THE ROLE OF ULTRAVIOLET RADIATION IN THE DEVELOPMENT OF SKIN CANCER AND NON-HODGKIN LYMPHOMA IN CANADA

by

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Abstract

Background: Exposure to ultraviolet radiation (UVR) is an established cause of melanoma and non-melanoma skin cancer (NMSC) and moderate exposure is hypothesized to be protective against some non-cutaneous cancers, including non-Hodgkin lymphoma (NHL). The first aim of this thesis was to estimate the current and future burden of melanoma and NMSCs associated with UVR and modifiable UVR behaviours in Canada. The second aim was to explore the relationship of time spent in the sun and the risk of NHL in a Canadian setting.

Methods: The burden of skin cancer associated with UVR in 2015 was estimated by comparing 2015 rates of melanoma and NMSCs with estimated rates of a 1920 birth cohort for melanoma and with rates of less exposed body sites (trunk and legs) for NMSCs. Skin cancer attributable to modifiable UVR behaviours (indoor tanning, sunburn, and sunbathing) was estimated using relative risks relevant to Canada by conducting meta-analyses and prevalence of exposures from a nationally representative survey. A prospective cohort study examining the risk of NHL was conducted using self-reported questionnaire data from three Canadian cohorts that were linked to cancer incidence data. Multivariable Cox proportional hazards models, using age as the time-scale was employed to investigate this relationship with control for relevant confounders.

Results: For 2015, we estimated that 62.3% of melanomas, 80.5% of basal cell carcinomas (BCC), and 83.0% of squamous cell carcinomas (SCC) were attributable to UVR, while 29.7% of melanomas, 46.0% of BCCs, and 17.4% of SCCs were attributable to modifiable UVR behaviours. Compared to individuals spending < 30 min/day in the sun the risk of developing

NHL was 0.84 (95% CI: 0.55-1.28) for 30-59 minutes, 0.63 (95% CI: 0.40-0.98) for 1-2 hours, and 0.91 (95% CI: 0.61-1.36) for > 2 hours.

Conclusions: Prevention efforts aimed at modifiable UVR behaviours are crucial for reducing the burden of skin cancer in Canada, while moderate exposure to the sun may reduce the risk of NHL. Further research is required to clarify the optimal UVR exposure patterns in terms of preventing the development of both cutaneous and non-cutaneous cancers, including NHL.

Co-Authorship

This thesis presents the work of Dylan O'Sullivan in collaboration with his supervisors, Dr. Will King, and Dr. Darren Brenner, as well as co-authors. Component 1 of this thesis (manuscripts 1, 2, and 3) originated within a larger project aimed at quantifying the burden of cancer in Canada attributable to modifiable risk factors, known as the Canadian population attributable risk of cancer (ComPARe) study. The ComPARe study was a collaborative, pan-Canadian study that involved a partnership with the Canadian Cancer Society. Primary investigators of the ComPARe study included Dr. Darren Brenner (Co-PI), Dr. Christine Friedenreich (Co-PI), Dr. Stephen Walter, Dr. Will King, Dr. Eduardo Franco, Dr. Paul Demers, Dr. Paul Villeneuve, Dr. Prithwish De, Dr. Robert Nuttall, and Dr. Perry Hystad. Component 2 of this thesis (manuscript 4) is part of a larger project funded by the Canadian Institutes of Health Research (CIHR) aimed at examining the relationship of exposure to ultraviolet radiation and several non-cutaneous cancer sites. Primary investigators of this project include Dr. Will King (PI), Dylan O'Sullivan, Dr. Darren Brenner, and Dr. Cheryl Peters.

Chapter 4, Manuscript 1: *Indoor tanning and skin cancer in Canada: A meta-analysis and attributable burden estimation.* This manuscript is presented in the format as published in the journal *Cancer Epidemiology* (O'Sullivan et al. Cancer Epidemiol. 2019 Jan 9;59:1-7. doi: 10.1016/j.canep.2019.01.004; Publisher: Elsevier). Co-authors on this manuscript were Darren Brenner, Paul Demers, Paul Villeneuve, Christine Friedenreich, and Will King on behalf of the ComPARe Study Group. Study conception, analysis, interpretation of results and writing of the manuscript was performed by Dylan O'Sullivan under the supervision of Will King and Darren Brenner, with feedback from Paul Demers, Paul Villeneuve, and Christine Friedenreich.

Chapter 5, Manuscript 2: *The current and future burden of melanoma attributable to ultraviolet radiation in Canada.* This manuscript is presented in the format as published in the journal *Preventive Medicine* (O'Sullivan et al. Prev Med. 2019 May;122:81-90. doi: 10.1016/j.ypmed.2019.03.012; Publisher: Elsevier). Co-authors on this manuscript were Darren Brenner, Paul Villeneuve, Stephen Walter, Paul Demers, Christine Friedenreich, and Will King on behalf of the ComPARe Study Group. Study conception, analysis, interpretation of results and writing of the manuscript was performed by Dylan O'Sullivan under the supervision of Will King and Darren Brenner, with feedback from Paul Villeneuve, Stephen Walter, Paul Demers, and Christine Friedenreich.

Chapter 6, Manuscript 3: *The current burden of non-melanoma skin cancer attributable to ultraviolet radiation and related risk behaviours in Canada*. Co-authors on this manuscript were Darren Brenner, Paul Villeneuve, Stephen Walter, Paul Demers, Christine Friedenreich, and Will King on behalf of the ComPARe Study Group. Study conception, analysis, interpretation of results and writing of the manuscript was performed by Dylan O'Sullivan under the supervision of Will King and Darren Brenner, with feedback from Paul Villeneuve, Stephen Walter, Paul Demers, and Christine Friedenreich. This manuscript has been prepared for submission to the journal *Cancer Epidemiology, Biomarkers & Prevention*.

Chapter 7, Manuscript 4: *Time spent in the sun and the risk of developing non-Hodgkin lymphoma: A Canadian cohort study*. Co-authors on this manuscript were Troy Hillier, Darren Brenner, Cheryl Peters, and Will King. Study conception, analysis, interpretation of results and writing of the manuscript was performed by Dylan O'Sullivan under the supervision of Will King and Darren Brenner, with feedback from Troy Hillier and Cheryl Peters. This manuscript has been prepared for submission to the journal *Environmental Health Perspectives*.

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Table of Contents

List of Figures

List of Tables

List of Abbreviations

AC	Attributable cases
AIDS	Acquired immunodeficiency syndrome
ATP	Alberta's Tomorrow Project
BMI	Body Mass Index
BCC	Basal cell carcinoma
BCGP	British Columbia Generations Project
CaG	Quebec's CARTaGENE
CCHS	Canadian Community Health Survey
CI	Confidence interval
ComPARe	The Canadian Population Attributable Risk of Cancer Study
CPTP	Canadian Partnership for Tomorrow Project
CTR	Counterfactual Scenario
HIV	Human immunodeficiency viruses
HPV	Human papillomavirus
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
IPAQ	International Physical Activity Questionnaires
NMSC	Non-melanoma skin cancer
NHL	non-Hodgkin lymphoma
NSS2	The Second National Sun Survey
OHS	The Ontario Health Study
PAF	Population attributable fraction
PAR	Population attributable risk
PIF	Potential impact fraction
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PUVA	Photochemotherapy
PYTPAQ	Past Year Total Physical Activity Questionnaire
ROS	Reactive oxygen species
RR	Relative risk
SEER	Surveillance, Epidemiology, and End Results Program
SCC	Squamous cell carcinoma
SNP	Single nucleotide polymorphism
SPF	Sun protection factor
UVA	Ultraviolet A radiation
UVB	Ultraviolet B radiation
UVC	Ultraviolet C radiation
UVR	Ultraviolet radiation

Chapter 1

Introduction

1.1 Background and Rationale

Solar ultraviolet radiation (UVR) is a ubiquitous, and largely unavoidable exposure that could be both beneficial and detrimental to the initiation of cancer depending on the intensity and duration of exposure throughout the life course. The causal relationship between exposure to solar UVR and cutaneous malignancies (melanoma and non-melanoma skin cancers [NMSC]) is established (1). Melanoma is most strongly associated with very intense intermittent periods of sun exposure (2), while NMSC (basal cell carcinoma and squamous cell carcinoma) are most strongly linked to chronic or continuous patterns of sun exposure (3). A certain level of sun exposure is potentially protective for other cancer sites through immune function (4), the production of vitamin D (5), and maintenance of normal circadian rhythm patterns (6) – all of which have been shown to have antiproliferative effects. On the other hand, high levels of sun exposure may increase cancer risk through direct DNA damage (7), immunosuppression (8), oxidative stress (9), inflammation (10), and alterations to the epigenome (11).

A considerable body of evidence supports an association between the occurrence of NMSC and elevated risk for developing other cancers, particularly non-Hodgkin lymphoma (NHL) (12). These correlations suggest that high UVR exposure may be detrimental for the incidence of NHL. A pooled analysis of 10 case-control studies and a recent meta-analysis have observed statistically significant protective associations for recreational time spent in the sun or sunbathing on NHL risk (13,14). In contrast,

occupational sun exposure has been linked to an increased risk of developing NHL (15). However, this association could be confounded by the known relationships with occupational exposure to pesticides and benzene (16), necessitating non-occupational studies of high levels of exposure to the sun. Among this body of literature, there are few cohort studies that have examined this relationship, and the shape of the relationship has not been well characterized.

Artificial exposure to UVR, on the other hand, is avoidable and represents a different dimension of UVR exposure. Indoor tanning produces 10-15 times stronger UVR than midday sun and produces a different ratio of UVR wavelengths compared to the sun (17). Consistent epidemiologic and experimental studies have demonstrated that UVR-emitting tanning devices are causes of melanoma and NMSCs (18). The type of wavelengths produced by indoor tanning devices are relatively ineffective at promoting vitamin D synthesis and circadian rhythm maintenance (19), while at the same time can promote detrimental biological effects (20,21). A meta-analysis including 15 studies on the use of indoor tanning devices and the risk of developing non-cutaneous cancers observed a suggestive increased risk of developing hematologic malignancies, including non-Hodgkin lymphoma, with the use of indoor tanning devices (22).

Population attributable risk (PAR) methods can be utilized to quantify the proportion of a disease that is attributed to or caused by a specific exposure. Estimates of the current and future burden of cancer in specific geographical regions attributable to known and probable causes are required for informing the cancer prevention programs and optimal resource allocation. Skin cancer has been increasing over time in Canada (23) and different patterns of UVR exposure confer different risks of skin cancer (3).

Estimates of the burden of skin cancer attributed to specific patterns of exposure to UVR are necessary to inform prevention efforts.

In order to set priorities for public health in relation to UVR exposure, and to provide effective communication of the risks associated with this exposure to health practitioners and the general public, we also need to understand whether UVR exposure is associated with the risk of other cancer sites. While there have been previous studies on the association between exposure to ultraviolet radiation and non-cutaneous cancer sites (24), more rigorous research is required. NHL is the most studied cancer site with UVR and has the most support in terms of biologic plausibility. However, previous results have only been examined in case-control studies, which are subject to selection and recall bias, and do not fully explore patterns of exposure to UVR (14). While NHL accounts for 4% of all cancers in Canada, its incidence rate continues to increase (25). Little is known about the role of modifiable risk factors in the etiology of NHL (16), and the suggested relationship with UVR merits investigation.

1.2 Overview of Thesis and Study Design

This thesis consists of two components, both of which are aimed at informing efforts to reduce the burden of cancer in Canada associated with UVR exposure. The first component examines an established UVR-cancer relationship (melanoma and NMSC) through the estimation of Canadian-specific population attributable risks (PAR) and potential impact fractions (PIF) of changing behaviours, while the second is a novel investigation of the relationship of time spent in the sun and the risk of developing NHL using data from provincial prospective cohort studies in Canada.

1.3 Thesis Objectives

This thesis consists of two related components addressing an overall theme of cancer risk in relation to UVR exposures. The first component focuses on the estimation of the burden of cancer in Canada due to established UVR-cancer relationships. Specific objectives are:

1) To estimate PARs and PIFs for indoor tanning and different subtypes of skin cancer (melanoma and NMSC [basal cell carcinoma and squamous cell carcinoma]) in Canada.
2) To estimate PARs and PIFs for different types of solar UVR exposure and melanoma in Canada.
3) To estimate PARs for different types of solar UVR exposure and NMSC in Canada.

The second component focuses on the examination of the potential association between UVR and NHL. Specific objectives are:

1) To determine the association between time spent in the sun and the risk of developing NHL using data from Canadian prospective cohort studies.
2) To determine if the association between time spent in the sun and the risk of developing NHL is influenced by sun protection behaviours or pattern of exposure (intermittent vs. chronic).

1.4 Thesis Structure

This thesis is structured as a manuscript-based thesis. The next chapter contains a literature review which provides a general overview UVR and relationships of exposure

to UVR with skin cancers and NHL. In addition, methods for population attributable risk studies and previous studies for UVR exposure and skin cancer are described. A review of cohort studies on sun exposure and non-cutaneous cancer, as well methodological issues relevant to data sources and exposure metrics will be discussed. Following the literature review is an abbreviated methods section that expands on the descriptions of methods included in the manuscripts. Following the methods section, four manuscripts are included. The first manuscript estimates PARs for melanoma and NMSC associated with indoor tanning in Canada and has been published in *Cancer Epidemiology* (26). The second manuscript estimates PARs and PIFs for melanoma in relation to solar UVR in Canada and has been published in *Preventive Medicine* (27). The third manuscript estimates PARs for NMSC in relation to solar UVR in Canada and is formatted for submission to *Cancer Epidemiology, Biomarkers & Prevention*. The fourth manuscript examines the relation of exposure to solar UVR and the risk of developing NHL using data from Canadian prospective cohort studies and is formatted for submission to *Environmental Health Perspectives*. Finally, the last chapter of this thesis is a general discussion of the main findings from each of the four manuscripts, potential biases, and includes a discussion of overall conclusions and future research directions suggested by the thesis as a whole.

1.5 Epidemiologic Contribution of Thesis

This thesis involves the application of the principles of epidemiology, biostatistics and observational research to several challenging issues in the estimation of population attributable risk and cancer etiology. The first component of this thesis consists of novel

population attributable risk methodologies, meta-analysis methods, and cancer incidence projections. The second component of this thesis consists of the use of large epidemiologic cohort data, combining disparate data with a meta-analysis approach, and advanced statistical analyses, including the use of cox proportional hazard models and performing complex interaction analyses.

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ultraviolet radiation in Canada. Prev Med **2019**;122:81-90 doi 10.1016/j.ypmed.2019.03.012.

Chapter 2

Literature Review

2.1 Introduction

Solar ultraviolet radiation (UVR) and artificial UVR from indoor tanning devices are both established causes of melanoma and non-melanoma skin cancers (NMSC) (1,2). In contrast, moderate amounts of exposure to solar UVR may be protective against some non-cutaneous cancers, including non-Hodgkin lymphoma (NHL), but more research is required (3). In order to set public health priorities and messaging for the public around UVR exposure, we must determine the burden of skin cancer associated with UVR and different patterns of UVR, as well as investigate suspected relationships with other cancer sites and other diseases.

2.2 Ultraviolet Radiation

An invisible, omnipresent yet modifiable exposure, solar ultraviolet radiation (UVR) has the potential for either protective or detrimental effects on the body via different biological mechanisms. Exposure to artificial sources of UVR, such as indoor tanning devices, can also have an influence on human health. On the electromagnetic spectrum, UVR ranges from 100 to 400 nanometers (nm) and is categorized by three wavebands: UVA (320-400 nm), UVB (280-320 nm), and UVC (100-280 nm), with only UVA and UVB able to penetrate the Earth's atmosphere (4). UVA is long-range UV radiation that is not readily absorbed by the ozone layer, with approximately 95% reaching the Earth's surface (5). UVB, on the other hand, is short-wave UV radiation, of which the majority is absorbed by the ozone layer, with only 5% reaching the Earth's

surface (5). While UVA is not as energetic as UVB, it penetrates deeply into the skin (dermis) and can cause immediate tanning and premature skin aging (6). UVB can only penetrate the outer layer of the skin (epidermis) and can cause delayed tanning, sunburns, and cutaneous synthesis of vitamin D (6). Artificial tanning devices emit a similar amount of UVB as solar radiation, but emits 10-15 times the level of UVA (7).

There are several factors that can have an influence on the intensity or strength of ambient UVR that humans come into contact with and include time of day, season, ozone layer thickness, weather conditions, surface reflections, altitude, and latitude. UVR is strongest during the middle of the day and during summer months (8). In areas with depleted ozone and less cloud coverage – more UVR will make it to the Earth and with stronger intensity (9). Reflection of UVR off of surfaces can lead to secondary exposure and this is more prominent among bright surfaces, such as snow (9). UVR is strongest at high altitudes and lower latitudes (proximal to the equator) (8).

The detrimental effects that UVR can have on the human body include genotoxic effects in the skin, immunosuppression, chronic inflammation, oxidative stress, and alterations to normal patterns of DNA methylation. Beneficial effects include improved immune function, the synthesis of vitamin D and circadian rhythm maintenance through the release of serotonin and melatonin. The following section will detail these biologic effects and their relationship with the development of cancer. Figures 2.1 and 2.2 display summaries of the detrimental and beneficial effects of ultraviolet radiation in relation to cancer risk.

2.2.1 Detrimental Effects of UVR

2.2.1.1 Genotoxic Effects

Both UVA and UVB can cause direct DNA damage in the skin. When UVR hits the surface of the skin, molecular lesions, known as pyrimidine dimers are formed from thymine or cytosine bases in DNA (10). While these premutagenic lesions alter the structure and interactions of DNA, they are typically repaired within seconds by photolyase reactivation or nucleotide excision repair (10). If the number of these lesions accumulate and overwhelm repair mechanisms, some may go uncorrected and lead to permanent somatic mutations (10). UVR induces a unique mutational signature that is characterized by a large number of CC > TT dinucleotide mutations at dipyrimidines and is found in skin cancers (11). Both UVB and UVA have been shown to cause mutations in tumor suppressor genes, oncogenes, and other key regulatory genes leading to tumorigenesis in the skin (12,13).

2.2.1.2 Immunosuppression

The human body's natural response to tissue damage is to send chemical signals through the immune system to begin the healing process. Exposure to UVR can cause direct DNA damage through the formation of pyrimidine dimers, which can lead Langerhans cells and dendritic cells to migrate to lymph nodes and downregulate skin immune response (14). In addition to DNA damage, the absorption of photons in the epidermis by chromophores can also stimulate the migration of the aforementioned immune cell and mast cells to lymph nodes (14). The migration of these cells to lymph nodes cause immune cells to migrate inefficiently to target tissues. Given that the skin is an innervated tissue, there is considerable release of neuropeptides upon UVR exposure

and this can initiate neuroendocrine pathways in the skin that are linked to both local and systemic immunosuppression (15).

