.4%)

[1] n (%)

Table 6.8 Univariate binary logistic regression analyses of occupational sun exposure history.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Occupational Sun Exposure History		0.054		0.10		**0.024**		0.072		0.16
Very Low	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Low	1.24 (0.93-1.64)		1.20 (0.89-1.60)		1.73 (1.09-2.75)		1.25 (0.92-1.69)		1.15 (0.75-1.76)	
Moderate	1.03 (0.67-1.58)		1.02 (0.65-1.59)		0.82 (0.32-1.81)		1.01 (0.63-1.61)		1.12 (0.58-2.05)	
High	2.05 (1.07-4.04)		2.03 (1.04-4.05)		3.31 (1.27-8.08)		2.21 (1.12-4.47)		2.37 (0.96-5.54)	
Very High	2.56 (1.00-7.38)		2.42 (0.91-7.12)		2.07 (0.30-9.30)		2.37 (0.84-7.16)		3.29 (0.93-11.2)	

[a] OR = Odds Ratio, CI = Confidence Interval
p-values significant at ≤0.05 are **bolded**

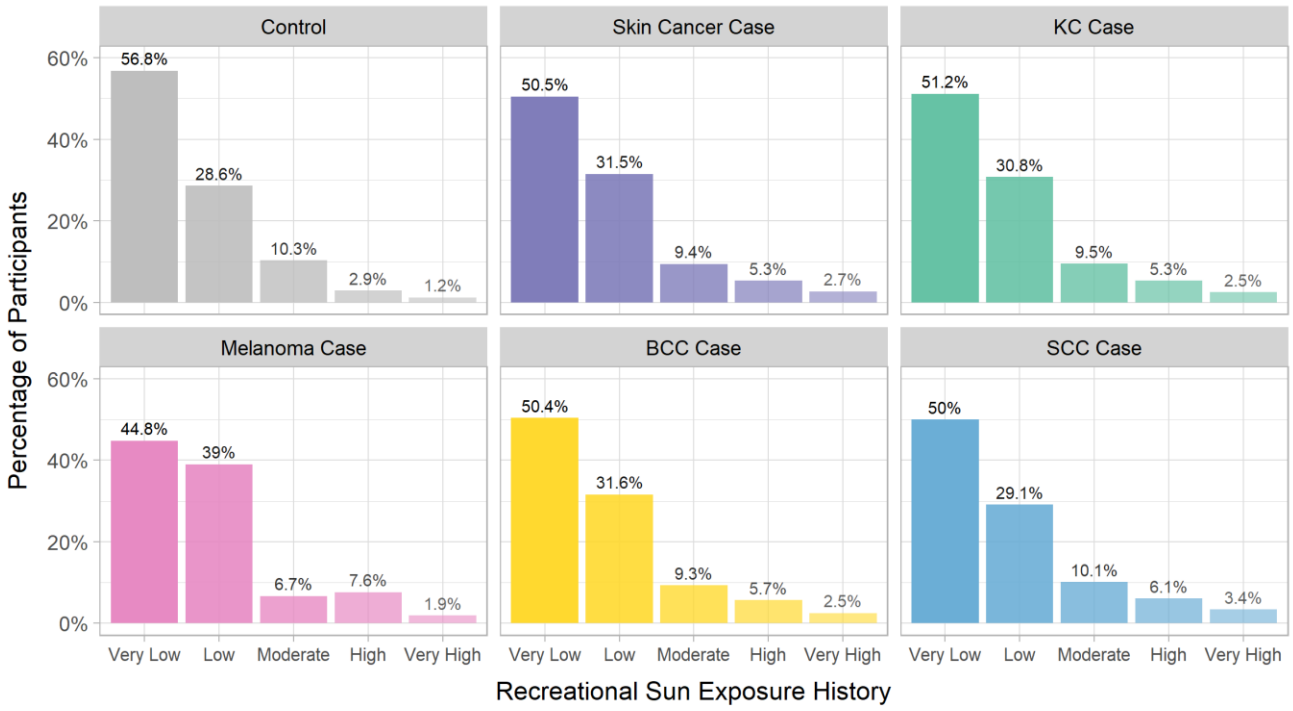

Figure 6.5 Distribution of occupational sun exposure history by outcome.

6.5 Lifetime Recreational Sun Exposure

Moderate lifetime recreational sun exposure was most commonly reported (47%) by our study participants, while very low (2.2%) and very high (8.5%) exposures were rarely reported (**Table 6.9**). For all skin cancer types, the distribution of cases was skewed towards greater lifetime recreational sun exposure compared to the distribution of controls (**Figure 6.6**). Despite expecting to see more cases compared to controls having a very low recreational sun exposure, we did not observe a large discrepancy. BCC cases (1.4%) had a slightly smaller proportion of participants with very low exposures compared to controls (2.1%), while SCC cases (2%) had similar proportions to controls. A slightly greater proportion of melanoma cases (3.8%) had very low exposures compared to controls.

Recreational sun exposure history was significantly associated with all types of skin cancer (**Table 6.10**). However, looking into the specific categories, only subjects in the very high category compared to the very low category showed significantly increased BCC risks (OR 3.26, CI 1.07-11.3). None of the categories reached significance for melanoma and SCC.