2.2.1.3 Inflammation

Inflammation is the immune system's response to harmful stimuli, and is therefore an important defense mechanism for the human body. Acute inflammatory responses initiate cellular and molecular events that minimize the tissue damage, and restore the tissue to homeostasis through the movement of plasma, leukocytes, antibodies and complement from the blood into the tissue (16). However, repeated stimuli can lead to chronic inflammation, which can have detrimental biological effects (16). During chronic inflammation, neutrophils are replaced with macrophages and T cells, which produce cytokines (17). Cytokines have been shown to result in DNA adduct formation and DNA damage from reactive species (18). In particular, there is evidence that cytokines are capable of supressing key tumor suppressor genes, such as TP53, and can contribute to oncogenic mutations (19). Finally, chronic inflammation can result in increased angiogenesis, which can contribute to cellular proliferation of malignant cells (20). When UVR causes DNA damage through the formation of pyrimidine dimers, pro-inflammatory cytokines and tumor necrosis factors are released, which can initiate the carcinogenic processes highlighted (21).

2.2.1.4 Oxidative Stress

Oxidative stress occurs when there is an imbalance between the production of free radicals and the body's ability to counteract their damaging effects through neutralization with antioxidants. Reactive oxygen species (ROS) are comprised of both free radical and non-free radical intermediates (22). ROS serve an important purpose in cell signaling, but

the free radical component makes them highly reactive (22). ROS have been shown to increase genetic instability through mutations, inactivation of repair enzymes, promotion of cell-survival signaling, and angiogenesis (22). UVR can induce oxidative stress directly by affecting cellular components or through photosensitization mechanisms (23).

2.2.1.5 DNA Methylation

DNA methylation involves the transfer of a methyl-group to cytosine residues in CpG dinucleotide pairs, and plays an essential role in maintaining cellular function (24). Levels of DNA methylation throughout the genome vary according to genomic location. Concentrated CpG dinucleotides, known as CpG islands, occur primarily in transcription start sites and are unmethylated to promote transcription (25). CpG dinucleotides in less concentrated contexts (distal from gene promoters or associated with repeat elements) are typically methylated to support chromosomal stability (25). The maintenance of methylation of less concentrated CpG dinucleotides occurs through one-carbon metabolism, where folate is the primary methyl donor. Exposure to UVR can lead to the degradation of folate, which in turn can lead to disruptions of one-carbon metabolism and loss of methylation that promotes chromosomal stability (26). Alterations to the DNA methylome can also occur indirectly from reactive oxygen species (26). The development of several cancer sites have been associated with pre-malignant losses of methylation in regions that are distal to gene promoters, including repetitive elements (27).

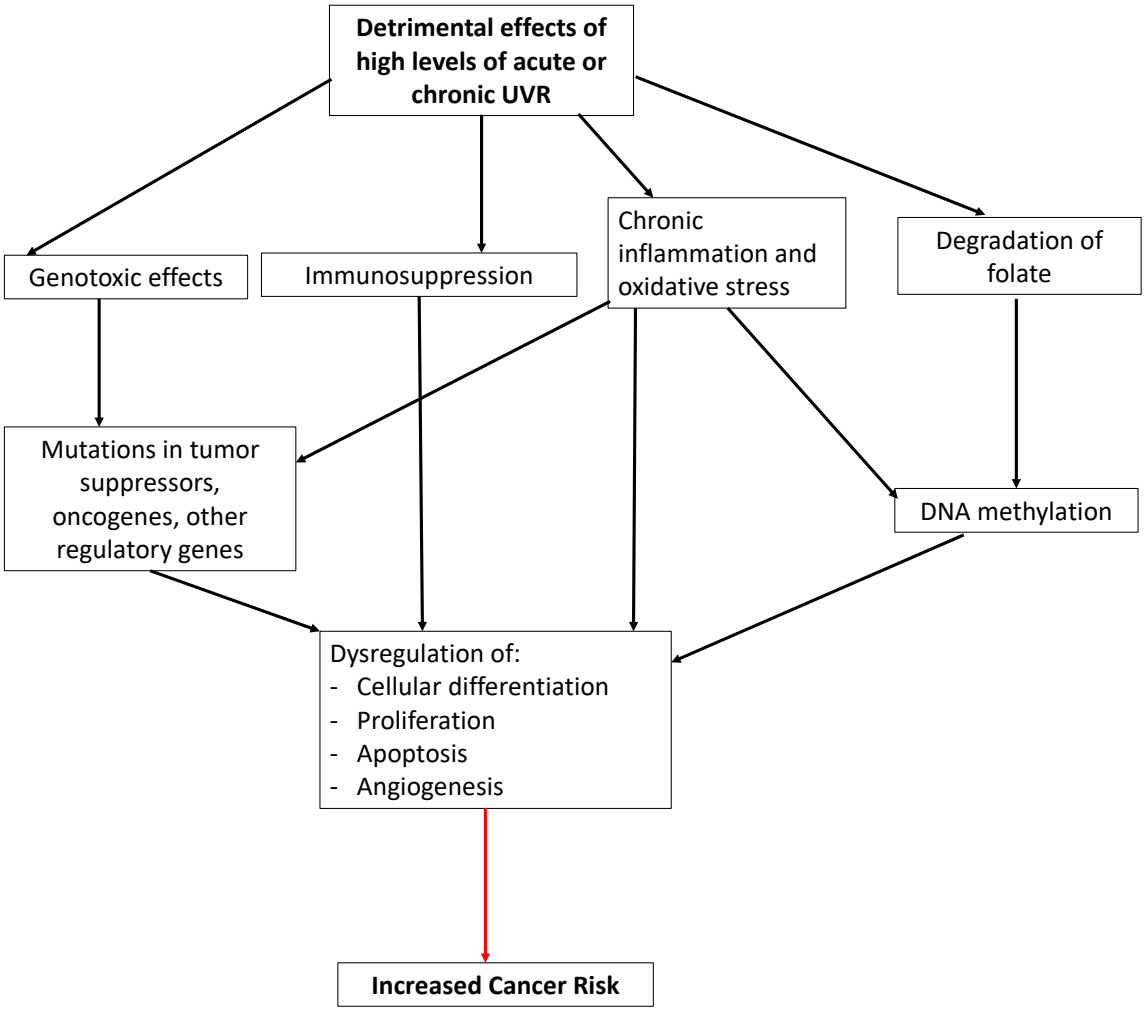

Figure 2.1 Summary of the detrimental effects of ultraviolet radiation

2.2.2 Beneficial Effects of UVR

2.2.2.1 Immune Function

While DNA damage in the skin from exposure to UVR can induce immunosuppression, moderate exposure to the sun can improve immune function. In the skin there is a high density of T lymphocytes, nearly double that circulating in the blood, and these lymphocytes continually perform immune surveillance (28). Low doses of blue light irradiation from the sun can trigger the synthesis of hydrogen peroxide in T cells,

which has been shown to enhance T-cell motility (29). Improved immune function through T-cell motility could decrease cancer risk through improved regulation of cellular proliferation and apoptosis. In addition, solar UVR has been shown to upregulate TH-2 cells, which are required for humoral immunity against tumor associated antigens and help to regulate anti-inflammatory responses (30).

2.2.2.2 Vitamin D

During exposure to sunlight, 7-dehydrocholesterol in the skin absorbs UVB radiation and is converted to pre-vitamin D3, which is then isomerized into vitamin D3 (31). Vitamin D is metabolized by the liver and kidneys into its circulating form (25-hydroxyvitamin D) and into its biologically active form (1,25-dihydroxyvitamin D)(31). Vitamin D can be also be obtained from supplementation or diet through consumption of dairy, meat, fish products, and fortified cereals, but it is difficult to obtain an adequate amount of vitamin D from these sources.

Beyond the role of vitamin D in the maintenance of metabolic functions and skeletal health through its regulation of calcium and phosphate metabolism, it also elicits biological responses that can prevent cancer. Vitamin D has been shown to regulate cellular proliferation and differentiation through its ability to increase the activity tumor suppressor genes, such as TP53 and cyclin-dependent kinase inhibitor proteins (32). In addition, vitamin D has the ability to induce apoptosis and inhibit angiogenesis (32).

2.2.2.3 Melatonin and Serotonin

Melatonin and serotonin play a vital role in maintaining the body's circadian rhythm (internal clock). Melatonin is produced by the pineal gland in the brain in the absence of daylight and is necessary to put the body in a sleep-ready state (33). The

precursor to melatonin is serotonin, which is acetylated and methylated to yield melatonin (33). Light at night can lead to a reduction in melatonin and result in a disruption in the body's circadian rhythm (33). Serotonin, on the other hand, is released with exposure to the sun, therefore insufficient time spent in the sun could lower serotonin levels and thereby melatonin at night (33).

Melatonin has a suggested protective effect against cancer through the reduction of proinflammatory cytokine production and its role as an immunomodulator (34,35). Melatonin can also prevent tumour development by inhibiting angiogenesis and has anti-apoptotic properties (36). Melatonin also acts as an antioxidant, which can neutralize free radicals – limiting their carcinogenic potential (37).

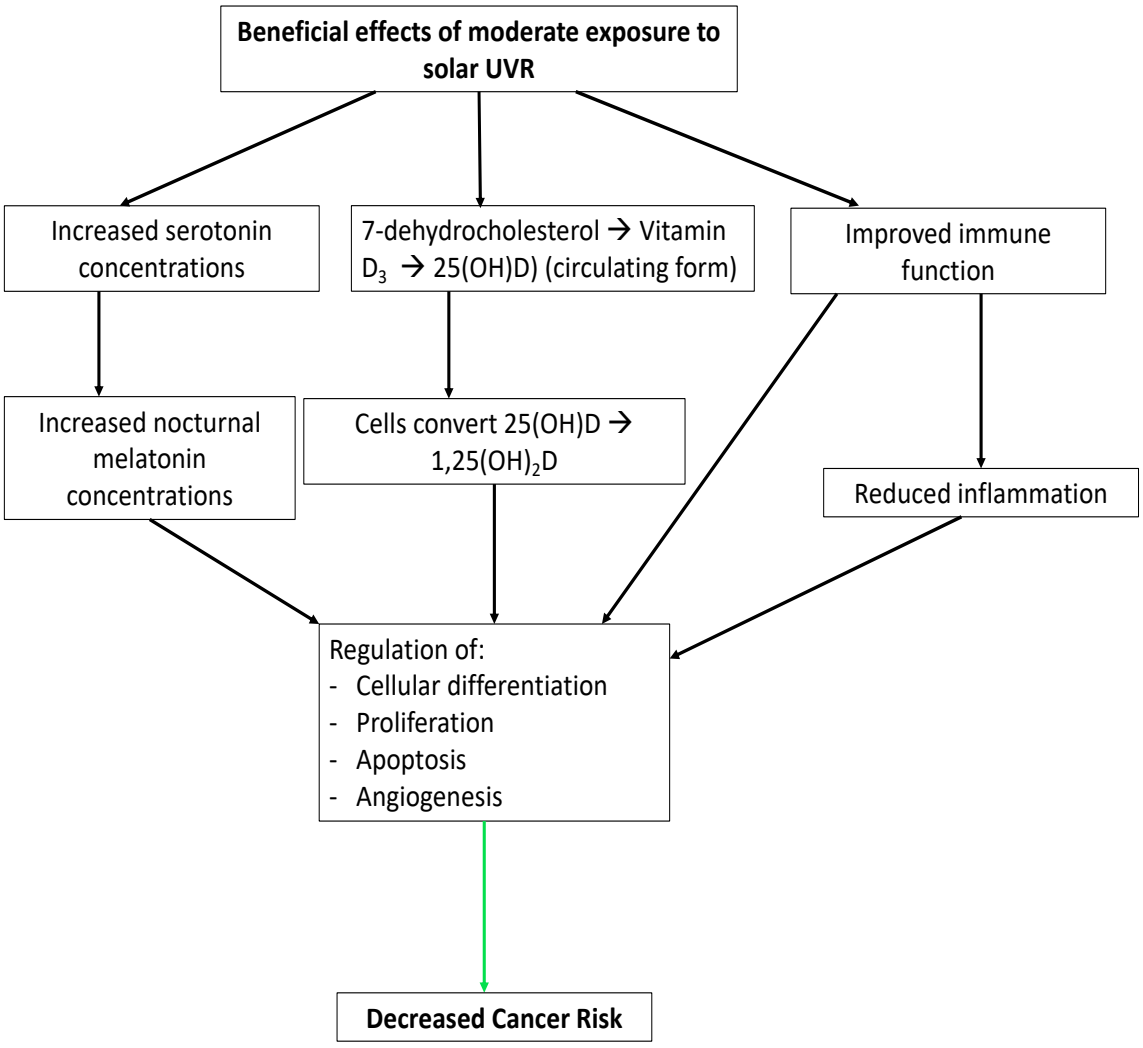

Figure 2.2 Summary of the beneficial effects of ultraviolet radiation

2.2.3 UVR in Canada

Ultraviolet radiation exposure is highly variable and dependent on geographical location. Due to being located at a northern latitude, Canada does not have consistent exposure to solar UVR. That is, Canadians go long periods of time with little exposure to the sun in winter months and then a few months of potentially intense exposure. Direct sun exposure during the winter months is limited since the cold temperatures lead to the

majority of skin being covered. Shorter days from October to March have reduced daylight hours, leading to lower vitamin D levels and potential circadian disruptions (38,39). Despite the conscious efforts of Canadians to reach the suggested levels of vitamin D through diet and supplementation, most Canadians fail to meet recommended levels of vitamin D (40) largely in relation to limited time spent outdoors and insufficient solar UVR during winter months. More importantly, using serum vitamin D measurements, the Canadian Health Measures Survey found that over a third of Canadians were vitamin D insufficient (41). During summer months, on the other hand, nearly one third of Canadians spend greater than two hours a day in the sun and one third had at least one sunburn (42-44). In addition, ambient UVR in Canada varies considerably due to difference in latitude, altitude, and cloud coverage. For example, Calgary, Alberta, though at lower latitude than the national average, is situated at a higher latitude and elevation than most major metropolitan areas and receives mores hours of sunshine per year than other cities across Canada (38).

The nature of exposure to artificial tanning devices also varies geographically due to disparate restrictions across countries. While Brazil and Australia have banned indoor tanning devices (45), Canada only restricts use to those over the age of 18 (46). However, minors can still use tanning devices with signed consent from a guardian. Similar to other countries, indoor tanning users in Canada are required to wear protective glasses and all commercial equipment must display labels that detail the health risks of indoor tanning, including that it can cause cancer (46). While indoor tanning devices in Europe are limited in intensity to an ultraviolet index of 12, there are no restrictions in terms of intensity, frequency, or duration of use in Canada for owners or users (45). In 2006, the

past year use of indoor tanning devices in Canada for individuals over the age of 16 was estimated to be 9% (43). No previous study has estimated the lifetime use of indoor tanning devices in Canada.

2.3 Ultraviolet Radiation and Skin Cancer

2.3.1 Anatomy of the Skin

The skin is the largest organ in the body and is made of three distinct layers: the epidermis, dermis, and the hypodermis (47). The epidermis is the outermost layer that provides a waterproof barrier for the body and creates skin tone (47). The dermis is below the epidermis and contains connective tissue, hair follicles, and sweat glands (47). The hypodermis is the lowest part of the skin and is made of fat and connective tissue (47). The epidermis is made up of keratinocytes, melanocytes, and Langerhans cells (47). Keratinocytes make up approximately 95% of cells in the epidermis and include basal and squamous cells (47). Basal cells produce new skin cells as old ones die off, while squamous cells are flat, thin cells that begin in the middle layer of the epidermis, eventually move to the outer layer (47). The skin's color is created by melanocytes, which produce the pigment melanin. The epidermis is also composed of Langerhans cells (immune cells), which initiate responses to skin damage (47).

2.3.2 Descriptive Epidemiology of Skin Cancer

An estimated 8,000 new cases of melanoma in 2020 (48) and 78,300 new cases of NMSC were diagnosed in 2015 in Canada (49). Melanoma is the deadliest form of skin cancer, and while it is most common among older adults, it has become the one of the most common cancers among young adults (< 50 years of age) in Canada (50). Among NMSC cases, approximately 77% are basal cell carcinoma (BCC) and 23% squamous

cell carcinoma (SCC) (50). BCC has a high survival rate and tends to occur in younger individuals, while SCC has a greater propensity to metastasize and typically occurs in older adults (51). Although rarely fatal the high incidence of NMSC results in a significant burden of disease in terms of morbidity (52) and health care costs (53). In addition, individuals that develop NMSC are at an increased risk of developing subsequent NMSCs and are also at an increased risk for developing melanoma and some non-cutaneous cancers (54).

In contrast to other cancer sites, early stage melanomas are often treated in an outpatient setting where automated surveillance systems do not always exist, and are therefore susceptible to underreporting (55). While underreporting is still a small concern for melanoma in Canada, evidence from Ontario suggests that nearly all cases are now being captured (56). NMSC, on the other hand, is almost exclusively treated outside of a hospital and many without histologic confirmation, such that it is difficult to record these as cancer events. Because of this, many cancer registries in Canada do not attempt to register cases of NMSC. Of the six provinces (Saskatchewan, Alberta, Manitoba, Quebec, New Brunswick, and Newfoundland and Labrador) that currently register NMSC cases, Manitoba is the only registry that has historically collected incidence data (50).

The incidence rate of both melanoma and NMSCs increases exponentially with age. The rate of melanoma is less than 20 cases per 100,000 for adults under the age of 50, but increases to 85 cases per 100,000 for men between 85 and 90 and to 40 cases per 100,000 for women between the ages of 80 and 85 (50). Prior to the age of 50, BCC is less than 175 cases per 100,000 and SCC is under 25 cases per 100,000 for both sexes. After the age of 80, BCC increases to 1000 cases per 100,000 for men and 650 cases per

100,000 for women, while SCC increases to 825 cases per 100,000 for men and 475 cases per 100,00 for women. With the exception of women under the age of 40, men have a higher incidence of melanoma and BCC in Canada and the US (50,57). The higher incidence among young women is hypothesized to be due to greater exposure to UVR, while the higher incidence for middle aged and older men is hypothesized to be partially androgen driven (58). All three of the primary types of skin cancer disproportionately occur in Caucasian populations and among individuals with light skin tones. Risk of melanoma in Caucasians is 10-15 times higher than for non-white Hispanics and Aboriginals, and more than 20 times greater than the risk for Asians and Blacks (59). This disparity in the incidence of skin cancer by ethnicity reflects an extreme interaction between skin pigmentation and UVR exposure (59). However, there are also likely other genetic factors, such as DNA repair variants that contribute to the low incidence among Asians (60). Within ethnic groups there is some evidence that the biologic effects of UVR can vary based on skin pigmentation (61), but there is limited research on differences in skin cancer risk (62).

2.3.3 Risk Factors for Skin Cancer

While UVR exposure, both from the sun and artificially through indoor tanning, is considered the most prominent risk factor for melanoma, it is also associated with a family history of skin cancer, a weakened immune system, and the number of moles, as well as the presence of atypical nevi – from which melanomas typically develop (63). While the number of moles and presence of atypical nevi have a strong hereditary basis, they can also arise from exposure to UVR, and therefore represent unique risk factors in that they can be both independent risk factors and/or mediators of the UVR-melanoma

relationship (64). Other possible risk factors are exposure to ionizing radiation, pesticides, fluorescent lighting, PUVA (psoralen and ultraviolet A) therapy, and alcohol consumption (63). Unlike melanoma, NMSCs do not develop from nevi and do not have a pre-neoplastic lesion. In addition to UVR exposure, common risk factors for NMSC include ionizing radiation, arsenic exposure, PUVA therapy, and a weakened immune system (51). There is some evidence that skin-related exposure such as photosensitizing agents and skin trauma are associated with NMSC, but it is inconclusive (51). Similarly, there is limited evidence of associations for lifestyle/behavioural factors, such as that alcohol consumption, smoking, and HPV infection (51).

2.3.4 UVR and Skin Cancer

Epidemiologic evidence for the causal role of UVR exposure in the development of skin cancer is conclusive (1). Ambient UVR is strongest at low latitudes and descriptive studies of Caucasian populations show positive association between the incidence of skin cancer and residence proximal to the equator (59). Evidence from a large number of case–control and cohort studies is generally consistent with positive associations with residence in sunny environments throughout life, in early life and even for short periods in early adult life with all types of skin cancer (59). The body site distribution of skin cancer favors sites usually exposed to the sun, such as the head and neck or the forearms (65). Finally, individuals with a history of solar keratoses (a marker of accumulated sun exposure) are at an increased of melanoma (66).

Independent from the effect of latitude, the behavioral patterns of UVR exposure associated with the three types of skin cancer are complex and in some cases divergent. Positive associations are consistently observed between a history of sunburn and

measures of intermittent exposure to the sun (such as particular sun-intensive activities, outdoor recreation or vacations) and melanoma, as well as for BCC (66-68). In contrast, chronic sun exposure (such as through occupation) may be associated with a small reduction in melanoma risk (overall) in comparison to intermittent exposure (59), but is a prominent risk factor for SCC (59) and BCC (68). The lower risk of melanoma associated with chronic exposure is only observed at high latitudes, such as in Canada. This relationship is hypothesized to be an artificial product of including individuals with high levels of intermittent exposure in the referent group, rather than a true biological relationship (59). However, chronic exposure may lead to greater melanin production, which could protect the skin from some potential damage arising from intermittent exposures (59). While these are the general relationships, there is some variation among less common subtypes of melanoma and BCC. All three of the primary types of skin cancer demonstrate positive associations with the use of indoor tanning devices (69,70). However, the risk of skin cancer associated with indoor tanning is dependent on the strength of and time allowed in the device – for which regulations differ considerably across countries (45).

2.3.5 Sun Protection Methods and Skin Cancer

Recommendations to reduce the harmful effects of solar UVR to the skin include sun avoidance during peak hours of the day, skin coverage via clothing and hats, seeking shade, and use of sunscreen with a high sun protection factor. Among the public in Canada, sunscreen use tends to be the most prominent sun protection method followed by sun avoidance and protective clothing (44). Despite the perception that sunscreen is protective against developing skin cancer, randomized controlled trials and epidemiologic

studies on this relationship have been inconsistent. Among the conducted randomized trials of sunscreen use, there has been evidence that regular sunscreen use can reduce the incidence of solar keratoses (71), SCC (72), and melanoma among phenotypically susceptible individuals (73). No protective effect was observed for the single trial on sunscreen use and BCC (72). All of the randomized trials were conducted in Australia, which has some of the highest ambient UVR in the world, and therefore makes the results difficult to generalize. Moreover, it is difficult to generalize results from randomized trials with controlled environments to real world conditions. Specifically, sunscreen would likely be applied more thoroughly and consistently when under investigation compared to a real world setting. A recent meta-analysis found that there was no overall association between the risk of melanoma and non-melanoma skin cancers with the use of sunscreen (74). Interestingly, this study also observed that at higher latitudes, sunscreen appeared to be less effective in preventing skin cancer (74). It has been hypothesized the lack of a relationship between sunscreen use and skin cancer could be due to compensation with greater sun exposure due to the belief of sufficient protection (75). Beyond the use of sunscreen, there are few studies that have assessed the relationship of other sun protection methods and the risk of skin cancer. Therefore, while these methods likely protect against skin cancer, the magnitude of this protective effect is unknown, particularly in countries at northern latitudes, such as Canada.

2.3.6 UVR Exposure and Skin Cancer in Canada

Given that risk estimates for sun exposure and indoor tanning are dependent on latitude and the regulations of indoor tanning devices vary by country, it is important to consider Canadian relevant studies. Only two studies in Canada have assessed the

relationship of intermittent sun exposure and sunburn with the risk of developing melanoma and both studies observed increased risks for both risk factors (76,77). One study assessed the relationship between sunburn and the risk of NMSC subtypes finding increased risks for both basal and squamous cell carcinomas (78). No studies in Canada, however, have assessed the relationship of intermittent sun exposure with the development of NMSC. In terms of indoor tanning, only one study for melanoma and one for the subtypes of NMSC have been conducted in Canada – both studies observed increased risks with the ever use of indoor tanning devices (76,79). In addition to providing risk estimates that are relevant to Canada, these studies provide Canadian specific prevalence estimates for ever engaging in UVR risk behaviours.

Two population-based surveys have been conducted to estimate the prevalence of risk factors for skin cancer in Canada. The Canadian Community Health Survey (CCHS) is an annual survey that captures the prevalence of indoor tanning and sunburn, but does not capture intermittent sun exposures, such as sunbathing. In contrast, the 2006 Second National Sun Survey (NSS2) captures information on all UVR risk factors and their joint distributions – providing a comprehensive assessment of these behaviours in Canada (42).

2.4 UVR and Non-Cutaneous Cancer Risk

A certain level of exposure to solar UVR may be protective for non-cutaneous cancer sites through improved immune function, production of vitamin D, and maintenance of normal circadian rhythm patterns. On the other hand, higher levels of exposure to UVR may increase the risk of developing non-cutaneous cancers through mechanisms of immune suppression (80), inflammation (21), oxidative stress (81) and

DNA methylation aberrations (26). The literature on non-cutaneous cancer sites is focused primarily on non-Hodgkin lymphoma (NHL), breast cancer, colorectal cancer, and prostate cancer (3). Of these non-cutaneous cancer sites, NHL is the most studied, and the current literature provides some evidence for a potential U shape relationship. That is, moderate exposure is protective, whereas higher levels of exposure are not protective and may even increase the risk of developing NHL.

2.5 Ultraviolet Radiation and Non-Hodgkin Lymphoma

2.5.1 Non-Hodgkin Lymphoma

NHL is the most common hematologic malignancy in the world and occurs most commonly in North America, Europe, and Australia (82). NHL is a heterogenous group of malignant neoplasms of the lymphoid tissues and consists of more than 40 major subtypes with distinct genetic, morphologic, and clinical features (83). The most common subtypes include diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), follicular lymphoma, peripheral T-cell lymphoma, marginal zone lymphoma, and Burkitt lymphoma (83). These subtypes are commonly combined into B-cell and T-cell lymphomas, where B-cell lymphomas comprise approximately 85% of NHL cases (83).

2.5.2 NHL Incidence and Mortality in Canada

In 2020, NHL is projected to comprise 4.6% of cancer incidence in Canada, accounting for 10,400 total cases (48). NHL also contributes considerably to mortality in Canada, accounting for a projected 3.5% of cancer-related deaths in 2020 (48). The occurrence of NHL is higher in men than in women (84) and disproportionately occurs among Caucasians and older individuals (84). While the risk of NHL increases with age,

it is also a common cancer among children, adolescents, and young adults (48). In combination with Hodgkin lymphoma, NHL is the third most common cancer among children, and the fifth most common cancer among adolescents and young adults (< 50 years of age) in Canada (48). There is great geographical variation in the incidence of NHL with the highest rates occurring in North America, Europe and Oceania (84). However, there are also several African countries that have a high incidence of NHL, but the incidence on the continent is highly variable across countries and is largely attributable to infectious agents (84). Between 1983 and 2015 the age-standardized incidence rate of NHL has annually increased by 1.3% in Canada, making it one of the fastest increasing cancers among both sexes in Canada (85). Despite this continued increase in the incidence of NHL, risk factors are largely unknown. Given the large geographic variation in incidence of NHL and that hereditary factors are hypothesized to only account for a small percentage of cases, the exploration and confirmation of the role of modifiable risk factors implicated in the etiology of these cancers is warranted.

2.5.3 Established and Suspected Risk Factors

2.5.3.1 Genetic

The only established genetic risk factor for NHL is having a first degree relative (parent, child, or sibling) that has had NHL (86,87). In addition to family history of NHL, there is some evidence that specific inherited mutations or genetic variants increase the risk of NHL. Germline mutations in genes involved in DNA repair and immunodeficiency have been associated with the development of NHL, but none of these have sufficient evidence to be confirmed risk factors. Evidence from a large international pooled analysis of case-control studies indicate that single nucleotide polymorphisms in

tumor necrosis factor and interleukin-10 genes, which are involved in inflammatory and immune responses are associated with an increased risk of NHL (88). This association was especially strong for diffuse large B-cell lymphomas – the most common subtype of NHL. There is also evidence that polymorphisms in genes involved in the human leukocyte antigen complex are associated with an increased risk of NHL (89). There is inconsistent evidence from case-control studies that gene variants involved in folate metabolism, which affect DNA synthesis and methylation are associated with an increased risk of NHL (84). Overall, there is limited evidence of genetic factors involved in the etiology of NHL, and hereditary factors are hypothesized to account for a small percentage of cases.

2.5.3.2 Medical Conditions and Medications

Increased risk of NHL is associated with several autoimmune disorders, including rheumatoid arthritis, celiac disease, systemic lupus erythematosus and Sjogren's syndrome (84). Autoimmune disorders are suspected to increase the risk of NHL due to altered T-cell function, which may inhibit full immune responses toward emerging malignant cells (90). It is also suspected that chronic inflammation from the disorder plays a role in promoting the development of distant NHL. While the associated risks are high, the occurrence of these diseases are rare and therefore contribute to a low proportion of NHL cases. A small increased risk with type II diabetes has been observed in several studies, but the underlying mechanism underlying this relationship is not well understood (91). It is hypothesized that individuals with diabetes have altered immune function induced by chronic inflammation, and that this may contribute to cell proliferation of lymphocytes (92). An increased risk of NHL with the previous diagnosis

of other hematologic malignancies, breast cancer, and skin cancer have been observed (84). Potential mechanisms underlying these relationships include inherited susceptibility to cancer, exposure to a shared causative agent, immunosuppression from the malignancy, or as a result of treatment for the cancer (radiation or chemotherapy) (84).

Consistent associations with immunosuppression therapy including non-steroidal anti-inflammatory drugs, corticosteroids, and immunosuppressants for conditions such as inflammatory bowel disease and autoimmune disorders have been observed (84). However, it is possible that these associations are a product of confounding by indication since the conditions that prompt treatment could also be related to the development of NHL. The risk of NHL with an organ or bone marrow transplantation has been consistently reported, but only accounts for a small proportion of cases (84). Several vaccinations have been associated with a decreased risk of NHL, while an increased risk with the Bacille Calmette-Guerin vaccination has been observed – the mechanism behind this remains unclear (84).

2.5.3.3 Infectious Agents

Several infectious agents have been linked to an increased risk of NHL overall or for specific subtypes. An increased risk of NHL with having human immunodeficiency viruses (HIV)/AIDS has been consistently reported with risks over 100 for B-cell lymphomas (93). Hepatitis C virus infection is associated with a small but consistent increased risk of NHL (94,95). Additionally, helicobacter pylori, a virus primarily implicated in causing stomach cancers, is associated with mucosa-associated lymphoid tissue tumors and possibly certain types of B-cell lymphomas (96). Finally, Epstein-Barr virus, a ubiquitous human herpesvirus that infects greater than 90% of the worldwide

population, is implicated as a co-factor for the development of NHL among immunodeficient patients (97). Despite several infectious agents being associated with increased risk of NHL, the majority are only associated with specific subtypes or the prevalence of the infectious agents on a population level are relatively low. Indeed, a recent study estimated that only 0.3% of NHL cases in Canada are attributable to infections (98).

2.5.3.4 Occupation

There are no established occupational exposures that increase the risk of NHL. There is some evidence that certain occupations are at increased risk of NHL, including farmers, hair dressers and barbers, welders, and people who work in certain industries, such as rubber, printing and forestry (99,100). The most plausible occupational exposures linked to an increased risk of NHL are exposure to pesticides (100,101), and benzene (102).

2.5.3.5 Lifestyle Factors

There are currently no lifestyle behaviours that are established risk factors for the development of NHL. The lifestyle factors with the strongest evidence for a link to NHL include alcohol consumption and excess weight. Alcohol consumption has been linked to a decreased risk of NHL in both case-control and cohort studies (103). The reason for this relationship is unclear, but it has been postulated that moderate consumption of alcohol may enhance immune response and that antioxidants that are found in some alcoholic beverages could improve insulin sensitivity (103). Overweight and obese BMI were associated with increased risk of NHL in a large meta-analysis (104). Despite strong relationships with many cancer sites, there is little evidence that tobacco smoking and

physical activity are associated with the risk of developing NHL. Smoking was weakly associated with the risk of NHL in a recent meta-analysis, but this association was mainly driven by an association with T-cell lymphomas (105). In a meta-analysis of 13 studies, physical activity was associated with a small decreased risk of NHL, but only among individuals in the highest exposure category (106). A recent Canadian study provides some evidence that vigorous lifetime physical activity is associated with a lower risk of NHL, while moderate and low-intensity physical activity is not (107). In terms of diet, vegetable intake or fruits and vegetables combined, but not fruits alone is associated with a decreased risk of NHL (108). Red meat consumption has been associated with an increased risk of NHL, but the findings primarily come from case-control studies and there is a high degree of heterogeniety across studies (109). Frequent use of hair dyes, especially among females has been consistently associated with a higher risk of NHL (110). There is limited evidence for relationships with reproductive factors and NHL risk, such as menopause, age at menarche, age at first birth, use of oral contraceptives, or use of hormone replacement therapy (84,111). A few studies have observed that long sleep durations were associated with an increased risk of NHL (112,113). Long sleep durations may be related to the presence of comorbidities or chronic health conditions that contribute to poor quality sleep, but these comorbidities may confound this relationship. However, there is plausibility that long sleep durations lead to circadian rhythm disruption and increase the risk of NHL through that mechanism.

Table 2.1 Risk Factors for Non-Hodgkin Lymphoma

Risk Factors	Established	Suspected	Limited Evidence
Genetic	Family history of NHL	Germline mutations in DNA repair	SNPs involved in folate metabolism
		SNPs in human leukocyte antigen complex	
		SNPs in tumor necrosis factor genes	
		SNPs in interleukin-10 genes	
Medical Conditions	Autoimmune disorders	Type II Diabetes	
	Immunodeficient disorders		
Medications	Immunosuppressant drugs		
	Previous cancer treatment		
Infectious Agents	HIV/AIDS	Helicobacter pylori	
	Hepatitis C		
	Epstein-Barr virus (immuno-suppressed only)		
Occupational exposures		Pesticides	
		Benzene	
Lifestyle Factors		Solar ultraviolet radiation	Smoking
		Alcohol consumption	Physical inactivity
		Excess body weight	Fruit and vegetable consumption
			Meat consumption
			Sleep duration
			Hair dyes

Abbreviations: AIDS = Acquired immunodeficiency syndrome; HIV = Human immunodeficiency viruses; SNP = single nucleotide polymorphism

2.5.3.6 Solar UVR and NHL Risk

In epidemiologic studies, the relationship between solar UVR and NHL risk has been investigated in relation to residence history linked to ambient UVR, recreational sun behaviour, total time spent in the sun, and occupational exposure (114). In addition, the relationship between a history of NMSC occurrence (as a proxy for chronic solar UVR exposure) has been examined in relation to the risk of subsequent development of non-cutaneous malignancies. In reviewing the epidemiologic literature on solar UVR exposures and NHL risk I have focused on studies of cancer incidence and not included mortality studies – since mortality outcomes are potentially problematic due to a plausible effect of UVR and vitamin D on cancer survival. In addition, ecologic studies were excluded from this review due to the methodological limitations of the ecologic fallacy (occurring when associations of groups of individuals are not the same as those for individuals) and confounding.

A recent meta-analysis on vitamin D status and the risk of developing NHL has summarized the evidence pertaining to UVR exposure, vitamin D, and NHL risk (114). When combining all types of exposure measures for UVR, Park et al. observed a significant lower risk of NHL associated with higher exposure to UVR. This association was more protective in case-control studies than cohort studies, indicating the potential for recall or selection bias among case-control studies or greater non-differential misclassification of exposure in cohort studies. Cohort studies typically make use of baseline exposure data, which is subject to imprecise measurement compared to complete exposure histories that can be ascertained in case-control studies. In contrast, dietary

vitamin D intake and serum/plasma 25-hydroxyvitamin D levels were not associated with the risk of NHL. The results of this meta-analysis are difficult to interpret, however, since pooling of disparate types of exposure to UVR can obscure a more nuanced relationship.

Among the included studies, four examined the association of ambient UVR and the risk of NHL. Of the prospective cohort studies, two observed lower risks with residence at higher ambient UVR (115,116), while one study observed a higher risk (117). The one case-control study observed a significant lower risk of NHL with increasing ambient UVR levels (118). Studies on ambient UVR do not account for variation in sun exposure habits and are therefore difficult to make causal inferences from those studies. It is plausible that living in an area with high levels of ambient UVR would be associated with less time in the sun, necessitating the consideration of ambient UVR only in the context of sun behaviour habits.