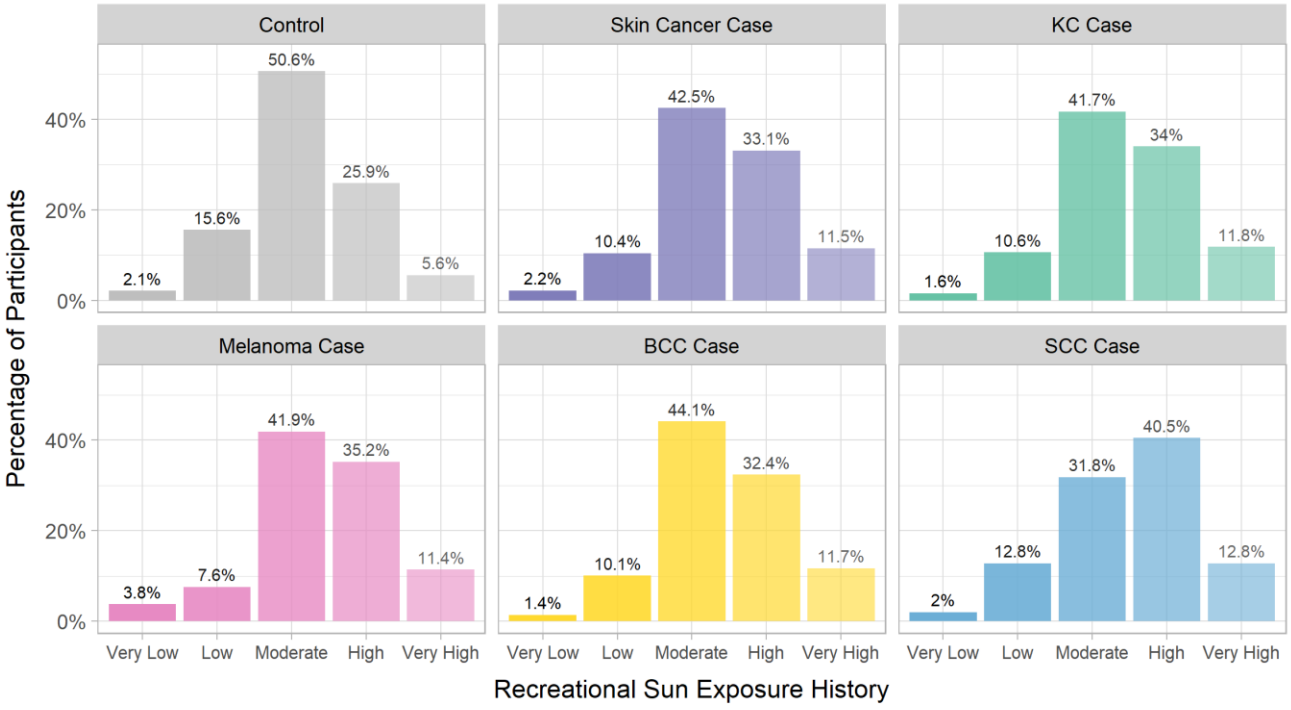

Figure 6.6 Distribution of recreational sun exposure by outcome.

Table 6.9 Distributions of recreational sun exposure history.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Recreational Sun Exposure History							
Very Low	22 (2.2%)	11 (2.1%)	11 (2.2%)	7 (1.6%)	4 (3.8%)	5 (1.4%)	3 (2.0%)
Low	131 (13%)	80 (16%)	51 (10%)	46 (11%)	8 (7.6%)	37 (10%)	19 (13%)
Moderate	468 (47%)	260 (51%)	208 (43%)	180 (42%)	44 (42%)	162 (44%)	47 (32%)
High	295 (29%)	133 (26%)	162 (33%)	147 (34%)	37 (35%)	119 (32%)	60 (41%)
Very High	85 (8.5%)	29 (5.6%)	56 (11%)	51 (12%)	12 (11%)	43 (12%)	19 (13%)
Unknown	2 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	0 (0%)	1 (0.3%)	0 (0%)

[1] n (%)

Table 6.10 Univariate binary logistic regression analyses of recreational sun exposure history.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Recreational Sun Exposure History		**<0.001**		**<0.001**		**0.010**		**<0.001**		**<0.001**
Very Low	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Low	0.64 (0.25-1.59)		0.90 (0.33-2.61)		0.28 (0.07-1.16)		1.02 (0.34-3.42)		0.87 (0.24-4.12)	
Moderate	0.80 (0.34-1.90)		1.09 (0.42-3.01)		0.47 (0.15-1.74)		1.37 (0.49-4.42)		0.66 (0.20-3.01)	
High	1.22 (0.51-2.93)		1.74 (0.66-4.84)		0.77 (0.25-2.89)		1.97 (0.69-6.40)		1.65 (0.50-7.51)	
Very High	1.93 (0.74-5.04)		2.76 (0.98-8.26)		1.14 (0.32-4.74)		3.26 (1.07-11.3)		2.40 (0.65-11.7)	

[a] OR = Odds Ratio, CI = Confidence Interval
p-values significant at ≤0.05 are **bolded**

6.5.1 Types of Recreational Sun Exposure

We endeavored to take a closer look into the effects of recreational sun exposure, and observe whether there was a difference in associations based on the type of recreational sun exposure. We had missing information from about a third of our participants regarding the type(s) of recreational sun exposure our patients participated in as we did not collect this data from the start of our study (**Table 6.11**). For sun tanning/outdoor sports history, water activities history, and gardening history, we had missing information from 298 participants. After we started collected data on those variables, we resolved to collect information on sun tanning history and outdoor sports history separately, so for these variables we have missing data from 319 and 315 participants respectively. Finally, we later also included walking history among the choices for recreational sun exposure, and this variable has missing information from 395 participants.

We did not find any of the individual types of recreational sun exposure to be significantly related to melanoma risk (**Table 6.12**). We did find an increased risk of BCC for participants that indicated of having sun tanning history (OR 1.40, CI 1.00-1.96), outdoor sports history (OR 1.44, CI 1.00-2.08), and gardening history (OR 1.57, CI 1.14-2.18). For SCC, increased risk was found for patients that had sun tanning history (OR 1.67, CI 1.07-2.61) as well as sun tanning/outdoor sports history (OR 2.26, CI 1.20-4.65). Neither history of water activities nor walking was associated with risks of any type of skin cancer.