In a pooled analysis of 5 published and 5 unpublished case-control studies, the InterLymph Consortium observed a significant protective effect for lifetime recreational time spent in the sun (weekend exposure), but not for total time spent in the sun (119). Total time spent in the sun 10 years prior to diagnosis was associated with a decreased risk of NHL – indicating that exposure later in life might be of particular importance (119). Additionally, there was some evidence that exposure at lower latitudes was more protective and that B-cell lymphomas were more strongly associated compared to T-cell lymphomas. In contrast, one study observed a lower risk of NHL associated with recreational sun exposure during teenage years (120). Beyond the pooled analysis, three case-control studies have observed decreased risks of NHL associated with recreational sun exposure (121-123) and two other case-control studies have observed a lower risk of

NHL associated with total time spent in the sun (124,125). In contrast, two case-control studies found no evidence of an association with time spent in the sun (118,126), and two other studies observed higher risk of NHL associated with higher levels of time spent in the sun (127,128). Only two prospective cohort studies have been conducted on this relationship (115,129). Compared to less than 7 hours in the sun per week between the ages of 20-39, Freedman et al., 2010 observed relative risks of 1.26 (95% CI: 0.80-1.96) for 7-14 hours per week, 0.82 (95% CI: 0.49-1.36) for 14-21 hours per week, and 0.71 (95% CI: 0.41-1.22) for greater than or equal to 21 hours per week (115). This study relied on a follow-up questionnaire to determine outcome status, which could have led to some selection bias that may have biased the results of the study. Compared to less than one sunbathing vacation per year between the ages of 10-39, Veierød et al., 2010 observed a relative risk of 1.00 (0.64-1.54) associated with one or more sunbathing vacations per year during that age period (129).

Evidence for a relationship of high levels of chronic exposure to the sun and NHL come from studies on previous NMSCs and occupational exposures. A strong body of evidence supports an association of the occurrence of NMSC with elevated risk for developing other malignancies (particularly NHL), providing some evidence of a potential relationship between chronic sun exposure and risk for NHL (54). However, it is also plausible that this association is due to common genetic factors, such as polymorphisms in DNA repair or cell cycle control, which could be common risk factors for NMSC and other cancer sites. In a recent meta-analysis occupational sun exposure was significantly associated with developing NHL – providing some more definitive evidence of a potential increased risk with high levels of exposure (130). Overall, the current literature on exposure to solar UVR and NHL risk indicates a potential U-shape relationship.

2.5.3.7 Limitations of Previous Research

One of the major limitations of the current body of literature on the relationship of exposure to solar UVR and NHL risk is that the majority of the evidence for a protective relationship comes from case-control studies (114). Case-control studies are potentially subject to recall and selection bias, since the outcome has already occurred when participants consent to the study. While the degree of recall bias is difficult to determine, indications of selection bias can be deduced from examining response rates among cases and controls. If response rates are low and differential between cases and controls there is potential that entry into the study was related to the exposure and could bias effect estimates. The pooled analysis by Kricker et al. had response rates of 70% for cases and 50% for controls (119) – indicating the potential for selection bias. Similar patterns of response rates occurred in several of the other case-control studies examining the relationship of exposure to solar UVR and NHL risk. Given the potential for both recall and selection bias among this literature, prospective cohort studies with detailed exposure assessment and little loss to follow-up would provide further evidence for a true relationship between UVR and NHL risk. Of the two prospective cohort studies on this relationship, Freedman et al., 2010 relied on a follow-up questionnaire to determine outcome status, which could have led to some selection bias that may have biased the results of the study (115). Specifically, if a subset of participants that developed NHL dropped out of the study before the follow-up questionnaire and if the loss to follow-up was related to time spent in the sun then the results of the study would be biased. The other prospective cohort study focused on sunbathing vacations, which does not adequately capture the full extent of exposure to solar UVR (129). In addition to the

potential for recall and selection bias, several studies only adjusted for age, sex, and sun sensitivity in their analysis. In particular, adjustment for ambient UVR is important since it could influence the amount of time spent in the sun. Moreover, with the emergence of new suspected risk factors for NHL, it important to conduct studies that adjust for all established and potential risk factors that may also be associated with time spent in the sun, including alcohol consumption, excess weight, diet, smoking, and physical activity (84).

From an analytic standpoint, there is a lack of studies that have examined the shape of the relationship of time spent in the sun with meaningful categories. That is, many studies used study-defined categories (quartiles) that are difficult to compare across studies and to inform potential prevention efforts. Study-defined categories also make it difficult to examine potential non-linear relationships since the distribution within a study can result in categories of exposure that are awkwardly distanced. Nonetheless, estimates from disparate study categories can be combined using advanced non-linear meta-analysis methods. More importantly, there is a lack of studies that examine the influence of different patterns of exposure on this relationship. Studies that have examined different patterns of time in the sun with the risk of developing NHL have done so by examining the risk associated with weekday and weekend exposures separately. It is imperative to incorporate combinations of working and non-working days, since different combinations (consistent or intermittent) could have divergent biological effects. Finally, the use of sun protection methods may modify the relationship of time spent in the sun and NHL risk, but no previous studies have examined this.

2.5.3.8 Biological Plausibility of the Relationship of Solar UVR and NHL

Potential biological mechanisms underlying a protective relationship between moderate levels of exposure to solar UVR and NHL are through enhanced immune function, synthesis of vitamin D, and circadian rhythm maintenance. Solar UVR has be shown to upregulate TH-2 cells, which are required for humoral immunity against tumor associated antigens and help to regulate anti-inflammatory responses (30). In addition, low doses of blue light irradiation from the sun can trigger the synthesis of hydrogen peroxide in T cells, which has been shown to enhance T-cell motility (28). Moderate levels of sun exposure can also promote vitamin D synthesis and circadian rhythm maintenance through regulation of melatonin and serotonin – both of which have been shown to have antiproliferative effects (131). However, dietary vitamin D intake and serum/plasma 25-hydroxyvitamin D levels have not been shown to be protective against the development of NHL (114). There is some evidence that shift-work is associated with an increased risk of hematologic cancers (132), which provides support for the circadian rhythm maintenance mechanism.

Potential biologic mechanisms underlying a relationship between high cumulative levels of UVR and risk of NHL include immune suppression, inflammation, oxidative stress and alterations to the epigenome. High levels of UVR exposure can induce systemic suppression of the immune system's ability to detect and attack malignant cells (80). Immune suppression through other pathways, such as infectious agents or treatments that weaken immune function are strongly linked to the risk of hematologic malignancies (133). The induction of lymphoid malignancies, mainly in the spleen and liver, in genetically modified mice exposed to solar-simulated UVR suggests that UVR-induced immune suppression

might increase cancer risk at body sites distant from the site of UVR exposure (134). Additionally, there is considerable evidence that melanoma can manifest in body site locations distal of localized UVR, suggesting a systemic effect (135). In addition, UVR can induce pro-inflammatory cytokine production (136), which has been linked to an increased risk of a number of cancer sites, including NHL (137). Alterations to the DNA methylome can occur through degradation of folate (dysregulation of methyl donation in one-carbon metabolism) or indirectly from oxidative stress (reactive oxygen species) (26).

2.6 Population Attributable Risk

The population attributable risk (PAR), also referred to as population attributable fraction, is the proportion of a disease in a specific population that is attributable to a specific exposure (138). A PAR represents the proportion of a disease that could be prevented if the exposure was theoretically removed from a population and therefore informs public health interventions. PARs assume a causal relationship between the exposure and disease, and that there is a conceivable counterfactual where the exposure can be eliminated. PAR estimates for modifiable exposures are necessary for decision-makers and public health practitioners to prioritize targets for prevention. A population impact fraction (PIF) is an extension of a PAR and is based on situations where complete removal of an exposure is an unreasonable assumption. The PIF represents the potential burden of disease that could be prevented under different counterfactual scenarios and are important for informing decision making and evaluating the costs and benefits of specific interventions (139).

PARs can be estimated in relation to cancer where cancers are caused by risk factors related to lifestyle, environment, infectious agents, or occupational exposure that

can be reduced or eliminated. Given that PARs are based partly on risk factor prevalence, they are population and time specific. Comprehensive PAR estimates for several exposures related to cancer have been conducted for a number of populations, including the United Kingdom (UK) (140), United States (US) (141), Australia (142), France (143), and Brazil (144). In terms of Canada, comprehensive PARs have been estimated for Alberta (145) and Ontario (146). The Canadian Population Attributable Risk of Cancer (ComPARe) study, which was initiated in 2015 and ended in 2019, has estimated PARs and PIFs for several exposures and is the basis for part of this thesis (147). Specifically, this thesis applies PAR and PIF to established relationships between UVR exposure and skin cancer risk.

2.6.1 Population Attributable Risk Methods

2.6.1.1 PAR Formulas and Input

PARs are typically estimated by applying the prevalence of the exposure that is specific to the target population and a relative risk (RR) estimate associated with the exposure that is generalizable to the target population from a meta-analysis to a PAR formula. The most common PAR formula was created by Levin (138), and uses the prevalence of exposure in the population of interest (usually ascertained from population-based surveys), but assumes that there is no confounding in the association between the exposure and disease of interest.

$$PAR = \frac{Pe\ (RR - 1)}{1 + [Pe\ (RR - 1)]}$$

PAR = Population attributable risk

Pe = Prevalence of exposure in the general population

RR = Relative Risk

When using adjusted RRs, Miettinen's formula is preferred, but it requires the prevalence of exposure among cases, which is only available within the data of an individual study, and unavailable when applying RRs to exposure prevalence in a target population (148).

$$PAR = Pc\ X\ \frac{RR - 1}{RR}$$

PAR = Population attributable risk
Pc = Prevalence of exposure among cases
RR = Relative Risk

Therefore, Levin's formula is typically used with confounder adjusted RRs with the caveat that it is an approximation since the formula assumes no confounding (138).

2.6.1.2 Relative Risk

RR estimates for PARs are often used from meta-analyses of relevant studies or from a large cohort study that represents the population of interest. Important considerations for choosing a RR for the exposure-cancer relationship is that the RR is unbiased, is generalizable to the population from which the prevalence estimates are being sampled, and the characterization of being "at risk" is consistent with available prevalence data. In terms of biases, it is important to employ estimates of RR that come from studies where the probability of recall and selection bias are low. It is also important to include studies with adequate exposure measurement, since non-differential misclassification could also have a considerable influence on effect estimates. In

addition, the estimates of RR should come from studies that adjusted for all important confounders.

For many exposure-cancer relationships, unbiased RRs can be generalizable across populations since they are quantifying biological relationships. Instances where this assumption doesn't hold is in cases where exposures have different biological effects by ethnicity or when the nature of the exposure varies geographically. For instance, exposure to UVR has a different effect on the risk of skin cancer depending on ethnicity (skin pigmentation) (59). It would therefore be inappropriate to use RRs from studies of Caucasians to estimate a PAR among non-Caucasians. Environmental exposures, such as air pollution, radon, and UVR can vary geographically, since these exposures are composite measures of intensity and duration, and this needs to be considered in PAR estimates of these exposures. For instance, despite air pollution being measured on a similar scale across studies, the composition of air pollution is not captured, which could have varying biological effects on the risk of lung cancer (149). The composition of air pollution is dependent on the sources of the pollution, which can vary geographically and therefore PAR estimates of air pollution should only include studies that have similar compositions of air pollution as the target population. Ambient UVR also varies by geographic region (59), with countries further from the equator having lower ambient UVR, and therefore relative risks for different sun behaviours would only be generalizable from studies conducted at a similar latitude or distance from the equator.

2.6.1.3 Prevalence of Exposure

A key component of estimating the prevalence of exposure for a PAR estimate is determining an appropriate time between exposure measurement and diagnosis. The

temporal relationship between exposure and cancer diagnosis follows a sequence of relevant exposure period, induction period, latency period and cancer diagnosis. The exposure prevalence of consequence to cancer incidence at a given year is that occurring during the relevant exposure period. This biologically relevant time period from the initiation of exposure to the development of cancer is highly variable and depends on both the exposure and the cancer site. For some exposure-cancer sites, such as smoking and lung cancer, there is adequate literature on this time period and can be used to assign the year of exposure measurement. For other exposure-cancer relationships this period is difficult to determine that a common practice among PAR studies is to assume a 10-year period between exposure measurement and cancer incidence (140). Another option is to use large cohort studies with long follow-up and use the median or mean follow-up time from exposure to cancer diagnosis.

Another important component for determining exposure prevalence is to find a source that is representative of the population of interest and where the measure of the exposure is consistent with the form that was used to determine the RR for the cancer outcome. Prevalence data typically come from population-based surveys since they are most likely to represent the population of interest. In the absence of population-based surveys, a common practice is to use data from large sample cohort studies of the population of interest, which are typically less likely to be representative in comparison to population-based surveys with sampling weights.

2.6.1.4 Combining PAR estimates

When combining PAR estimates for multiple exposures for the same cancer site it is inappropriate to simply sum the estimates since a cancer could have multiple causes.

Therefore, estimates of the burden of cancer attributable to multiple exposures need to consider the overlap between exposures. The ideal scenario would be to estimate a combined PAR by incorporating joint distributions of exposures and the joint RRs of the exposures. However, this information is rarely available and therefore it is common to assume independent exposures and multiplicative RRs. With these assumptions the Miettinen-Steenland and Armstrong approach can be used to determine combined PAR estimates (148,150). When exposures are strongly associated and/or their interaction on cancer risk departs from multiplicative risk, this approach can lead to over or underestimations of the combined PAR depending on the direction of association and the magnitude of departure from multiplicative risk (151).

2.6.2 Population Impact Fraction Methods

Estimates of future PIFs require RRs, prevalence of exposure projections or assumed stable prevalence, cancer incidence projections and counterfactual exposure scenarios. Prevalence of exposure projections require historical prevalence data for the target population and ideally comes from longitudinal surveys that have consistent questions. Prevalence can be modeled in multiple ways including linear, logistic, multinomial logistic or exponential and depend on model fit and expert opinion for realistic projections (147). Cancer incidence can be projected by extrapolating past trends using various statistical models. Trends by age, year of diagnosis (period), year of birth (cohort) and hybrid (152,153) of these can be modeled. The choice of a model is dependent on model fit statistics, expert opinion, and accounting for unusual trends, such as changes in diagnostic definitions or introduction of screening tests, such as the PSA for prostate cancer. Counterfactuals, typically take the form of reductions in prevalence

based on known or hypothetical population interventions or for fixed prevalence reductions of 10%, 25%, and 50%, as some examples.

2.6.3 Population Attributable Risk Methods for UVR and Skin Cancer

The evaluation of the proportion of the total incident cases of melanoma and NMSCs that are attributable to UVR exposure is particularly challenging, since UVR exposure is ubiquitous and is dependent on one's place of residence (6). In addition, there is no truly unexposed population and it is difficult to capture the risk and distribution of relevant types of exposure. Given this challenge, previous PAR studies have relied on the method of estimation that calculates the difference between the skin cancer incidence in the target population and a theoretical 'unexposed' population (141,146,154-158).

$$PAR = \frac{Incidence_{population} - Incidence_{non-exposed}}{Incidence_{population}}$$

A common variant of this approach is to use the skin cancer rates in an earlier birth cohort (with assumed greater skin coverage and lower UVR exposure) as the non-exposed group in a comparison with current skin cancer rates (154). Parkin justified this approach by providing a photo of beachgoers in the 1920s where the majority of their skin was covered with clothing (154). This approach has been employed to estimate the PARs for UVR and melanoma for Ontario (146), the UK (154), France (156), and Australia (158), with PAR estimates of 85%, 85.9%, 83.5%, and 45%, respectively. The higher PARs for Ontario, UK, and France is partly due to the use of an earlier cohort compared to Australia. A limitation of these studies, however, is that they operated under

the assumption that all other independent risk factors and system level factors such as reporting and diagnosis practices were relatively constant between the two cohorts. Given this assumption, the change in incidence in melanoma was solely attributable to increased UVR exposure – primarily behavioral (modifiable) and to some extent higher ambient UVR (less modifiable) – due to ozone depletion (159). However, in most populations this assumption is not satisfied due to shifts in ethnic distribution and improvements in the reporting of skin cancer.

A less common variation is to use the incidence rate on non-exposed body sites in a comparison with the rate of skin cancer on exposed body sites. This approach has been employed for both Australia (157) and France (155), estimating PARs of 97% and 95%, respectively. This approach is typically difficult to implement since it requires detailed anatomical locations of the malignancies, which most cancer registries do not report. A recently used method is to compare skin cancer rates to nearby geographic areas with a lower incidence of skin cancer. This approach provides an estimation of the proportion of skin cancer cases that could be prevented if a population adopted the behaviours of a nearby population, such as another province with lower rates of skin cancer. This approach, however, relies on the assumption that ambient UVR is similar between these populations and that there are no differences in diagnostic or reporting practices of these populations. Additionally, it operates under the assumption that the ethnic distribution of the populations are similar, if the rates are not adjusted. This approach has been employed for both Australia and France, estimating PAFs of 17.7% and 47%, respectively (156,158).

The method of PAR estimation based on prevalence of exposure and RR estimates of non-occupational UVR risk factors (indoor tanning, sunburn, and intermittent UVR exposure) is typically under-used, as the measurement of exposure and the corresponding risk is difficult to capture. However, this approach to PAR estimation is relevant, since it represents the proportion of skin cancer cases that could be reduced by the modification of individual behaviours. Previous studies that have used this approach to estimate a PAR have only done so for one or two of the UVR risk factors (69,156,160-162). In addition, these groups have used summary RR estimates that were derived from meta-analyses that included all published studies. This is problematic in the context of UVR exposure, since ambient UVR is dependent on latitude (59) and regulations for indoor tanning devices vary widely across countries (45). Therefore, these exposures would confer a different risk depending on the geographical context. Moreover, within the category of "ever exposure", which is commonly used in epidemiologic studies of UVR risk factors and skin cancer, there is a broad range of frequency and duration – and in some studies or contexts these may not apply to the population for which the PAR is being estimated. Further, many studies in these meta-analyses do not control for host characteristics or other UVR risk factors, which obscures the independent effect of each UVR risk factor on the risk of skin cancer. Finally, certain studies adjust for factors on the causal pathway, such as the number of nevi, which would inappropriately bias estimates towards the null. The global burden of disease project estimated a risk factor PAR, by averaging study specific PARs using the Miettinen formula (148) for any measure of solar UVR exposure (163). This approach would be susceptible to similar issues mentioned above, and is also difficult to translate to public

health messaging since the estimate is a mix of many different types of exposure. Beyond PAR estimates for UVR risk behaviours and skin cancer, PIF estimates are important for informing potential interventions related to these behaviours. However, only one previous study has conducted this type of analysis for UVR risk behaviours and estimated that approximately 45% of skin cancer cases in four European countries could be prevented in 2050 by protecting people during outdoor work and exposure from UVR during outdoor hobbies (164).

2.7 Cohort Study: The Canadian Partnership for Tomorrow Project

The Canadian Partnership for Tomorrow Project (CPTP) is an ongoing prospective cohort study of Canadians aged 30-74 at the time of enrolment. CPTP is comprised of five provincial and regional cohorts (British Columbia's Generations Project (BCGP), Alberta's Tomorrow Project (ATP), Ontario's Health Study (OHS), Quebec's CARTaGENE (CaG) and Atlantic's Partnership for Tomorrow's Health (Atlantic PATH)) (165). Of these cohorts, each were initiated for different reasons and with different goals. ATP was initiated to support investigations into factors that influence cancer and chronic disease risk (166), while CaG was primarily initiated to support research examining gene-environment interactions and phenotypes on chronic disease risk (167). Both BCGP and OHS were primarily initiated to support a pan-Canadian platform to investigate chronic disease risk factors (168,169). Finally, Atlantic PATH was initiated to investigate risk factors for chronic diseases with a particular focus on exposures that are specific to the Atlantic provinces (170). A visual summary of the cohorts is presented in Figure 2.3.

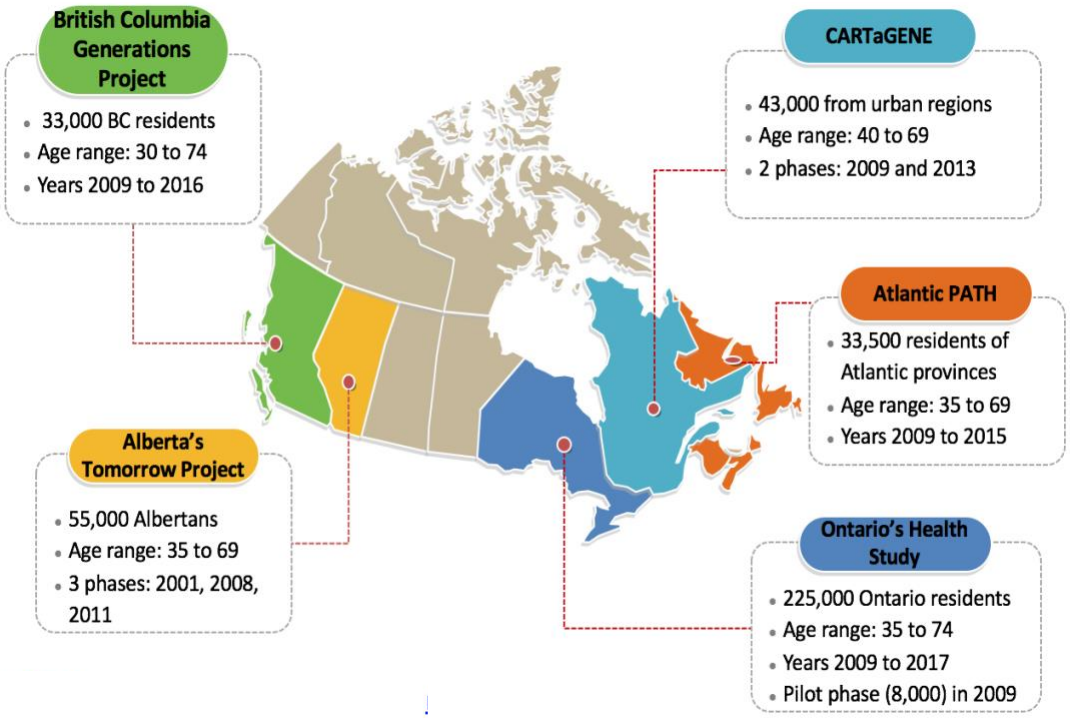

Figure 2.3 Summary of the different cohorts included in the Canadian Partnership for Tomorrow Project

BCGP has enrolled approximately 30,000 British Columbia residents between the ages of 30 and 74 during the years of 2009 to 2016. ATP was initiated in 2001 and has enrolled approximately 55,000 participants between the ages of 35-69 who were enrolled in the study at three different time points – 2001 (phase 1), 2008 (phase 2), and 2011 (phase 3). OHS has recruited over 225,000 Ontario residents in the age range of 35-74 between 2009 and 2017. While the majority of OHS participants were sampled from the entire province, the pilot phase (8,000 participants) only recruited participants from Mississauga, Owen Sound, and Sudbury. CaG has enrolled approximately 43,000 participants between the ages of 40 and 69 who were enrolled in two phases occurring in

2009 and 2013. CaG recruited participants from six regions in Quebec, including Montreal, Quebec City, Sherbrooke, Saguenay, Gatineau, and Trois-Rivieres. Atlantic PATH has enrolled approximately 33,500 participants between 35 and 69 years of age that reside in one of the Atlantic provinces.

Canadian residents were eligible for participation in the regional cohorts if they resided in the province and met the cohort's age criteria. Overall, more than 300,000 participants have enrolled in one of the CPTP cohorts. Each participant of the five cohorts completed a baseline questionnaire, where most of the items were harmonized across cohorts (171). The participants of each cohort gave permission to be linked to cancer registries and health administrative databases, allowing for the assessment of a myriad of exposures with reliable cancer incidence data. ATP, OHS, and BCGP have been linked to their respective provincial cancer registries, while CaG has been linked to administrative databases. These databases include Med Echo for hospital claims and RAMQ for physician billing, which can be used to determine cancer outcomes. Atlantic PATH data has not yet been successfully linked to the cancer registries of the four Atlantic provinces.

Detailed assessment of baseline time spent in the sun, sun sensitivity, and sun protection habits were obtained for the majority of participants of ATP, CaG, and Atlantic PATH, while only for a subset of BCGP and OHS participants (171). In addition, participants provided their residential postal code at baseline which facilitates the linkage of ambient UVR data. The CPTP provides a platform to build on previous studies of solar UVR and non-cutaneous cancer risk by examining the relationship with

time spent in the sun, the influence of sun protection behaviours and different patterns of exposure (chronic or intermittent).

2.8 Summary

Exposure to ultraviolet radiation is a ubiquitous human exposure that could be both beneficial and detrimental to cancer development depending on the type and duration of exposure, as well as the cancer site. Both solar UVR and artificial UVR from indoor tanning devices are established causes of melanoma and NMSC (1,2). On the other hand, moderate amounts of exposure to solar UVR may be protective against some non-cutaneous cancers through improved immune function (30), production of vitamin D (172), and maintenance of normal circadian rhythm patterns (131).

Skin cancer has been increasing in Canada since 1984 and has become a growing burden in terms of morbidity and health care costs (85). Population attributable risks are important estimates that can help inform decision-makers and public health practitioners to identify targets for prevention. There have been no previous PAR studies for UVR exposure or UVR risk factors for Canada. Overall, a reduction in skin cancer begins with an understanding of the UVR exposure patterns across Canada and the quantification of the proportion and number of skin cancer cases attributable to UVR exposure and related UVR behaviours.

In order to set priorities for public health in relation to UVR exposure, and to provide effective communication of the population-level risks associated with UVR exposure to health practitioners and the general public, we also need to understand the relationships with other cancer sites. While there have been studies on the association between exposure to UVR and non-cutaneous cancer sites (3), more research is required.

Of non-cutaneous cancer sites, NHL has the most support in terms of biologic plausibility and has been investigated in several previous studies. However, previous results have mainly come from case-control studies, which are potentially subject to recall and selection bias, and do not fully explore patterns of exposure to UVR (114).

The overall objective of this thesis is to help inform efforts to reduce the burden of cancer in Canada associated with UVR exposure. The first component of this thesis aims to improve and expand upon previous PAR methods for UVR exposure and to provide the first UVR PAF and PIF estimates for melanoma and NMSC for Canada. The final component of this thesis aims to help clarify the relationship of time spent in the sun and the risk of NHL using data from Canadian prospective cohort studies.

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Chapter 3

Methods

3.1 Summary

This chapter provides an overview of the epidemiologic and biostatistical methods used in this thesis. The thesis is presented in manuscript format, and where in-depth descriptions are present in the manuscripts, they are only briefly described here. This chapter focuses on methods which were essential to the completion of this thesis, the design and methodologic decisions made, but where it may not have been possible to completely describe these methodological details in a manuscript. In particular, this chapter is focused on the most important methodological considerations relevant to manuscript 4 (Chapter 7).

3.2 Component 1: Population Attributable Risk and Potential Impact Fractions for UVR and Skin Cancer

The in-depth description of the methods utilized in the first three manuscripts of this thesis can be found in chapters 4-6. Briefly, the focus of these papers were to estimate the current and future burden of skin cancer in Canada associated with ultraviolet radiation (UVR) and UVR risk behaviours (indoor tanning, sunburn, and sunbathing).

Chapter 4 focuses on the estimation of population attributable risks (PARs) for melanoma and non-melanoma skin cancer (NMSC) associated with indoor tanning in Canada. PARs were estimated using Levin's PAR formula (1); relative risk estimates for each skin cancer subtype that were relevant to exposure in Canada were estimated

through our own meta-analyses and the prevalence of indoor tanning was estimated from the Second National Sun Survey (NSS2) (2). Detailed methodological descriptions for the meta-analyses are included in the manuscript.

Chapter 5 focuses on the estimation of PARs and population impact fractions (PIFs) for melanoma in relation to UVR in Canada. The PAR associated with UVR in 2015 was estimated by comparing Canadian melanoma incidence rates in 2015 to estimated incidence rates of a 1920 birth cohort; rates were adjusted for changes in reporting and ethnicity. We estimated PARs for modifiable UVR risk behaviors (sunburn and sunbathing) using prevalence data from the NSS2 (2) and relative risks that were generalizable to Canada from our own meta-analyses of relevant studies. A combined UVR risk behaviour PAR (indoor tanning, sunburn, and sunbathing) was estimated using joint exposure distributions and multiplicative relative risks (3). The future burden of melanoma associated with UVR risk behaviors was estimated using the potential impact fraction framework (3) and potential reductions in exposure prevalence of 10% to 50% from 2018 to 2042.

Chapter 6 focuses on the estimation of PARs for NMSC in relation to UVR in Canada. The PAR associated with UVR in 2015 was estimated using an approach developed by Armstrong and Kricker (4), which compares current incidence rates (2015) with incidence rates on body sites less exposed to UVR (trunk and legs) after adjusting for estimated surface areas of the sites. The same methods utilized in Chapter 5 were used to estimate PARs for modifiable UVR risk behaviours and NMSC.

3.3 Component 2: Time Spent in the Sun and the Risk of Non-Hodgkin Lymphoma

The focus of manuscript 4 (chapter 7) was to investigate the relationship between time spent in the sun and risk of NHL using baseline residence and sun behaviour information from prospective cohorts in Canada (Alberta's Tomorrow Project (ATP) (5), Ontario's Health Study (OHS) (6), and Quebec's CARTaGENE (CaG) (7)). In addition, this chapter sought to determine if the relationship of time spent in the sun and NHL risk varies by the use of sun protection or pattern of exposure (chronic versus intermittent). Several methodologic decisions were made while conducting this study. First, because this study included multiple cohorts and phases within cohorts – which had disparate accrual time periods, study methods, and data elements – pooling the studies required a meta-analytic approach. Second, advanced statistical analyses were required including: using age as the time-scale in cox proportional hazard models and testing interactions using data combined with a meta-analytic approach. This section details the data sources and methodological decisions involved in this study.

3.3.1 The Canadian Partnership for Tomorrow Project (CPTP)

The Canadian Partnership for Tomorrow Project (CPTP) is a prospective cohort study created to examine the effect of genetics, behaviours, family history, and the environment on risk for chronic diseases, including cancer (8). It consists of five regional prospective cohort studies comprised of over 300,000 Canadians aged 30-74 and is the basis for this study (8). Data from three of the five regional cohorts that make up the CPTP (ATP, OHS, and CaG) were used for the analyses included in this thesis. ATP was initiated in 2000 and has enrolled approximately 55,000 participants to date who were enrolled in the study at three different time points – 2001 (phase 1), 2008 (phase 2), and

2011 (phase 3). Only participants in the first two phases of ATP were included in this study since participants in the third phase were not asked questions on time spent in the sun. CaG has enrolled approximately 43,000 participants to date who were enrolled in two phases occurring in 2009 and 2013. Participants were enrolled evenly between the two phases and participants filled out similar questionnaires with respect to sun exposure measures and other lifestyle factors. OHS has recruited over 225,000 Ontario residents between 2009 and 2017. Of these participants, approximately 8,000 were enrolled during the pilot phase of the cohort and approximately 6,000 participants answered questions pertaining to time spent in the sun. Table 3.1 presents the differences and similarities between cohorts and phases of cohorts with respect to exposure variables, potential confounders, and outcome variables.

Table 3.1 Differences and similarities between cohorts and phases of cohorts with respect to exposure variables, potential confounders, and outcome variables

	Cohorts			
	Phase 1 of Alberta's Tomorrow Project	**Phase 2 of Alberta's Tomorrow Project**	**Quebec's CARTaGENE**	**Ontario's Health Study**
Exposures				
Time spent in the sun				
Sun protection				
Patterns of exposure				
UVR related covariates				
Ambient UVR				
Skin tone				
Vitamin D intake				
Potential confounders				
Sex				
Family history of NHL				
Household income				
Body mass index				
Physical activity				
Alcohol consumption				
Tobacco smoking				
Fruits and vegetables				
Meat consumption				
Sleep duration				
Outcome (NHL)				

***Green oval indicates that the variable is present and similar to the majority of the cohorts and phases. Orange oval indicates that the variable is present but in a different form than the majority of cohorts. Red oval indicates that the variable is not present in the dataset. A pie symbol indicates that the variable is present for a subset of the cohort.

3.3.2 Harmonization of Exposure Variables

The primary measure of exposure to ultraviolet radiation in this study was time spent in the sun. In the second phase of ATP and in the other cohorts, participants were questioned about how much time they typically spent in the sun on weekdays and weekends separately and could choose one of the following categories: <30 min/day, 30

min-1 hour/day, 1-2 hours/day, 2-3 hours/day, 3-4 hours/day, and > 4 hours/day. In contrast, participants in the first phase of ATP were asked: "During this past June through August, on a typical day outdoors, approximately how much time did you spend in the sun between 11am and 4pm?" Respondents could choose one of the following categories: <30 min/day, 30 min-1 hour/day, 1-2 hours/day, and >2 hours/day. To harmonize with the first phase of ATP, the midpoint of each category for weekday and weekend was taken. For greater than 4 hours the midpoint used was 4.5 hours. Mid-points were multiplied by 5 for weekday and 2 for weekend, and then these were summed for a weekly total and divided by 7 for a daily total. We then categorized the continuous daily totals to categories that were consistent with the first phase of ATP.

The secondary objective of this study was to explore effect modification of sun protection behaviours on the relationship of time spent in the sun and the risk of NHL. In the second phase of ATP and in the other cohorts, participants were asked how often they used sun protection including sunscreen lotion, hat, or protective clothing when they are in the sun for 30 min or more. Participants could answer: never, rarely, sometimes, often and always. In the first phase of ATP, only a subset of the participants were asked about sun protection behaviours in a follow-up survey conducted in 2004. Participants were asked how often they seek shade, wear a hat, wear protective clothing, use sunscreen on their face, and use sunscreen on the rest of their body when they spend more than 30 min or more in the sun – all in separate questions. Participants could answer: never, rarely, sometimes, often and always. To harmonize these data, we removed the question on seeking shade and took the most protective answer out of the other four questions for each participant. In this study, we considered sun protection for the participants if they

answered often or always. The referent group were participants that typically spend less than 30 min in the sun, while the exposure categories were 30 min to 2 hours/day and greater than 2 hours/day. Each of the exposure categories were stratified by sun protection (yes or no).

The third objective of this study was to explore if there were differences in the relationship of time spent in the sun and risk of NHL by the pattern of exposure (chronic vs. intermittent). For the pattern of exposure analysis we categorized participants based on their exposure during both weekdays and weekends. Since, this analysis requires both weekday and weekend exposure, the first phase of ATP was not included. The referent category for this analysis was participants that typically spend less than 30 min in the sun on both weekdays and weekends. We estimated the risk of NHL compared to this referent category for any combination with a prevalence in the study population > 5%. To test for statistical differences by patterns of exposure we further classified exposure into three categories: intermittent (< 30 min on weekday and > 2 hours on weekend), continuous (> 2 hours on weekdays and weekends), and moderate (all other exposure categories).

3.3.3 Ambient UVR

Since the strength of the sun may be related to how much time an individual spends in the sun and could have differing biologic effects on the human body, we tested ambient UVR as both an effect modifier and confounder. Global UVB surfaces (gIUV) from years 2004-2013 were constructed by Beckham et al. 2014 using data from NASA's ozone monitoring instrument satellite (9). The data are presented at a resolution of 0.25 x 0.25 degree latitude and longitude (13 x 24 km). These data are freely available to download and is comprised of several erythemal UVR variables including annual mean,

mean UVR of highest month, mean UVR of lowest month, sum of monthly mean during highest quarter, and sum of monthly mean during the lowest quarter. Given that participants in this study answered questions on time spent in the sun that pertained to summer months, we chose to use the sum of the monthly mean during the highest quarter of the year. To link this data to Canadian postal codes, we used the Postal Code Conversion File, which contains the latitude and longitude for each 6-digit postal code in Canada. Since postal codes can change, we chose the 2008 file because it most closely corresponds to the average enrollment period of the participants involved in this study. We then reduced the data to correspond to 3-digit postal codes by averaging the 6-digit post codes in each of the 3-digit areas. The 3-digit postal code ambient data was then linked to participant's residence at baseline. The values from this database have been validated for Canada using ground-based measures from four Brewer stations in Canada (Eureka, Toronto, Churchill, and Saturna Island) (10).

3.3.4 Skin Tone

Skin tone was considered as both an effect modifier and potential confounder in this study. In the second phase of ATP and in the other cohorts, skin tone was categorized into two groups based on skin reaction to the sun after spending one hour in the sun without protection after several months of not being in the sun. The light skin tone group consisted of individuals that mildly burned with some tanning, had a severe sunburn for a few days with peeling, or a severe sunburn with blisters. The medium/dark skin tone group consisted of individuals that had no skin reaction to the sun or turned darker without a sunburn. In the first phase of ATP, participants were asked about the untanned skin color of their upper arm and could answer: light (white, fair, ruddy), medium (olive,

light brown, medium brown), or dark (dark brown, black). We combined the medium and dark skin tone groups to be consistent with the other cohorts.

3.3.5 Potential Confounders

Variables considered as potential confounders included established and suspected risk factors for non-Hodgkin lymphoma. These included sex, a family history of non-Hodgkin lymphoma, body mass index (BMI), physical activity, alcohol consumption, tobacco smoking status, fruit and vegetable consumption, meat consumption, sleep duration, and household income. Variables related to exposure to ultraviolet radiation were also considered, including ambient UVR, dietary vitamin D intake and skin tone. We used a backwards elimination approach with a liberal p-value of 0.2 to determine inclusion of potential confounders in the final models (11).

Harmonized variables across cohorts and phases were sex (male/females), family history of non-Hodgkin lymphoma (yes or no), household income (< $50,000, $50,000 to $100,000, and ≥ $100,000), tobacco smoking status (never, former, or current), and fruit and vegetable consumption (under recommendations (4 servings per day) for both fruits and vegetables, meet recommendations for fruit or vegetable consumption, or meet recommendations for both).