Table 6.11 Distributions of recreational sun exposure variables.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Sun Tanning History							
No	430 (43%)	238 (46%)	192 (39%)	170 (39%)	41 (39%)	140 (38%)	54 (36%)
Yes	254 (25%)	124 (24%)	130 (27%)	117 (27%)	24 (23%)	102 (28%)	47 (32%)
Unknown	319 (32%)	152 (30%)	167 (34%)	145 (34%)	40 (38%)	125 (34%)	47 (32%)
Outdoor Sports History							
No	197 (20%)	117 (23%)	80 (16%)	72 (17%)	17 (16%)	61 (17%)	27 (18%)
Yes	491 (49%)	245 (48%)	246 (50%)	219 (51%)	49 (47%)	184 (50%)	76 (51%)
Unknown	315 (31%)	152 (30%)	163 (33%)	141 (33%)	39 (37%)	122 (33%)	45 (30%)
Sun Tanning/Outdoor Sports History							
No	125 (12%)	78 (15%)	47 (9.6%)	40 (9.3%)	12 (11%)	35 (9.5%)	11 (7.4%)
Yes	580 (58%)	295 (57%)	285 (58%)	257 (59%)	55 (52%)	216 (59%)	94 (64%)
Unknown	298 (30%)	141 (27%)	157 (32%)	135 (31%)	38 (36%)	116 (32%)	43 (29%)
Water Activities History							
No	309 (31%)	166 (32%)	143 (29%)	129 (30%)	27 (26%)	111 (30%)	45 (30%)
Yes	396 (39%)	207 (40%)	189 (39%)	168 (39%)	40 (38%)	140 (38%)	60 (41%)
Unknown	298 (30%)	141 (27%)	157 (32%)	135 (31%)	38 (36%)	116 (32%)	43 (29%)
Gardening History							
No	400 (40%)	226 (44%)	174 (36%)	150 (35%)	37 (35%)	124 (34%)	55 (37%)
Yes	305 (30%)	147 (29%)	158 (32%)	147 (34%)	30 (29%)	127 (35%)	50 (34%)
Unknown	298 (30%)	141 (27%)	157 (32%)	135 (31%)	38 (36%)	116 (32%)	43 (29%)
Walking History							
No	76 (7.6%)	38 (7.4%)	38 (7.8%)	32 (7.4%)	6 (5.7%)	28 (7.6%)	12 (8.1%)
Yes	532 (53%)	286 (56%)	246 (50%)	217 (50%)	54 (51%)	187 (51%)	67 (45%)
Unknown	395 (39%)	190 (37%)	205 (42%)	183 (42%)	45 (43%)	152 (41%)	69 (47%)

[1] n (%)

Table 6.12 Univariate binary logistic regression analyses of recreational sun exposure variables.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Sun Tanning History		0.10		0.088		0.68		**0.050**		**0.025**
No	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Yes	1.30 (0.95-1.77)		1.32 (0.96-1.82)		1.12 (0.64-1.93)		1.40 (1.00-1.96)		1.67 (1.07-2.61)	
Outdoor Sports History		**0.024**		**0.033**		0.28		**0.047**		0.23
No	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Yes	1.47 (1.05-2.06)		1.45 (1.03-2.06)		1.38 (0.77-2.55)		1.44 (1.00-2.08)		1.34 (0.83-2.23)	
Sun Tanning/Outdoor Sports History		**0.018**		**0.011**		0.57		**0.025**		**0.011**
No	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Yes	1.60 (1.08-2.40)		1.70 (1.13-2.60)		1.21 (0.64-2.47)		1.63 (1.06-2.55)		2.26 (1.20-4.65)	
Water Activities History		0.70		0.78		0.52		0.94		0.76
No	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Yes	1.06 (0.79-1.43)		1.04 (0.77-1.42)		1.19 (0.70-2.03)		1.01 (0.73-1.40)		1.07 (0.69-1.66)	
Gardening History		**0.029**		**0.009**		0.41		**0.006**		0.13
No	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Yes	1.40 (1.04-1.88)		1.51 (1.11-2.05)		1.25 (0.73-2.10)		1.57 (1.14-2.18)		1.40 (0.90-2.16)	
Walking History		0.54		0.68		0.69		0.65		0.41
No	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Yes	0.86 (0.53-1.39)		0.90 (0.55-1.50)		1.20 (0.51-3.27)		0.89 (0.53-1.51)		0.74 (0.38-1.55)	

[a] OR = Odds Ratio, CI = Confidence Interval
p-values significant at ≤0.05 are **bolded**

6.6 Lifetime Frequency of Sunny Holidays

Quite a lot of our study participants (48%) had gone on many lifetime sunny holidays, while much fewer participants (12%) had never gone on a sunny holiday (**Table 6.13**). Compared to controls, it was more common for cases to have a greater lifetime frequency of sunny holidays, with a greater proportion of cases to controls having had many holidays and a smaller proportion of cases to controls having had no holidays (**Figure 6.7**). Having a history of sunny holidays was significantly associated with risk of BCC, but not melanoma or SCC (**Table 6.14**). While an increased BCC risk was found for participants with a history of sunny holidays, this increase in risk was significant only for those with many lifetime sunny holidays (OR 1.69, CI 1.10-2.63).