Physical activity was measured in all of the cohorts, but different instruments were used. In the first phase of ATP, physical activity was measured with the Past Year Total Physical Activity Questionnaire (PYTPAQ) (12) and was measured with the International Physical Activity Questionnaire (IPAQ) (13) in the other cohorts. Both of the questionnaires are validated with accelerometer data, but the PYTPAQ tends to overestimate (12) and the IPAQ tends to underestimate (13), which makes these measures

inappropriate to apply in a combined analysis. For each cohort or phase, physical activity was categorized into quartiles. Alcohol consumption was also measured in all cohorts, but different questions were asked. In the first phase of ATP, drinking status (ever or never) and the number of drinks consumed in a week were quantified. In all of the other cohorts, drinking status and number of times consuming alcohol drinks is a week were quantified. For the first phase of ATP we categorized alcohol consumption as never drinker, former drinker, less than or equal to 1 drink/day, and > 1 drink/day. In all of the other cohorts we categorized alcohol consumption as never drinker, former drinker, drinks 2 or less times a week, and drinks more than 2 times a week.

BMI was included for all of the cohorts except for the second phase of ATP (15.4% of total study population), and was categorized according to the World Health Organization classification of normal weight (18 to < 25 kg/m^2), overweight (25 to < 30 kg/m^2), and obese (≥30 kg/m^2). Meat consumption was only included in the first phase of ATP and CaG (77.2% of total study population), and was categorized into three groups: less than 3 servings per week, 3-6 servings per week, and > than 6 servings per week. Sleep duration was only included in CaG (48.9% of total study population) and was categorized in three groups: < 7 hours/night, 7-9 hours/night, > 9 hours/night. Dietary vitamin D was only included for the first phase of ATP (28.3%) and a small subset of participants of CaG. Dietary vitamin D was categorized as based on recommendations and were < 400 IU/day, 400-800 IU/day, > 800 IU/day. Dietary vitamin D was only tested as a potential confounder in the first phase of ATP.

3.3.6 Outcomes

Cancer outcomes from all cohorts were collected through record or electronic billing data linkages. Participants of ATP were linked to the Alberta Cancer Registry up to 2017, while OHS questionnaire data was linked to the Ontario Cancer Registry up to 2017 by Cancer Care Ontario. Both cancer registries are highly regarded in North America and capture over 95% of incident cancer diagnoses (14). Since cancer incidence data through the Quebec cancer registry was not available for diagnoses after year 2010, cancer cases were identified using administrative databases, including Med Echo for hospital claims and RAMQ for physician billing. Incident cancer cases were identified using a validated algorithm (15). The use of administrative data for the ascertainment of cancer cases has been shown to have a higher degree of misclassification compared to registry data (15-17). To limit potential misclassification, we removed cancer events that had diagnostic codes corresponding to benign or pre-cursor lesions (non-invasive). To identify possible non-invasive diagnoses, we examined claim dates and changing event status for participants. If a participant did not have an invasive claim more than a year after their last non-invasive claim then the participant was changed to not having a cancer diagnosis during follow-up. For participants that had an invasive claim more than a year after the last non-invasive claim, the earliest date after the cessation of non-invasive claims was taken.

3.3.7 Combining Cohorts and Phases

Data from multiple study populations or cohorts can be combined through two different methods: a pooled analysis or a meta-analysis. A pooled analysis treats the data like it comes from a single sample and requires that every variable included in a model is harmonized across studies. One single model is run and a cohort term can be added to

control for the effect of cohort. A meta-analysis, on the other hand, treats each cohort as its own study and only requires the exposure of interest to be harmonized, but not the other covariates. An analysis is run on each cohort and then the effect estimates can be combined using a random effects meta-analysis. If the cohorts being combined have different versions of the same covariate or are not aligned in terms of the variables included, the meta-analysis approach is advantageous. In a pooled analysis, covariates must be harmonized by going down to the lowest common denominator among the cohorts, which can result in uncontrolled or residual confounding. The meta-analysis approach can get around this issue, since each cohort is analyzed separately and the best model can be chosen for each without making concessions. In addition, the meta-analysis approach could potentially result in more precision, since the most parsimonious model based on backwards selection for each cohort can be chosen. The meta-analysis approach can be problematic in terms of covariate selection if any of the cohorts are too small. Furthermore, determining interactions are more difficult since you can't simply add an interaction term to a model.

Given that there were discrepancies among cohorts with respect to the inclusion of certain potential confounders as well as differences in the measurement of other potential confounders, we analyzed each cohort or phase separately in this study and then combined with a meta-analysis. OHS and CaG were pooled together since the cohorts had the same data elements and OHS was too small to analyze on its own, since only participants from the pilot phase answered questions related to time spent in the sun.

3.3.8 Analysis of Prospective Cohort Data

Cox proportional hazards models with age as the time scale were used to examine the relationship between time spent in the sun and the risk of developing NHL. In this study, baseline time spent in the sun was assumed to represent typical adulthood exposure. Therefore, enrollment in the study (filling out the questionnaire) does not represent a meaningful timepoint in terms of disease risk. Using attained age as the time-scale makes the beginning of follow-up meaningful and has been shown to create the most robust adjustment for age in time-to-event analyses (18). Specifically, time-in-study as the time-scale, rather than age as the time-scale can bias estimates in a cox proportional hazard model if the exposure is associated with age and if there is a non-exponential relationship between age and disease (18). Therefore, using time-in study as the time scale can lead to residual confounding from age, since it assumes a functional relationship between age and the hazard rate.

Participants were censored at other cancer diagnosis, death (if information available - CaG), if they moved out of the province of their respective cohort, or at the date of the last linkage. Participants were censored at another cancer diagnosis, since cancer treatments (chemotherapy and radiation) increase the risk of NHL (19), and therefore a subsequent diagnosis of NHL could be due to treatment rather than time spent in the sun. To determine the most parsimonious model for each cohort, covariates were selected using backward elimination with a liberal p-value of 0.20 (11). The proportional hazard assumption was tested using the cumulative sums of martingale-based residuals method (20), which tests that each variable in the final model meets the proportional hazard assumption.

Risk estimates for each exposure category were pooled using a random effects meta-analysis model to yield summary estimates. Heterogeneity among effect estimates was quantified with the I^2 test statistic. For the exploratory sun protection analysis, a meta-regression was used to test for an interaction between the use of sun protection methods and each of the exposure categories. For the exploratory pattern of exposure analysis, compared to participants that spend < 30 min in the sun on both weekdays and weekends, effect estimates for each weekday and weekend combination with > 5% of participants are presented. To determine if there were differences by extreme patterns, we further classified exposure into three categories: high intermittent (< 30 min on weekday and > 2 hours on weekend), high continuous (> 2 hours on weekdays and weekends), and moderate (all other exposure categories). Meta-regression was performed to determine if there were statistical differences in these patterns of exposure and the risk of developing NHL. All analyses were performed using the R computing framework (www.r-project.org).

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Chapter 4

Indoor tanning and skin cancer in Canada: A meta-analysis and attributable burden estimation

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4.1 Highlights

• Over 10% of Canadian adults used an indoor tanning device in the past year and over a quarter had used an indoor tanning device in their lifetime.

• 7.0% of melanomas, 5.2% of basal cell carcinomas, and 7.5% of squamous cell carcinomas in Canada in 2015 were attributable to indoor tanning.

• The proportion of melanoma and non-melanoma skin cancer cases in Canada attributable to indoor tanning was greatest among young women.

4.2 Abstract

Background: Consistent epidemiologic and experimental studies have demonstrated that UV-emitting tanning devices cause melanoma and non-melanoma skin cancer. The purpose of this study was to estimate the relative risk of skin cancer associated with the use of indoor tanning devices relevant to Canada, to estimate the proportion and number of skin cancers in Canada in 2015 that were attributable to indoor tanning, and to explore differences by age and sex.

Methods: Skin cancer cases attributable to the use of an indoor tanning devices were estimated using Levin's population attributable risk (PAR) formula. Relative risks for skin cancer subtypes that were relevant to Canada were estimated through meta-analyses and prevalence of indoor tanning was estimated from the 2006 National Sun Survey. Age- and sex-specific melanoma data for 2015 were obtained from the Canadian Cancer Registry, while estimated NMSC incidence data were obtained from the 2015 Canadian Cancer Statistics report.

Results: Ever use of indoor tanning devices was associated with relative risks of 1.38 (95% CI 1.22-1.58) for melanoma, 1.29 (1.23-1.36) for basal cell carcinoma (BCC), and 1.49 (1.23-1.80) for squamous cell carcinoma (SCC). Overall, 7.0% of melanomas, 5.2% of BCCs, and 7.5% of SCCs in 2015 were attributable to ever use of indoor tanning devices. PARs were higher for women and decreased with age.

Conclusion: Indoor tanning contributes to a considerable burden of skin cancer in Canada. Strategies aimed at reducing use should be increased and a total ban or restrictions on use and UV-intensity should be considered by health regulators.

4.3 Introduction

Incidence rates of cutaneous malignant melanoma and non-melanoma skin cancer (NMSC) in Canada have been steadily increasing between 1986 and 2010 (1). The estimated age standardized incidence rate for melanoma in 2017 was 18.5 cases per 100,000 (7,300 cases) (2) and 198.4 for NMSC (78,300 cases) in 2015 (3). Melanoma is the most deadly form of skin cancer, and has become one of the most common cancers among young adults in Canada, particularly for females (1). Of NMSC cases, approximately 77% are basal cell carcinoma (BCC) and 23% are squamous cell carcinoma (SCC) (1). Although rarely fatal, the high incidence of NMSC represents a significant burden of disease in terms of morbidity, quality of life, social impact, and health care costs (4).

There is consistent epidemiologic evidence that indoor tanning causes melanoma and non-melanoma skin cancer (NMSC) and in 2012 the International Agency for Research on Cancer (IARC) classified artificial sources of ultraviolet radiation as carcinogenic (class 1) to humans (5). Indoor tanning is similar to sun exposure for ultraviolet B (UVB) radiation exposure, but is 10 to 15 times stronger than sun exposure for ultraviolet A (UVA) radiation (6). With longer wavelengths than UVB radiation, UVA rays penetrate more deeply into the skin than UVB, and can cause mutations in tumor suppressor genes or other oncogenes, both directly through DNA damage and indirectly through oxidative stress (7). Moreover, UVA has been shown to be relatively ineffective at inducing pigmentation changes that can attenuate the potentially damaging effects of future exposure to UVR, as UVB does (8). Additionally, indoor tanning devices have been shown to induce harmful burns, which an estimated two-thirds of users

experience at least once (9). While indoor tanning devices in Europe are limited in intensity to an ultraviolet index of 12, Canada and the USA do not place restrictions on owners or users (10). In addition, there is some evidence that the risk of skin cancer associated with ever use of indoor tanning devices is greater in North America than in Europe (11), which could be a reflection of varying use patterns and device restrictions.

Population attributable risks (PAR) for skin cancer associated with indoor tanning have previously been estimated for Europe (12,13), France (14), Australia (13), and the United States (13), but not for Canada. Two main limitations of these previous studies is that they did not restrict the studies included in the PAR estimates for ever use of indoor tanning devices to those with a relevant exposure distribution to their own population, and they included studies that did not control for confounding from exposure to solar UVR exposure. Therefore, not only does a Canadian estimate require an exposure distribution for Canada, but it also requires a relative risk estimate that is applicable to the types of devices and usage patterns which represent Canadian indoor tanning exposure.

While Brazil and Australia have banned indoor tanning devices (10), Canada only restricts use to those over the age of 18 (15). In addition, indoor tanning users in Canada are required to wear protective glasses and all commercial equipment must display labels that detail the health risks of indoor tanning, including that it can cause cancer (15). However, minors can still use tanning devices with signed consent from a guardian, and restriction in terms of intensity, frequency, or duration of use are not mandated in Canada (15). Therefore, attributable burden estimates have important implications for policy and preventive initiatives aimed at reducing the burden of skin cancer in Canada. Thus, the objective of this study was to estimate the risk of skin cancer associated with the ever use

of indoor tanning devices that is relevant to Canada and to quantify the proportion and number of skin cancer cases in Canada that could be attributed to indoor tanning in 2015. A secondary objective included exploring the extent to which PAR estimates varied by age, sex, and province.

4.4 Materials and Methods

This manuscript is part of The Canadian Population Attributable Risk of Cancer (ComPARe) study – a project aimed at quantifying the number and proportion of cancer cases in Canada, now and in the future, that could be prevented through changes in the prevalence of modifiable exposures associated with cancer. The methods for this study have previously been described (16).

The proportion and number of skin cancer cases in Canada that occurred in 2015 that were attributable to the use of indoor tanning devices (tanning bed, sunlamp or tanning light) was estimated using summary relative risks relevant to Canada derived from our own meta-analyses and were applied in combination with estimates of the prevalence of ever use of indoor tanning devices in Canada with the traditional PAR method (17).

4.4.1 Estimating Relative Risks

The most common exposure metric used for indoor tanning in epidemiologic studies is the ever use of an indoor tanning device (tanning bed, sunlamp or tanning light). In different parts of the world the duration and lifetime frequency of exposure for individuals with ever use of an indoor tanning device can vary considerably and therefore it is necessary to consider studies that reflect the reality of use in Canada. To identify these appropriate studies, we restricted our inclusion to studies with a frequency of use

distribution similar to Canada or a similar overall prevalence if the former was not reported. Additionally, individuals who use indoor tanning devices tend to spend more time in the sun, which implies the need for estimates of risk that control for exposure to solar ultraviolet radiation to determine the independent contribution of indoor tanning to the development of skin cancer.

To quantify the risk of developing each of the three types of skin cancer associated with ever use of indoor tanning devices, we conducted a systematic review using the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The literature search was conducted in PubMed, including all studies published up to August 2018 on the relationship of indoor tanning and the risk of skin cancer. The search terms used were as follows: “artificial UV” or “artificial ultraviolet” or “artificial light” or “indoor tanning” or “non-solar ultraviolet”, “solaria” or “solarium” or “sunbathing” or “sunbed” or “sunlamp” or “tanning bed” or “tanning booth” or “tanning parlour” or “tanning salon” and “melanoma” or “basal cell carcinoma” or “BCC” or “squamous cell carcinoma” or “SCC” or “non-melanoma skin cancer” or “NMSC.” Abstract and title screening was performed by DO’S. In the initial screening process, articles were deemed suitable for full-text review if they had been performed in adult humans, involved a skin cancer outcome, and were of relevance to the research question (assessed some measure of artificial UVR) or assessed solar UVR – to capture studies that include indoor tanning as a secondary analysis. Full-text review was conducted by two independent reviewers (DO’S and WDK). Reviews and meta-analyses were excluded from this study and we made no restriction on the language of studies assessed for inclusion. Reference lists and other secondary sources were examined for

additional relevant articles. The final inclusion criteria for studies included in the quantitative meta-analysis were studies: 1) reporting an effect estimate that was adjusted for important confounding variables (including host characteristics and an adequate measure of exposure to solar UVR); 2) that did not adjust for variables on the causal pathway (dysplastic nevi); contained an appropriate control group (was not related to exposure to UVR); 3) that had a summary of the exposure distribution (for example, approximately 30-50% of users had greater than ten times of use) or overall prevalence (for example, 8-28% ever use) of indoor tanning similar to the largest Canadian study (Walter et al. (18)). If multiple papers reported results on the same study population, we used the paper with the longest follow-up that reported an effect estimate of "ever" use of an indoor tanning device – or could be derived from what was reported. If a prospective study reported effect estimates for different periods of life, the period that best approximated lifetime exposure was used.

For the purposes of this study, hazard ratios and odds ratios were treated as approximations of relative risk. Relative risk estimates were weighted using the inverse variance method assuming a fixed effects model given our strict inclusion criteria. Heterogeneity among studies was investigated with the Q-test and the I^2 statistics (19). To assess publication bias we visually reviewed funnel plots and employed both Egger's weighted linear regression (20) and Begg's rank correlation tests (21). Given that the Begg's and Egger's tests are underpowered in meta-analyses with few studies (22), in the presence of statistically insignificant publication bias, we also employed the trim and fill approach to ensure the validity of our results. All analyses were performed using the R computing framework (www.r-project.org).

4.4.2 Estimating Prevalence of Exposure

The temporal relation between exposure and cancer diagnosis follows a sequence of relevant exposure period, induction period, latency period, and cancer diagnosis. The exposure prevalence of consequence to cancer incidence in a given year is that occurring during the relevant exposure period. In the majority of epidemiologic studies of this relationship, use of indoor tanning devices has been represented as "ever" exposed and therefore the prevalence of exposure in the target population at the end of the relevant exposure period is desired. The range of exposure, induction, and latency periods are difficult to establish for the indoor tanning-skin cancer association. We targeted a five-year lag between exposure prevalence and cancer incidence, hence requiring prevalence data from 2010. Prevalence was based on the 2006 National Sun Survey (NSS2) (23) to represent the target year of 2010.

To estimate PARs, the same exposure metric must be used for both the risk of skin cancer and for the prevalence of exposure in the population. Prevalence estimates for the ever use of indoor tanning devices are not available in Canada and therefore the prevalence of ever use was estimated by applying a conversion factor to past year exposure. Estimates of the prevalence of use of indoor tanning devices among Caucasians in the past year by age and sex were extracted from the 2006 NSS2. Prevalence data was restricted to Caucasians, since a small proportion of non-Caucasians use indoor tanning devices, but studies assessing skin cancer risk restrict to Caucasians and therefore relative risks are not generalizable to these individuals. The specific question in the NSS2 asked participants: "During the past 12 months, have you used any artificial tanning equipment such as tanning bed, sunlamp, or tanning light for any reason including medical reasons."

Age-specific conversion factors were estimated to convert “use in the past year” to “ever use” using a meta-analysis on the international prevalence of indoor tanning, which summarized the differences in prevalence of exposure for “ever exposed” and “exposed in the past year” (24). Within that meta-analysis, we used the results of a subgroup analysis that restricted to studies from North America. Using this study, we divided the prevalence of use in the past five years or ever use by the prevalence of use in the past year for each age group and derived conversion factors to apply to the past year prevalence from the NSS2.

4.4.3 Cancer Incidence and Target Population

Melanoma incidence data by age and sex in 2015 were obtained from the Canadian Cancer Registry. The overall number of estimated NMSC cases in 2015 were obtained from the Canadian Cancer Statistics report (3). These estimates were based on incidence data from four provincial registries (Alberta, Manitoba, New Brunswick and Newfoundland) and extrapolated to the rest of Canada. Age, sex, and histological subtype distributions were estimated from NMSC data obtained from the Manitoba Cancer registry and were applied to the number of NMSC cases estimated by the Canadian Cancer Statistics report.

Given that the relative risks for indoor tanning are primarily derived from studies that only include Caucasians, and that the majority of melanoma cases in Canada occur in Caucasian populations (98.9%) (25), our PAR estimates only apply to the Caucasian population of Canada. To estimate the number of attributable cases, the Caucasian-specific PARs were applied to 98.9% of the skin cancer cases in Canada.