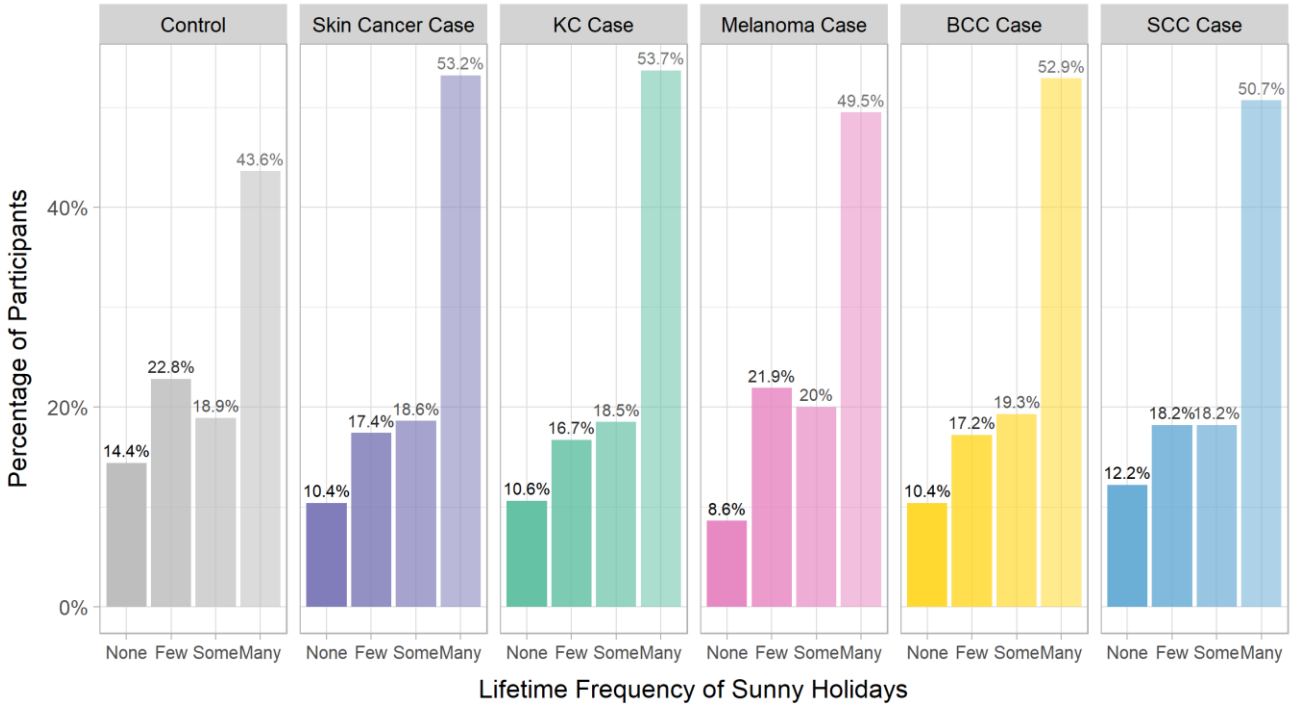

Figure 6.7 Distribution of lifetime frequency of sunny holidays by outcome.

Table 6.13 Distributions of lifetime frequency of sunny holidays.

	Total N = 1,003[1]	Control N = 514[1]	Skin Cancer N = 489[1]	Keratinocyte Carcinoma N = 432[1]	Melanoma N = 105[1]	BCC N = 367[1]	SCC N = 148[1]
Lifetime Frequency of Sunny Holidays							
None	125 (12%)	74 (14%)	51 (10%)	46 (11%)	9 (8.6%)	38 (10%)	18 (12%)
Few	202 (20%)	117 (23%)	85 (17%)	72 (17%)	23 (22%)	63 (17%)	27 (18%)
Some	188 (19%)	97 (19%)	91 (19%)	80 (19%)	21 (20%)	71 (19%)	27 (18%)
Many	484 (48%)	224 (44%)	260 (53%)	232 (54%)	52 (50%)	194 (53%)	75 (51%)
Unknown	4 (0.4%)	2 (0.4%)	2 (0.4%)	2 (0.5%)	0 (0%)	1 (0.3%)	1 (0.7%)

[1] n (%)

Table 6.14 Univariate binary logistic regression analyses of lifetime frequency of sunny holidays.

	Skin Cancer		Keratinocyte Carcinoma		Melanoma		BCC		SCC	
Variable	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**	**OR (95% CI)[a]**	**p-value**
Lifetime Frequency of Sunny Holidays		**0.009**		**0.007**		0.36		**0.018**		0.42
None	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Few	1.05 (0.67-1.66)		0.99 (0.62-1.59)		1.62 (0.73-3.86)		1.05 (0.64-1.73)		0.95 (0.49-1.87)	
Some	1.36 (0.86-2.16)		1.33 (0.83-2.13)		1.78 (0.79-4.30)		1.43 (0.87-2.35)		1.14 (0.59-2.26)	
Many	1.68 (1.13-2.52)		1.67 (1.11-2.53)		1.91 (0.94-4.31)		1.69 (1.10-2.63)		1.38 (0.79-2.51)	

[a] OR = Odds Ratio, CI = Confidence Interval
p-values significant at ≤0.05 are **bolded**

Chapter 7: Discussion

This thesis endeavored to explore the associations between a wide range of risk factors and risk of melanoma, BCC, and SCC for a clinic population in Canada. For this end, 1003 patients (489 skin cancer cases and 514 controls) were recruited and surveyed from a dermatology clinic in Vancouver, BC. Our study population included 105 melanoma, 367 BCC, and 148 SCC cases, and there were at least 120 patients that had more than one type of skin cancer. In this final chapter, we summarize our results, discuss these findings with regards to published literature, and outline avenues for future research.

7.1 Summary of Key Findings

7.1.1 Melanoma

We found 13 risk factors to be significantly associated with risk of melanoma: age, gender, history of actinic keratosis, transplant history, alcohol consumption, eye colour, hair colour, Fitzpatrick skin type, nevus density, lentigo density, history of childhood sunburns, history of adulthood sunburns, and occupational sun exposure history. In addition, having a family history of melanoma significantly increased risk of melanoma (OR 1.84). Apart from age, the strongest risk factor for melanoma based on univariate analyses was presence of many lentigines (OR 9.44). Fitzpatrick skin type I (OR 9.43), Fitzpatrick skin type II (OR 8.19), red hair (OR 1.80-24.7), green and blue eyes (OR 5.04 & 3.52) and current and former alcohol consumption (OR 4.45 & 4.64) were also strong risk factors for melanoma. Having a history of actinic keratosis (OR 3.59), having childhood and adulthood sunburns (OR 3.59 for >20 childhood sunburns, OR 2.61 for >20 adulthood sunburns), presence of some/many nevi (OR 2.05), and being male (OR 1.55) were also significant risk factors, though with more modest effects. These findings are consistent with the literature, as

other studies have also found these variables to be associated with an increased melanoma risk.[21,33,37,38,45,46,51]

Transplant history was also significantly associated with melanoma, but decreased rather than increased risk of melanoma (OR 0.10, CI 0-0.72). This finding is not in line with those from other studies that showed transplant recipients to have a greater risk of melanoma.[26] This discrepancy may be due to our study being based on a clinic population. It is widely reported that transplant recipients are at a higher risk of skin cancer compared to the general population, and thus recipients are recommended to be regularly monitored for malignancies.[27,73] There may be protective effects that come with frequent dermatology visits. Another possibility is that most of the transplant recipients in our study had recent transplants and have not yet developed melanomas. Closely connected to having a history of transplants is the use of immunosuppressants. We did not find a significant relationship between use of immunosuppressants and melanoma risk. Again, our results are not consistent with previous research that reported a positive association between immunosuppressant usage and risk of melanoma.[29] As our participants were all surveyed from a dermatology clinic, our controls are more likely to resemble cases compared to controls taken from a general population. This may play a role in the discrepancies we see for immunosuppressants and transplant history. In addition, as all our analyses were univariate, we did not account for effects of confounding with other risk factors such as age. Further investigation, especially through multivariate analysis, should be done to further explore the relationship of transplant history and immunosuppressants with melanoma risk in our study population.

Presence of atypical nevi is also considered to be an important risk factor for melanoma, but for our study we failed to find a significant association between this variable and risk of melanoma. As well, despite strong links between sun exposure (especially intermittent sun exposure) and

melanoma, our study did not detect significant associations between tanning bed sessions, recreational sun exposure, frequency of sunny holidays, and risk of melanoma. We did find childhood/adulthood sunburns and occupational sun exposure to be significantly related to increased melanoma risk. Some of our sun exposure measures were significant and some were not; this brings to mind how a systematic review of melanoma risk prediction models reported measures of sun exposure and sunburn history to be included in models only half the time when considered for inclusion.[14] Possible reasons for this include lack of reliability and validity of questions regarding sun exposure, due to issues of recall bias, response bias, and subjectivity. The difficulty in capturing measures of sun exposure was noted for our study as well; quite a few of our participants expressed issues with memory and subjectivity when asked to recall their sunburn or sun exposure history. Our findings, along with the those from the systematic review suggest the need for research into how measures of sun exposure can be more reliably captured. Of course, the same limitations as above stand regarding our study design and population; our findings may not be as significant and of greater effect due to our controls being taken from a clinic, and adjustment for possible confounders should be done to properly investigate the relationship of our risk factors with melanoma.

We found participants with a high lifetime occupational sun exposure to have an increased risk of melanoma (OR 3.31). This finding contradicts results from a systematic review that found high occupational sun exposure to be associated with a decreased risk of melanoma. Further research is needed to investigate this relationship, desirably with a better method of capturing occupational sun exposure history as above mentioned.

7.1.2 BCC

There were 17 statistically significant risk factors for BCC: age, gender, history of actinic keratosis, immunosuppressant history, smoking, eye colour, hair colour, Fitzpatrick skin type, nevus density, atypical nevi, freckle density, lentigo density, history of childhood sunburns, history of adulthood sunburns, UV radiation treatment history, recreational sun exposure history, and history of sunny holidays. Age was strongly related to increased BCC risk, with the odds of BCC being 305 times greater for those aged 60 compared to 18. Other strong risk factors for BCC were presence of some and many lentigines (OR 17.2 & 22.8), having a history of actinic keratosis (OR 9.94), light eye colour (OR 9.84 for green, OR 6.08 for grey, OR 5.23 for blue), Fitzpatrick skin type I and II (OR 6.84 & 4.63), red hair (OR 4.96), and red hair (OR 6.46). A very high lifetime history of recreational sun exposure (OR 3.26), history of childhood and adulthood sunburns (OR 2.78 for >20 childhood sunburns, OR 2.73 for >20 adulthood sunburns), having a history of UV radiation treatment (OR 2.32), many lifetime sunny holidays (OR 1.69), having freckles (OR 1.56 for some freckles), being male (OR 1.53), having a history of immunosuppressants (OR 1.53), and former smoking (OR 1.42) were also significant risk factors though with smaller effects. Our findings match those from previous studies that found these variables to be associated with a greater risk of BCC.[17,18,24,28,35,36,41,48,52]

We found former smoking (OR 1.42) to be significantly associated with BCC risk. Studies have not suggested a clear relationship between smoking and BCC so far. One systematic reported no significant association between smoking and BCC, while another found former smokers to have a significantly increased risk of BCC for women.[30,32] We could potentially conduct further analyses for smoking by testing associations separately for men and women, as did previous studies.

We found presence of nevi (OR 0.46, CI 0.33-0.66 for some/many nevi) to be significantly associated with a decreased risk of BCC. Further, having even 1-2 atypical nevi significantly decreased BCC risk, with presence of 3+ atypical nevi strongly associated with a decreased risk (OR <0.09). While there are no reports to our knowledge of the relationship between atypical nevi and keratinocyte carcinoma, there are two studies that found presence of nevi to be associated with an increased risk of BCC.[35,39] Our findings for nevi directly contradict those from these studies. Perhaps there are factors arising from the nature of our population (clinic-based) that have contributed to this finding. However, a convincing rationale is lacking and further research should be conducted to uncover the associations between nevi, atypical nevi, and keratinocyte carcinomas.

We did not find a significant relationship between transplant history and risk of BCC, although the literature reported a 10-fold increase in risk.[27,28] Perhaps we did not have enough power to detect a significant difference, but given that we had over 350 BCC cases, a better explanation may be that our controls and cases had similar characteristics regarding these risk factors for skin cancer due to both being sourced from a dermatology clinic. As such, we may have different findings from studies with population-based controls.

We did not find a significant association between family history of melanoma and either BCC or SCC. This finding is not consistent with results from a recent prospective study that found an increased risk of KCs for those with a family history of melanoma.[22] As few studies have reported findings on the potential relationship of family history of melanoma and risk of KCs, further investigation may be needed to confirm if a significant relationship exists.