4.4.4 Population Attributable Fraction Estimations

Age- and sex-specific exposure prevalence and summary relative risk estimates were used with Levin's formula (17) to estimate age- and sex-specific PARs:

$$PAR = \frac{Pe\ (RR - 1)}{1 + [Pe\ (RR - 1)]}$$

PAR = Population attributable risk
Pe = Prevalence of exposure in the general population
RR = Relative Risk

To estimate the excess attributable cases we multiplied the age- and sex-specific PARs by the skin cancer incidence data for each age and sex category and the numbers of attributable cases were summed. The total number of attributable cases was then divided by the total incident cases in that year to derive overall PARs associated with indoor tanning. The same methods were used to estimate PARs for specific Canadian provinces.

To estimate 95% confidence intervals for PAR estimates, Monte Carlo simulation methods were used where the relative risk values were drawn from a log-normal distribution derived from the RR and its associated variance estimated from 95% CIs, while prevalence values were drawn from a binomial distribution with parameter n as the number of survey participants and parameter p as the prevalence of exposure estimated from the survey. We simulated 10,000 samples and used the 2.5th and 97.5th percentiles of the resulting PAR distribution as the lower and upper limits of its 95% CI (26,27).

4.5 Results

4.5.1 Estimated Risk of Skin Cancer Associated With Indoor Tanning

We identified 759 unique studies in the initial PubMed search (Figure 1). Thirty-nine studies from the PubMed search and 18 additional studies identified from reference lists and secondary sources underwent full-text review. After full-text screening and applying our exclusion criteria, 11 studies examining the association of indoor tanning with at least one of the skin cancer subtypes were included in the quantitative analysis. The primary reasons for exclusion were a lack of control for confounding (n = 21) and a non-Canadian specific exposure distribution or prevalence (n=10). The specific reasons of exclusion for each individual study in the full-text review is presented in Supplemental Table 1.

Characteristics of the 11 studies investigating the association of indoor tanning and the risk of skin cancer that were relevant to Canada are presented in Table 1 (18,28-37). A total of 3,315 melanoma cases, 6,335 basal cell carcinoma cases, 583 squamous cell carcinoma cases, and 78,809 healthy individuals were examined in these studies. The majority of the included studies were conducted in North America (n = 7), while three studies were conducted in Europe and one in Australia.

There was little evidence of heterogeneity in the relative risk estimates for any of the skin cancer subtypes (I_2 = 26%, 0%, 0% for melanoma, BCC, and SCC, respectively) and therefore fixed effect meta-analyses were conducted for each subtype for the ever use of indoor tanning devices. The meta-analysis for melanoma yielded a relative risk of 1.38 (95% CI 1.22 to 1.58; Figure 2). There was some statistical evidence of publication bias for melanoma (p = 0.06), but the trim and fill approach did not identify any unpublished studies. There was no evidence of publication bias for BCC (p = 0.5) or SCC (p = 0.8)

and meta-analysis relative risks were 1.29 (95% CI 1.23 to 1.36) for BCC and 1.49 (95% CI 1.23 to 1.80) for SCC, respectively (Figure 2).

4.5.2 Estimated Prevalence of Indoor Tanning in Canada

The 2006 past year prevalence of indoor tanning and the estimated prevalence of ever using an indoor tanning device by age and sex among Canadian Caucasians are shown in Table 2. Based on data from the NSS2 and the application of our conversion factors it was estimated that, among Caucasian Canadians over the age of 16, 10.6% used an indoor tanning device in the past year and 26.3% had used an indoor tanning device at least once in their lifetime. Women had higher ever and past year use of indoor tanning devices than men in all age groups. Among women, both past year and ever use of indoor tanning devices was highest among young adults (16-24 years) and decreased with age. Among men, the youngest age groups (16-24 and 25-44 years) had similar past year use of indoor tanning devices, while the oldest age group (45+ years) had considerably lower use. The middle age group (25-44 years) had greater ever use of indoor tanning devices than both the youngest (16-24 years) and oldest age groups (45+ years). Provincial-specific prevalence estimates are presented in Supplemental Table 2.

4.5.3 Estimated Population Attributable Risk of Melanoma and Non-Melanoma Skin Cancer in Canada in 2015

Estimated age- and sex-specific PARs for indoor tanning and each skin cancer subtype are presented in Table 4. In 2015, 7.0% of melanomas (482 cases), 5.2% of BCCs (3,025 cases), and 7.5% of SCCs (1,524 cases) were attributable to indoor tanning, accounting for 5.9% of all skin cancer in Canada (5,031 cases). For each of the subtypes, the PARs were higher for women than for men. While for women the PAR estimates

decreased with age, the highest PAR for men occurred in the middle age group (30-49). Measures of uncertainty (95% CIs) are presented in Supplemental Table 3. Sex-specific PARs for Canadian provinces are presented in Supplemental Table 4. Overall, Alberta had the highest proportion of melanoma and non-melanoma skin cancer cases attributable to indoor tanning, while British Columbia had the lowest burden.

4.6 Discussion

In this study, patterns of indoor tanning use relevant to Canada were associated with a relative risk of 1.38 for melanoma, 1.29 for basal cell carcinoma, and 1.49 for squamous cell carcinoma. Overall, we estimated that 7.0% of melanomas, 5.2% of BCCs, and 7.5% of SCCs in Canada in 2015 were attributable to the use of indoor tanning devices. In addition, we found that there were considerable differences in PAR estimates by age, sex, and province. In particular, PAR estimates were highest for women in all age groups, particularly among the youngest age group. In contrast, the largest PAR for men occurred in the middle age group, which could be evidence of a reduction of indoor tanning among the most recent cohorts of men.

The most recent meta-analyses on indoor tanning and the risk of melanoma and NMSC have observed relative risks for the ever use of an indoor tanning devices of 1.16 for melanoma (11), 1.29 for BCC (13) and 1.67 for SCC (13). Differences in summary relative risk estimates in this study may be attributable to our stringent exclusion criteria, where distinct from previous studies were criteria based on control for confounding and an exposure distribution similar to Canada. If we removed these criteria we observe relative risks closer to those reported in previous meta-analysis, 1.23 (95% CI 1.11 to 1.37) for melanoma, 1.28 (1.22 to 1.35) for BCC and 1.72 (95% CI 1.48 to 2.00). Our

confounding exclusion criteria were aimed at obtaining an unbiased effect estimate, in particular with respect to not controlling for factors in the causal pathway and controlling for sun exposure behaviours. The rationale behind the exposure distribution criteria was that "ever exposed" might be associated with disparate frequency of exposure in different studies. We sought to obtain a relative risk estimate for an exposure that was similar to what we could expect in Canada.

In a previous analysis, Wehner (13) estimated that the proportion of melanoma cases in the United States, Europe, and Australia attributable to indoor tanning were 8.1%, 9.4%, and 2.6%, respectively. In an earlier analysis, Boniol (12) estimated that 5.6% of melanomas in Europe were attributable to indoor tanning, after calculating country-specific PARs and then pooling the results. The proportions estimated for the US and Europe by Wehner (13) are slightly higher than estimated for Canada. While this higher estimate may reflect a true difference in PAR, it is likely that the estimates are inflated because of the use of an overall exposure, rather than age- and sex-specific estimates, as we have done here. This is because the youngest age groups tend to contribute to a higher prevalence, but to a lower number of attributable cases, given the rarity of skin cancer in younger age groups. Indeed, in a sensitivity analysis that we conducted using an overall exposure prevalence for Canada resulted in considerably greater PAR estimates with 8.9% for melanoma, 7.1% for BCC, and 11.4% for SCC. Wehner and colleagues (24) in a subsequent study are the only previous investigators to have estimated PARs for NMSC in relation to indoor tanning. They estimated for the US and Europe that 9.3% and 10.8% BCCs, and 19.2% and 21.8% SCCs are attributable to indoor tanning use, which are substantially higher than those reported herein. In addition

to the points previously raised, the difference in PAR estimates primarily reflects the difference in relative risk estimates used for SCC. Finally, our incorporation of ethnicity in our methods is novel and an important consideration, particularly in countries with considerable ethnic diversity.

Despite a dose-response relation between cumulative use of indoor tanning devices and skin cancer development, the most common exposure metric used in epidemiologic studies is the ever use of an indoor tanning device. While collapsing the data into a dichotomous exposure variable does not affect the PAR for a single study (38), it does in a meta-analysis if the exposure distribution varies among the included studies. Given this issue, we selected studies that had an exposure distribution that was relevant to Canada which was a novel approach. Since patterns of indoor tanning in North America confer a greater risk of melanoma development than in Europe (11), the studies conducted by Wehner (13,24) and Boniol (13) for Europe were likely inflated by not restricting to studies with exposures relevant to Europe. In addition, we accounted for ethnicity in our estimations, and provide estimates of statistical uncertainty through a Monte Carlo approach – both of which are novel for PAR studies on indoor tanning and skin cancer.

The uncertainty involved in our conversion factor for past-year exposure to ever exposure is a limitation. Past year exposure is likely to be highly variable and susceptible to many different factors – rendering the conversion to ever exposure extremely difficult. A limited evaluation of the validity of our conversion factors comes from a study conducted in the Canadian province of Quebec that reports use in the past-year and the past 5-years (39). Conversion factors were generally lower (as expected) but of a similar

magnitude to our lifetime conversion factors. For example, for the age group 16-24 the past-year to 5-year ratio was 1.7 compared to our conversion of 1.9. For those aged 25-54 the past-year to 5-year ratio was 1.9 compared to our conversion factor of 2.7. The past-year to 5-year ratio, particularly for older adults, does not capture individuals that no longer indoor tan, but that did in their younger years. The decrease in past-year year prevalence by age provides evidence that this is common and that our conversion factor likely results in prevalence that is within a reasonable range of the true prevalence.

We have other limitations that must be acknowledged. The oldest age category (65+) had to be grouped because of the lack of reliable prevalence estimates from the NSS2 and an appropriate conversion factor for this age category. In addition, prevalence estimates from the NSS2 were based on self-reported behaviours, which could be susceptible to social desirability bias. For the meta-analysis component, we based the Canadian relevant exposure distribution on only one Canadian study, which may have led to misclassified inclusion or exclusion of some studies. Additionally, our meta-analyses for BCC and SCC included a small number of studies resulting in a large degree of uncertainty in the relative risk estimates. In addition, we relied on some older studies, however, a sensitivity analysis by publication date (before 2000 vs. in 2000 or after) found no difference in relative risk. Canada does not have a national surveillance system for NMSC and, consequently, many cases treated at clinics without confirmatory biopsies are not reported. This situation led to an underestimation of the number of NMSC cases attributable to indoor tanning. Moreover, because only the first NMSC occurring on each individual is reported and multiple NMSCs on the same individual may be caused by indoor tanning, our PAR estimates for NMSC would similarly be underestimated.

Finally, Miettinen's formula (40) is typically preferred when confounder adjusted relative risk estimates are used in the calculation of a PAR, but it was not possible to use this formula since it requires the availability of exposure distribution data among skin cancer cases.

While there is emerging evidence that moderate exposure to solar UVR may be protective against the risk of developing some non-cutaneous cancers (41), there is no evidence that a similar beneficial effect exists for indoor tanning. Indeed, it has previously been shown that the use of indoor tanning devices does not protect against solid non-cutaneous cancers and may even increase the risk of developing some hematologic malignancies (42). Given the lack of benefit of indoor tanning and the large burden of skin cancer attributable to it, efforts to reduce use are required or a total ban should be considered, as already been implemented in Australia and Brazil.

4.7 Conclusion

The rates of skin cancer in Canada have been consistently increasing over time and in this study we estimate that 7.0% of melanomas, 5.2% of BCCs, and 7.5% of SCCs in Canada in 2015 are attributable to indoor tanning. Given that indoor tanning is one of the risk factors for skin cancer that is most amenable to change through policies that limit or restrict use, strategies aimed at reducing use should be increased and a total ban or restrictions on use and UV-intensity should be considered by health regulators.

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4.11 Tables and Figures

Table 4.1. Characteristics of studies relevant to Canada investigating the association of indoor tanning with the risk of melanoma and non-melanoma skin cancers (n = 11).

Study and Location	Study design and Years of accrual	Population	Age (range)	Indoor tanning prevalence distribution
Bajdik, 1996 Alberta, Canada (Males)	Population Case-control 1983-1984	226 BCCs, 180 SCCs, 406 controls	25-79	8% ever
Bataille, 2004 United Kingdom	Hospital Based Case-control 1989-1993	413 melanomas, 416 controls	16-75	25% ever 43% > 30 lifetime uses
Chen, 1998 Connecticut, USA	Population Case-control 1987-1989	512 melanomas, 624 controls	> 18	19% ever 42% > 10 lifetime uses
Clough-Gorr, 2008 New Hampshire, USA	Population Case-control 1995-1998	423 melanomas, 678 controls	20-69	33% ever 45% > 10 lifetime uses
Cust, 2011 Australia	Population Case-control 2000-2002	604 melanomas, 479 controls	18-39	17.5% ever 32% > 10 lifetime uses

Han, 2006 (Nurses)	USA	Nested Case-control 1989-1998	200 melanomas, 804 controls	30-79	12% ever
Karagas, 2002	New Hampshire, USA	Population Case-control 1993-1995	603 BCCs, 540 controls	25-74	14% ever
Swerdlow, 1988	Scotland	Hospital Based Case-control 1979-1984	180 melanomas,120 controls	15-84	8% ever
Walter, 1999	Ontario, Canada	Population Case-control 1984-1986	583 melanomas, 608 controls	20-69	18% ever 43% > 10 lifetime uses
Westerdahl, 1994	Sweden	Population Case-control 1988-1990	400 melanomas, 640 controls	15-75	24% ever
Zhang, 2012 (Female Nurses)	USA	Prospective Cohort 1989-2009	5506 BCCs, 403 SCCs, 73,494 controls	25-62	12% ever

Table 4.2. Estimated prevalence of indoor tanning among Caucasian Canadians

Age (years)	Prevalence (95% confidence interval)		
	Past year (%)	Conversion Factor**	Ever use (%)
Men			
16-24	8.5 (5.8-12.4)	1.92	16.3 (11.1-23.8)
25-44	8.0 (6.4-10.0)	2.69	21.6 (17.2-26.9)
44+	4.4 (3.3-5.9)	2.69	11.8 (8.9-15.9)
Total	6.1 (5.2-7.2)	--	15.6 (13.3-18.4)
Women			
16-24	30.4 (25.7-35.4)	1.92	58.3 (49.3-68.0)
25-44	18.9 (16.7-21.2)	2.69	50.7 (44.9-57.0)
44+	9.0 (7.6-10.5)	2.69	24.2 (20.4-28.2)
Total	14.9 (13.7-16.2)	--	36.8 (33.8-40.0)
Overall	10.6 (9.8-11.5)	--	26.3 (24.3-28.5)

*Data from the Second National Sun Survey (2006)
**Conversion factor (past year vs. ever) derived from Wehner et al., 2014
Note: Total and overall prevalence calculated by population weighted average

Table 4.3. Melanoma and non-melanoma skin cancer cases and proportions attributable to indoor tanning in Canada in 2015

Age at Exposure	Age at Diagnosis	Melanoma			Basal cell carcinoma			Squamous cell carcinoma		
		Obs.	PAR	AC	Obs.	PAR	AC	Obs.	PAR	AC
Men										
16-24	20-29	40	5.0	2	170	4.7	8	8	12.5	1
25-44	30-49	470	7.5	35	2626	5.8	153	286	9.4	27
44+	>=50	3300	4.2	137	28429	3.3	935	12781	5.4	694
Total	Total	3810	4.6	174	31225	3.5	1096	13075	5.5	722
Women										
16-24	20-29	110	18.2	20	223	14.4	32	19	21.1	4
25-44	30-49	655	15.6	102	3004	12.7	381	318	19.8	63
44+	>=50	2290	8.1	186	23420	6.5	1516	7017	10.5	735
Total	Total	3055	10.1	308	26647	7.2	1929	7354	10.9	802
Total										
16-24	20-29	150	14.7	22	393	10.2	40	27	18.5	5
25-44	30-49	1125	12.2	137	5630	9.5	534	604	14.9	90
44+	>=50	5590	5.8	323	51849	4.7	2451	19798	7.2	1429
Total	Total	6865	7.0	482	57872	5.2	3025	20429	7.5	1524

Abbreviations: AC = Attributable cases due to exposure, Obs. = Observed cases, PAR = Population attributable risk

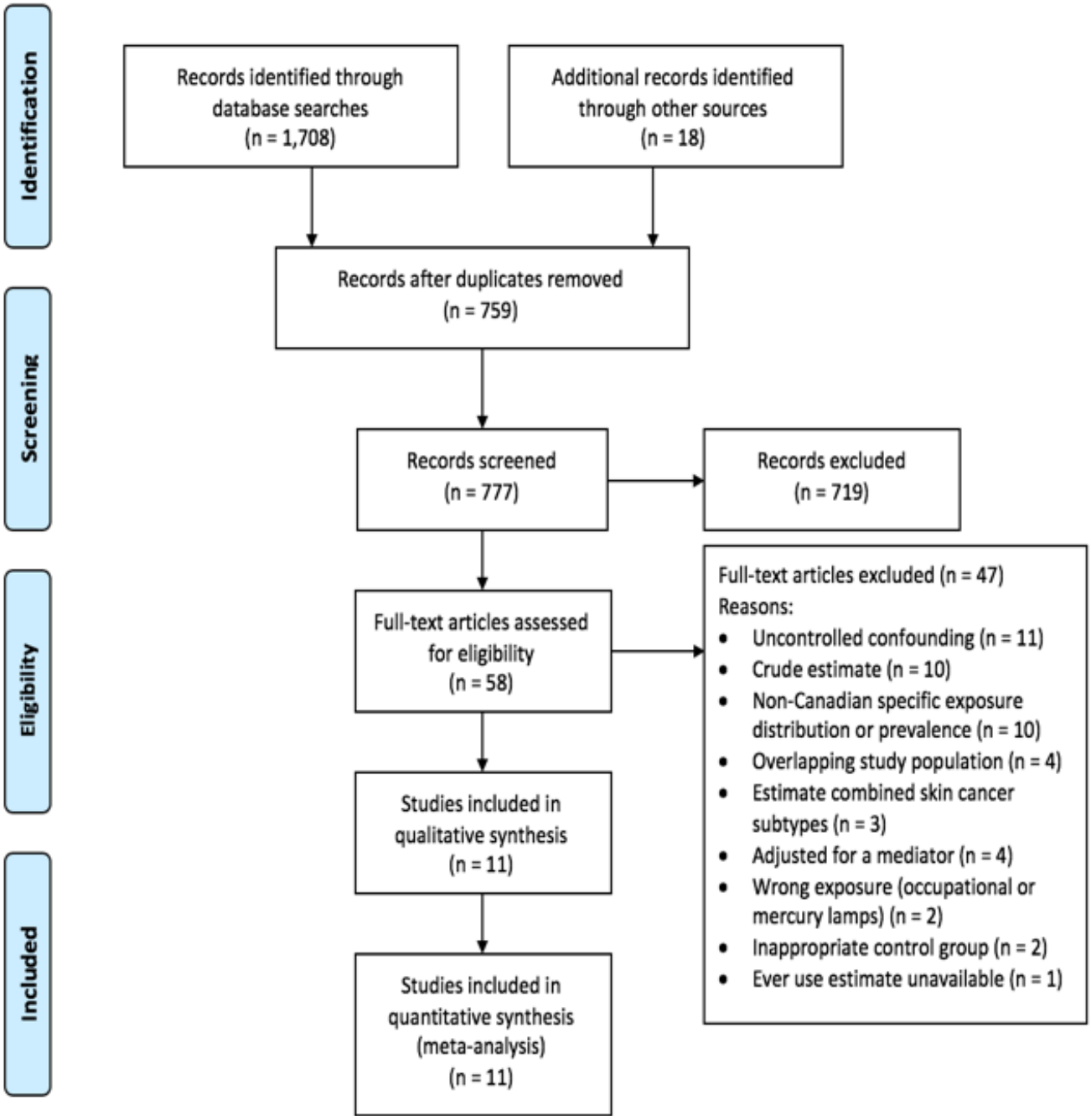

Figure 4.1 Flow diagram of the selection procedure of studies relevant to Canada assessing the relationship of indoor tanning with the risk of melanoma and non-melanoma skin cancers.