7.1.3 SCC

Risk of SCC was significantly associated with 15 variables: age, gender, actinic keratosis history, immunosuppressant history, eye colour, hair colour, Fitzpatrick skin type, nevus density, atypical nevi, lentigo density, history of childhood sunburns, history of adulthood sunburns, history of tanning beds, UV radiation treatment history, and recreational sun exposure history. Along with age (OR 1.13), strongest risk factors for SCC were light eyes (OR 24.5 for green, OR 13.2 for grey, OR 12.6 for blue), history of actinic keratosis (OR 19.6), having many lentigines (OR 18.8), Fitzpatrick skin type I and II (OR 13.7 & 8.31), and light hair colour (OR 8.56 for red, OR 3.77 for blonde). History of adulthood sunburns (OR 3.43 for >20 sunburns), history of childhood sunburns (OR 3.04 for >20 sunburns), history of UV radiation treatment (OR 2.76), immunosuppressant usage (OR 2.07), and being male (OR 2.02) were also significantly associated with a higher risk of SCC. These findings are consistent with findings from other studies that reported greater SCC risk for these variables.[17,18,20,23,25,27,36,40]

In the case of lentigines, not many studies have investigated its relation to skin cancer risk, and no studies have reported to our knowledge a positive association between lentigines and risk of SCC. As a key marker of sun exposure, we expect lentigines to be an important risk factor for not only SCC, but also BCC and melanoma. Though additional research may be necessary to further confirm this relationship, future skin cancer risk prediction models may benefit from including a measure for lentigines.

We found a significant relationship between lifetime recreational sun exposure and risk of SCC. Despite reaching significance, none of the individual levels of exposure had a significantly increased odds of SCC. Sun exposure is undoubtedly a key factor leading to development of SCCs; however, SCC is generally linked to cumulative or occupational sun exposure rather than

recreational sun exposure.[50,54] In our study though, we were not able to find a significant association between occupational sun exposure and SCC risk. Possible explanations for this include subjectivity associated with these questions regarding past sun exposure history, as well as effects stemming from controls being taken from a clinic rather than a general population.

Transplant history is another widely considered risk factor for SCC, as studies report risk of SCC to be 60-200 fold higher for transplant recipients.[20] Despite this finding from other studies, we did not find a significant association between a history of transplants and SCC risk. A potential explanation may be related to how our controls and cases are both sourced from a dermatology clinic, and therefore may have similar risk factor histories (including transplant history). Adjusting for confounders through multivariate analyses may potentially lead to different findings.

There were 3 variables that showed significant inverse relationships with SCC. Having some/many nevi compared to none/few nevi was associated with a decreased risk of SCC (OR 0.23, CI 0.12-0.40). As well, presence of even 1-2 atypical nevi increased risk of SCC (OR 0.41, CI 0.18-0.82). Our findings are not in line with a recent study that found no association between nevi and SCC.[39] Further research is needed to confirm a relationship between nevi and SCC and uncover potential explanations for this relationship. We also found lower risks of SCC for those that had 1-50 tanning bed sessions. Our results are not in line with those from previous studies that found tanning bed usage to be related to an increased risk of SCC.[57] Possible explanations for this discrepancy include effects of recall bias, response bias, and controls being taken from a dermatology clinic.

7.2 Lifestyle Factors and UV Exposure

For the lifestyle variables (drinking, smoking) and many of the risk factors related to UV exposure, we did not find significant associations despite expectations to find them. Previous studies

reported alcohol consumption to be related to an increased risk of melanoma, BCC, and SCC.[33,34] Our study did find a positive relationship between alcohol consumption and melanoma risk, as discussed above. However, we did not find a significant association between alcohol consumption and risk of KCs. Looking back at published reports, a positive relationship between drinking and BCC was found in cohort studies but not in case-control studies.[34] Similarly, pooled estimates showing increased risk of SCC for drinkers were from cohort studies.[34] This suggests cohort studies may be better fit for studying the association between alcohol consumption and risk of skin cancer, possibly due to social desirability bias. In addition, a dose-dependent increase of BCC and SCC risk with alcohol consumption was reported. In our study, we assessed alcohol consumption by putting participants into categories of never, former, and current drinkers. This format was chosen over the assessment of specific intake levels of alcohol, as our study included the collection of many other variables. Specific, rather than broad measures may be more effective for studying the association between drinking and risk of skin cancer. Researchers may want to consider collecting specific alcohol intake levels in future studies, provided the disadvantages (increased time and effort for participants, recall bias) do not outweigh the advantages.

In terms of smoking, previous studies found smokers to be at an increased risk of melanoma, and heterogenous findings were reported for the relationship between smoking and KCs.[30–32] We found smoking to be significantly associated with BCC, but not SCC or melanoma. Further, only former smokers were found to have significantly increased risks of BCC; we did not find a significant relationship between current smokers and any type of skin cancer. This may be reflective of our study population: both cases and controls were both recruited from a clinic and may have similar lifestyle choices. As well, social desirability bias may have played a role. Cases may have been more inclined to report favourable/healthier smoking habits considering their history and

considering that the interview was being conducted in a clinical setting. In terms of future research, it may be useful to conduct a sub-analysis of smoking and risk of skin cancer by gender, as many studies have separately reported the association between smoking and skin cancer for men and women.

UV exposure is considered to be the most important risk factor for skin cancer, and yet we failed to find significant positive associations between many measures of UV exposure and skin cancer. Studies have found risk of melanoma, BCC, and SCC to increase with a history of tanning bed usage.[56,57] In our study, no association with tanning bed usage was found for melanoma and BCC, and a decreased risk of SCC was found with tanning bed usage. Occupational sun exposure was reported in the literature to be related to a decreased risk of melanoma, and increased risk of BCC and SCC.[51,54,55] We found occupational sun exposure to be associated with an increased risk of melanoma. SCC was not found to be associated with occupational sun exposure overall. While the same was true for BCC, we did find participants with high compared to very low occupational sun exposure to have a significantly increased risk of BCC. Intermittent sun exposure (including recreational sun exposure and sunny holidays) was reported by previous studies to be related to an increased risk of melanoma and SCC.[41,42,49,51,54,55] Again, we did not find risk of skin cancer to be significantly associated with sunny holidays. We did find recreational sun exposure to be significantly related to skin cancer, with trends showing increasing odds with greater exposure. However, individual levels of exposure were not significant. The one exception was for BCC, where individuals with very high compared to very low recreational sun exposure had a significantly greater risk of BCC.

A common characteristic of these UV exposure variables is the difficulty associated with answering questions about these variables. These factors are collected through self-report, as only

participants themselves can answer to their history of sun exposure or tanning bed usage. The difficulty in answering these types of questions arises from issues of recall and subjectivity. It can be challenging to accurately remember how many sunburns you've had in the past. As well, it can be challenging to decide whether you've had a high or low recreational/occupational sun exposure, as everyone's sense of what high exposure is may differ. Perhaps specific standards to compare to should be provided. It would be of great help if future research could be conducted to find a reliable and valid method to assess these important measures of UV exposure.

7.3 Eye Colour vs. Hair Colour vs. Fitzpatrick Skin Type

Pigmentary factors (eye and hair colour) and sun sensitivity (Fitzpatrick skin type) are part of a person's innate characteristics. Individually, these are all consistently found to be associated with an increased risk of skin cancer.[21,25,35,36] However, perhaps due to the adjustment of confounding effects, skin cancer risk prediction models do not include all three of these variables together.[10,14,40,74] It may be interesting to see which of these 3 factors is most strongly associated with risk of skin cancer. We found risk of melanoma, BCC, and SCC to be significantly associated with all of these 3 factors. For melanoma, Fitzpatrick skin type had greatest effects, followed by hair colour then eye colour. For BCC and SCC, eye colour had greatest effects, followed by Fitzpatrick skin type then hair colour. Based on our findings, Fitzpatrick skin type is significantly and strongly related to all three types of skin cancer. For KCs, eye colour is a stronger risk factor than Fitzpatrick skin type, with higher odds ratios for blue and green eyes. Of course, our findings are from univariate analyses and results may differ once confounding is considered.

7.4 Strengths and Limitations

The main strength of our study regards the investigation of a wide range of risk factors simultaneously for melanoma, BCC, and SCC. A common limitation of other studies is the lack of key variables, and we sought to address this. In addition, researchers generally conduct separate studies for melanoma and KCs. As our study included all three types of skin cancer, it was easier to compare findings between the different types. Another strength is the validity of our cases and controls. Our cases and controls were confirmed through pathology reports, and thus our outcome variables were not subject to the misclassification or recall bias that may occur in self-reported studies. Finally, several phenotypic features (nevi, atypical nevi, lentigines) were assessed by physicians rather than through self-reports. Studies have shown that patients have difficulties in accurately counting the number of nevi/atypical nevi on their bodies.[75,76] By having physicians assess these pigmented lesions, we have opted for a more reliable and valid evaluation of these factors.

Limitations of our study include concerns for recall bias, response bias, generalizability, and confounding. Questions regarding history of sun exposure can only be answered through self-reports, and thus are subject to recall bias. Response bias may also have potentially occurred, especially in a clinic setting and if patients are aware of their skin cancer history.

While our focus on a clinic population has its advantages, it also comes with limitations. Our controls and cases may have had similar exposures to risk factors considering they were both referred to our clinic over concern of possible skin cancer. As such, the odds ratios we found are likely to be closer to the null value compared to odds ratios obtained from population controls and cases. Indeed, for quite a few of our variables, we failed to find significant associations despite expecting to find them based on literature. Regardless of these limitations, the aim of our study was

to examine associations between risk factors and skin cancer in a clinic population. Although our findings may not be generalizable to the general public, they should be generalizable for our intended clinical populations.

7.5 Future Directions

Our study examined associations between different risk factors and skin cancer, but as all our analyses were univariate, there are concerns for confounding. We will be addressing this concern by conducting multivariate analyses for our data. Our future goal is to develop and validate risk prediction models for melanoma and KCs for use in predicting skin cancer risk from patients who seek medical help. Thus, our study results could allow physicians to focus screening and surveillance for those at greater risk. Our findings could have applications not only in early detection, but also in prevention, through informing and educating individuals of their risk. We hope that our research will also be of use at the public health level as health interventions and policies can be developed to specifically target important risk factors.

We believe clinical risk prediction models could potentially benefit the health care system when used by general practitioners to aid their decisions in management and referral of patients. Dermatology is one of the specialties with the longest wait times in Canada.[77] If unnecessary referrals could be prevented by using these models to stratify patients based on their risk for skin cancer, dermatologists may be able to focus more on managing and treating those at high risk. Future avenues of research therefore include a comparison between patients from general practitioner offices to those from dermatology clinics. The risk prediction models developed from our study population may be used by general practitioners provided that patients from general practitioner offices and dermatology clinics do not significantly differ. Further investigation would be needed if

there is a significant difference between patients, as new data from general practitioners' offices should be collected to develop risk prediction models for use by general practitioners.

7.6 Conclusion

To the best of our knowledge, this is the first Canadian study to explore a wide range of risk factors in a clinic population for both melanoma and keratinocyte carcinomas. Overall, our findings were similar to those found in literature, but some of our associations did not reach significance, perhaps due to both our cases and controls being clinic-based. We found overlaps in risk factors between the different types of skin cancer, confirming the importance of age, gender, phenotypic factors, and sunburns for all 3 types of skin cancer. We also illustrated differences in risk factors between the different skin cancer types, with nevi and family history of melanoma being important risk factors for melanoma, and BCC showing clear ties to intermittent sun exposure. BCC and SCC had more common risk factors with each other than with melanoma. Further investigation is needed to properly elucidate associations between different risk factors and the 3 skin cancer types. The effect of confounding and interactions between risk factors should be considered, after which we may see changes in significance and strength of associations from the ones we found in this thesis. This study explored a wide range of risk factors for skin cancer, and will guide our next step in developing multivariate risk prediction models to be used in Canadian clinics.

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Appendices

Appendix A Data Collection Tools

A.1 Data Collection Form

Data Collection Sheet for Skin Cancer Risk Prediction Model Development

Personal/Medical Information			
Participant id:			
Date of birth (yyyy/mm): Age:	Sex: ☐ Male ☐ Female	Eye colour (check box and circle specific colour): ☐ Light: Blue/Green/Grey ☐ Medium: Hazel/ Light Brown ☐ Dark: Dark Brown ☐ Other: _____	Natural hair colour at age 20: ☐ Black ☐ Dark brown ☐ Light Brown ☐ Blonde ☐ Red
Personal history of skin cancer: ☐ Yes ☐ No ☐ Unsure If yes, specify date/type:		First degree family history of melanoma: ☐ Yes ☐ No ☐ Unsure If yes, specify date/type:	History of actinic keratosis: ☐ Yes ☐ No ☐ Unsure If yes, specify date/type:
History of transplants: ☐ Yes ☐ No If yes, specify date/type		History of immunosuppressive medications: ☐ Yes ☐ No If yes, specify date/type:	Other medications taken or medical history (please specify):

Behavioural Information			
Number of severe sunburns:		Number of tanning bed sessions: ☐ 0 ☐ 1-10 ☐ 11-50 ☐ 51-100 ☐ 101-499 ☐ ≥500	Exposure to radiation (eg. phototherapy, treatment for eczema/acne): ☐ Yes ☐ No Details:
As a child (<18 years) ☐ 0 ☐ 1-2 ☐ 3-5 ☐ 6-10 ☐ 11-20 ☐ >20	As an adult (≥18 years) ☐ 0 ☐ 1-2 ☐ 3-5 ☐ 6-10 ☐ 11-20 ☐ >20		

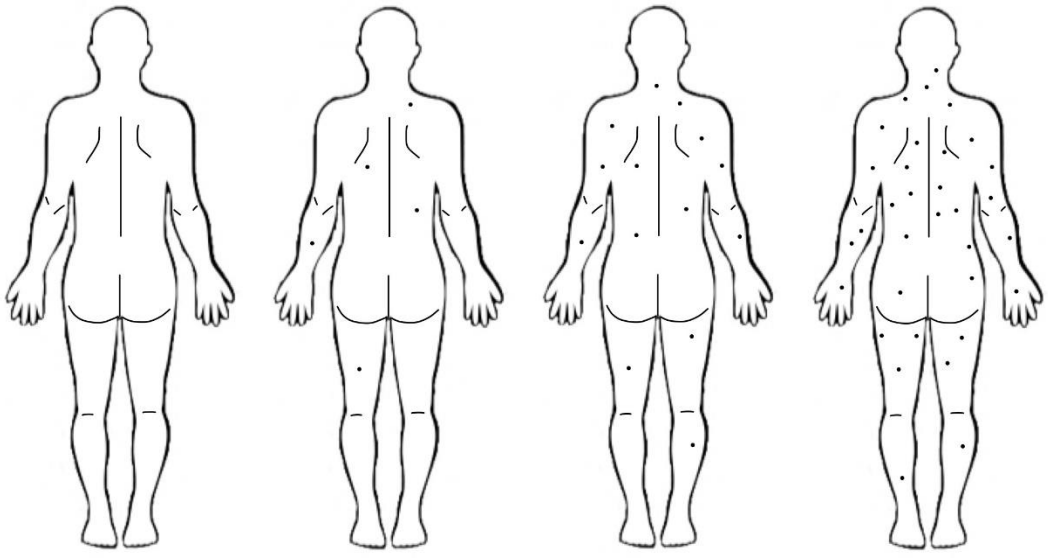
Lifetime sun exposure:		What type(s) of recreational sun exposure?
Occupational: ☐ Very low ☐ low ☐ moderate ☐ high ☐ Very high	Recreational: ☐ Very low ☐ low ☐ moderate ☐ high ☐ Very high	☐ Sun tanning ☐ Outdoor sports ☐ Water activities ☐ Gardening ☐ Walking

Places of Residence (country and ages) lived >6months:		

Average number of sunny holidays in winter (October-April):	Smoking status:	Drinking status:
☐ None ☐ Few (up to 1 every 10 years) ☐ Some (up to 1 every 5 years) ☐ Many (yearly) *sunny holidays: holidays to locations with a lot of sun	☐ Never ☐ Former ☐ Current	☐ Never ☐ Former ☐ Current

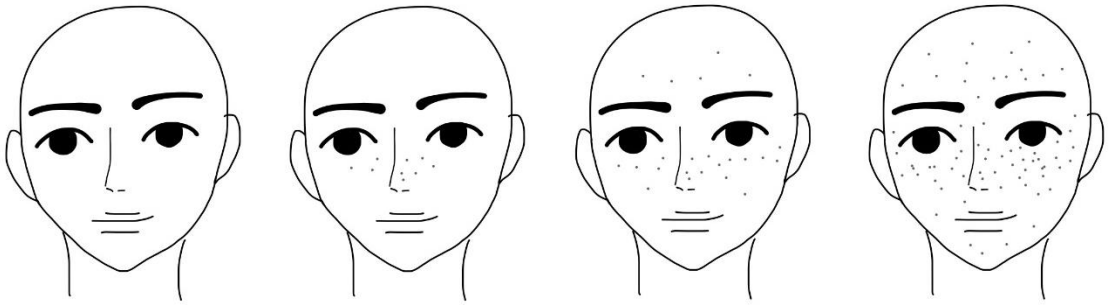
Clinical Information		
Fitzpatrick skin type: ☐ I ☐ II ☐ III ☐ IV ☐ V ☐ VI	Number of nevi >2mm on body (according to picture): ☐ None ☐ Few ☐ Some ☐ Many	Atypical nevi / moles larger than >5mm: ☐ 0 ☐ 1-2 ☐ 3-5 ☐ 6+
Density of freckles (according to picture): ☐ None ☐ Few ☐ Some ☐ Many	Density of lentigines: ☐ None ☐ Few ☐ Some ☐ Many	Skin Cancer Diagnosis: ☐ Yes ☐ No If yes, specify date/type:
Colorimeter result:		Raman id:

A.2 Nevi Density Diagram



None Few Some Many

A.3 Freckle Density Diagram



None Few Some Many