Description: A PRISMA flow diagram that details the inclusion and exclusion of studies considered for this meta-analysis.

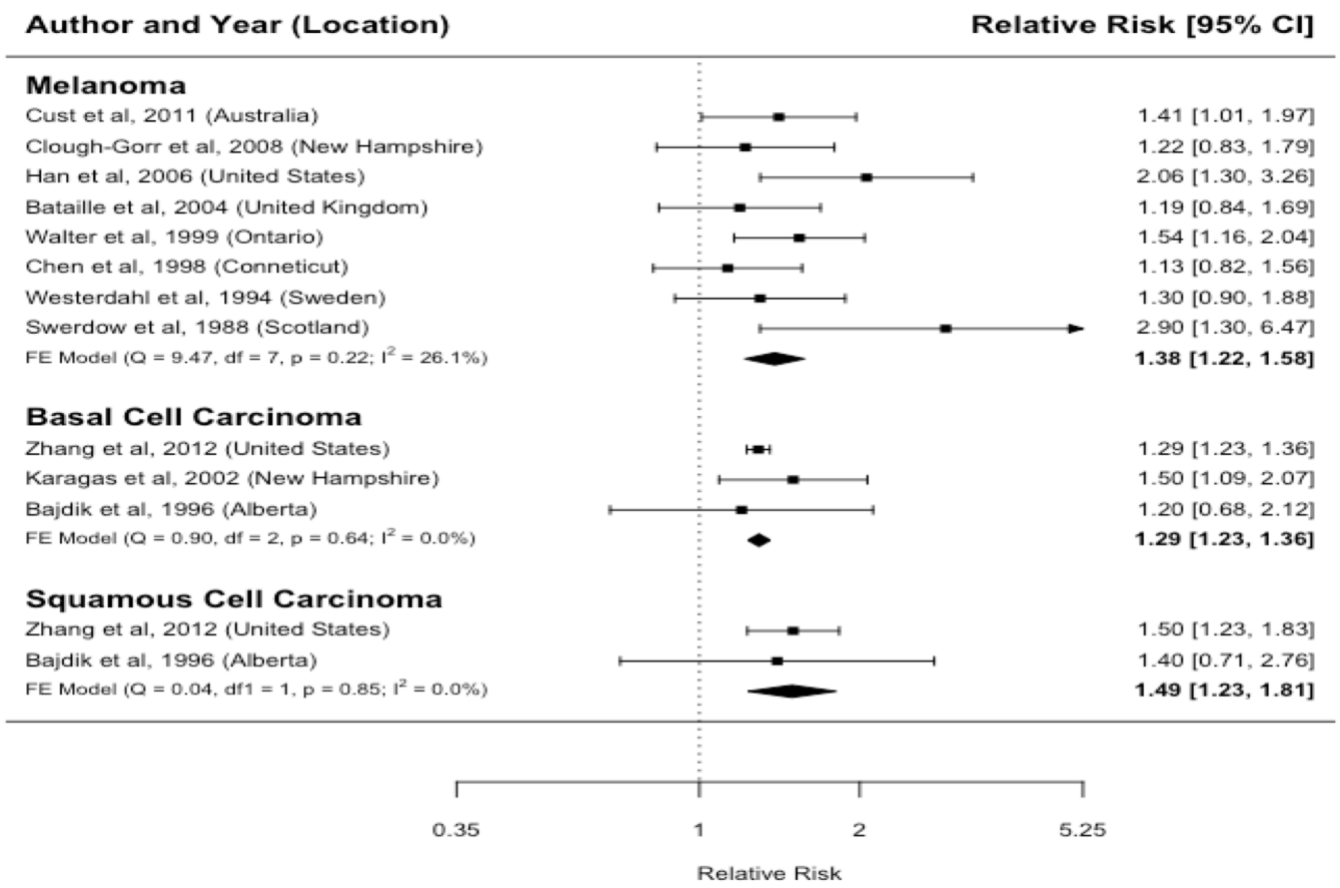

Figure 4.2. Estimated relative risks of skin cancer subtypes comparing ever users of indoor tanning devices to non-users that are generalizable to Canada.

Description. A forest plot that presents skin cancer subtype-specific relative risks from investigation of ever use of indoor tanning and skin cancer risk that are generalizable to use patterns in Canada.

Chapter 5

Estimates of the current and future burden of melanoma attributable to ultraviolet radiation in Canada

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5.1 Abstract

Exposure to ultraviolet radiation (UVR) is an established cause of cutaneous melanoma. The purpose of this study was to estimate the current attributable and future avoidable burden of melanoma related to exposure to UVR and modifiable UVR risk behaviors (sunburn, sunbathing, and indoor tanning). The population attributable risk (PAR) associated with UVR in 2015 was estimated by comparing Canadian melanoma incidence rates in 2015 to estimated incidence rates of a 1920 birth cohort. Rates were adjusted for changes in reporting and ethnicity. We estimated PARs for modifiable UVR risk behaviors using Caucasian prevalence data from the Second National Sun Survey and relative risks that are generalizable to Canada from meta-analyses of relevant studies. Attributable cases apply to 98.9% of melanomas in Canada that occur in Caucasians. We also estimated the future burden of UVR risk behaviors using the potential impact fraction framework and potential reductions in prevalence of 10% to 50% from 2018 to 2042. Adult sunburn and sunbathing were associated with increased risks of melanoma of 1.28 (95% CI: 1.15, 1.43) and 1.44 (95% CI: 1.18, 1.76), respectively. In 2015, we estimate that 62.3% of melanomas in Canada were attributable to exposure to UVR and that 29.7% were attributable to the combination of sunburn (7.4%), sunbathing (17.8%), and indoor tanning (7.0%). A 50% reduction in modifiable UVR behaviors could avoid an estimated 11,980 melanoma cases by 2042. Prevention strategies aimed at modifiable UVR behaviors are crucial to reduce the growing burden of melanoma in Canada.

5.2 Highlights

- 62.3% of melanomas diagnosed in Canada in 2015 were estimated to be attributable to exposure to ultraviolet radiation.
- Adult sunburn and sunbathing activities in Canada were associated with increased relative risks of melanoma of 1.28 (95% CI: 1.15, 1.43) and 1.44 (95% CI: 1.18, 1.76), respectively.
- 29.7% of melanomas in Canada in 2015 were estimated to be attributable to the combination of sunburn (7.4%), sunbathing (17.8%), and indoor tanning (7.0%)
- An estimated 11,980 melanoma cases could be prevented by 2042 by reducing the prevalence of exposure to modifiable ultraviolet radiation risk factors by 50%.

5.3 Introduction

Incidence rates of cutaneous malignant melanoma in Canada have increased steadily between 1970 and 2010 (1), and in 2017, an estimated 7,323 new cases of melanoma were diagnosed (2). While the overall relative increase in incidence during this time period has been larger for men than women, from 1992-2010 there have been greater relative increases for women (1). Exposure to ultraviolet radiation (UVR) from the sun is the primary risk factor for melanoma. The International Agency for Research on Cancer (IARC) has concluded that exposure to solar UVR is carcinogenic to humans and causes cutaneous malignant melanoma (3). More recently IARC recognized that artificial sources of UVR such as indoor tanning devices are also carcinogenic (4).

The classification of UVR as a human carcinogen draws on substantial epidemiological evidence. Ambient UVR is strongest at low latitudes and ecological studies of Caucasian populations show increased incidence of melanoma among those in close proximity to the equator (5). Evidence from a large number of case–control studies is generally consistent, showing positive associations with residing in areas with high ambient UVR throughout life, in early life, and even for short periods in early adult life (5). The body site distribution of melanoma favors sites usually exposed to the sun, such as the head and neck or the forearms (6). The behavioral patterns of UVR exposure that are associated with melanoma are complex and in some cases divergent. Positive associations are consistently observed between a history of sunburn and measures of intermittent exposure to the sun (such as sunbathing) and melanoma at all latitudes (7,8). Occupational and chronic patterns of exposure appear to be stronger risk factors at low latitudes, where ambient UVR is strongest (8). However, the lack of an association at higher latitudes could be a product of the referent group including individuals with high

levels of intermittent sun exposure and from the majority of this evidence coming from case-control studies that may be subject to recall bias (5,7).

Estimating the proportion of incident cases of melanoma that are attributable to UVR exposure is challenging, as solar UVR is a ubiquitous exposure and the carcinogenic effects are dependent on latitude and behavioral patterns (7,8). It is therefore difficult to capture the risk and distribution of relevant types of exposure for a specific population. Given this challenge, previous population attributable risk (PAR) studies for Ontario (9), the United Kingdom (10), France (11,12), the United States (13), Australia (14,15), Columbia (16) and worldwide (17) have relied on a method of estimation that calculates the difference between the melanoma incidence in the target population and a theoretical 'unexposed' population. The most commonly employed variant of this approach is to use the melanoma rates in an early birth cohort (with assumed greater skin coverage and lower UVR exposure) as the non-exposed group in a comparison with current melanoma rates. The method of PAR estimation based on prevalence of exposure and relative risk estimates for UVR risk factors is less frequently used since the measurement of exposure and the corresponding relative risk is difficult to capture. Additionally, these exposures merit specific methods in the estimation of PAR because of the high correlation between UVR risk factors (18,19). However, this approach to PAR estimation is important, since it represents the proportion of melanoma cases that could be reduced by the modification of individual behaviors.

In this study, we estimated the proportion and number of incident cutaneous melanoma cases in the Canadian population in 2015 that were attributed to UVR and modifiable UVR risk behaviors, including indoor tanning, sunburn, and sunbathing. In

addition, the potential impact fractions and number of melanoma cases that could be prevented up to 2042 under different scenarios of UVR risk behavior change were estimated.

5.4 Methods

5.4.1 Current Burden – Population Attributable Risk Estimation

The general methodologic framework for this project has previously been published (20) and a brief overview has been included in this special issue (21). Given the unique nature of UVR exposure, a modified approach was used for this risk factor. To estimate the proportion of melanoma cases in Canada in 2015 that were attributable to UVR exposure, a birth cohort comparison was conducted. To estimate attributable cases to different UVR risk behaviors the traditional risk factor approach was employed. Joint prevalence distributions were used to estimate a combined UVR risk behavior PAR. Occupational exposure to UVR was not considered in the ComPARe Study.

5.4.2 Birth Cohort Comparison

To estimate an overall PAR for UVR exposure, we used the direct approach to PAR estimation:

$$PAR = \frac{Incidence_{population} - Incidence_{non-exposed}}{Incidence_{population}}$$

In this analysis, Incidence $_{population}$ was the incidence rate of melanoma in Canada in 2015, and Incidence $_{non\text{-}exposed}$ was the estimated incidence rate of melanoma for a 1920 birth cohort in Canada. Using melanoma incidence data from 1971 to 2015 a log normal age-cohort model was fit and used to predict incidence rates for a 1920 birth cohort. The 1920

birth cohort was selected to avoid predicting incidence far outside of the range of the data.

Given that melanoma is often treated outside of hospital settings, there is potential for under-reporting to Canadian cancer registries, and capture-recapture studies from Ontario provide evidence of this (22,23). To account for this, the annual number of melanoma cases were inflated by the proportion of cases not reported, using capture rates from Ontario in 1976 (22) and 1993-2009 (23). A logistic regression model was used to extrapolate these capture rates to years without these data. Years 2004 and 2005 were removed from the model, since the capture rates were unusually low (66.8% and 51.4% compared to 88.7% and 96.0% in 2003 and 2006, respectively) and therefore not representative of national capture rates.

Melanoma rates differ by ethnicity (in particular rates are 20 times lower among Blacks and Asians compared to Caucasians) (24), and the ethnic distribution of the Canadian population has diversified in the most recent cohort. Given that the current evidence suggests that melanoma in Blacks and Asians is not attributable to UVR exposure to the same degree as in Caucasians, one method to account for the contemporary shift in ethnicity is to only apply this approach to Caucasians, Hispanics, and Aboriginals. The proportion of Blacks and Asians in years 1971 to 2015 was estimated using Canadian census data in five-year increments starting at 1971 and ending at 2016. Proportions between the census years were estimated by assuming a consistent increasing or decreasing trend. The numbers of melanoma cases in Blacks and Asians were estimated by applying the incidence rate from the US (SEER) to the number of Black and Asians in each year by age and sex. These melanoma cases were then

subtracted from the total number of reported adjusted melanoma cases, which were then divided by the number of Caucasians, Hispanics, and Aboriginals in the cohort to derive a rate.

Age- and sex-specific PARs were estimated to account for changes in the population distribution of age and sex between the two cohorts. The numbers of attributable cases in 2015 were summed and divided by the total cases to estimate an overall PAR.

5.4.3 UVR Risk Factor Approach

The proportion of melanoma cases in 2015 in Canada attributable to different UVR risk behaviors (indoor tanning, sunburn, and sunbathing) was estimated using the traditional risk factor approach that applies summary relative risks and population prevalence estimates to the Levin formula (25). The methods for estimating PARs for indoor tanning and the results for that analysis have been previously published (26).

5.4.3.1 Estimating Relative Risks Relevant in Canada

Given that ambient UVR varies across countries, it is important to consider studies that are generalizable to Canada. To determine relative risks for each UVR risk behavior, a systematic review and meta-analysis was conducted to identify studies that were relevant to the Canadian population. A full-text review of all studies included in the most recent review for the risk of melanoma associated with solar UVR behaviors (3), as well as a systematic review of studies published after 2007 were conducted. The literature search was conducted in PubMed using the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). All studies published between January 2008 and August 2018 were reviewed using the following search terms: “sun” or

"sunbathing" or "sunburn" or "sunlight" or "solar ultraviolet" or "sunbed" or "indoor tanning" or "artificial ultraviolet" and "melanoma". The latter terms relevant to indoor tanning were included to capture studies that include sunburn or sunbathing as secondary analyses. Abstract and title screening was conducted by DO'S, while full-text review was performed by two independent reviewers in a blinded review (DO'S and WDK). The final inclusion criteria for studies included in the quantitative meta-analysis were studies: 1) conducted at a northern latitude (> 39 N); 2) reported an effect estimate for adult or lifetime exposure; 3) adjusted for important confounders (host characteristics and other UVR risk behaviors in this study); 4) did not adjust for variables on the causal pathway (dysplastic nevi); 5) contained an appropriate control group (was not related to exposure to UVR); and 6) included all histological subtypes of melanoma. If two studies reported on the same population, the study with the largest sample size or with the most relevant exposure was included in the meta-analysis.

For studies that met our inclusion criteria we extracted the adjusted effect estimates for "ever" being exposed to the UVR risk factor. Some studies included in this analysis reported effect estimates for different levels of exposure rather than an overall estimate for "ever" being exposed. To obtain an "ever" exposed metric to match our prevalence estimates, effect estimates for exposure levels were combined using inverse variance weighting. The standard error for this estimate was computed using crude data to adjust for the degree of covariance among the exposure categories (27). If a prospective study reported effect estimates for different periods of life, the period that best approximated lifetime exposure was used. This best lifetime exposure period was

determined using the longest exposure window or exposure period closest to diagnosis that was not within the defined latency period.

For the purposes of this study, hazard ratios and odds ratios were treated as approximations of relative risk. DerSimonian and Laird random-effect models were used in all analyses (28). The degree of heterogeneity was estimated using the Q-test and the I^2 statistics (29). To assess publication bias we inspected funnel plots and employed both Egger's weighted linear regression (30) and Begg's rank correlation tests (31). Where there was evidence of publication bias, the trim and fill approach was employed to obtain a summary relative risk estimate. All analyses were performed using the R computing framework (www.r-project.org).

5.4.3.2 Estimating Prevalence of Exposure

UVR risk behaviors are represented as "ever being exposed" and therefore we required prevalence estimates at the end of the relevant exposure period. A lag period of five-years between exposure prevalence and cancer incidence was used – requiring prevalence data from 2010. Prevalence was based on the 2006 National Sun Survey (NSS2) (32) to represent the target year of 2010. Age-sex specific prevalence estimates of sunburn and sunbathing among Caucasians in the past year were obtained from the NSS2. Most studies assessing the association of UVR risk factors with melanoma derive relative risk estimates by comparing melanoma incidence rates among those who have "ever been exposed" to those who have not. Given this issue, conversion factors for each of the risk factors were estimated to convert "exposed in the past year" to "ever exposed". Conversion factors for adults were estimated by comparing ever exposure of the control group in a Canadian-specific study conducted in Ontario (33) to past year prevalence

estimates for Ontario from the First National Sun Survey (34,35). These conversion factors were then applied to the prevalence of exposure for the two oldest age groups and sex reported in the NSS2. Conversion factors for the youngest age group were not estimated due to a lack of data and, therefore, it was assumed that past-year exposure represented ever exposure in this age-group.

5.4.3.3 Cancer Incidence and Target Population

Melanoma incidence by age and sex in 2015 was obtained from the Canadian Cancer Registry. Given that the relative risks for UVR risk behaviors are primarily derived from studies that only include Caucasians, and that the majority of melanoma cases in Canada occur among Caucasians, our PAR estimates only apply to this subgroup. To apply our approach exclusively to Caucasians, UVR risk behavior prevalence for Caucasians was ascertained from the NSS2. To estimate the number of attributable cases, the Caucasian-specific PARs were then applied to 98.9% of melanoma cases in Canada.

5.4.3.4 Population Attributable Risk

Age- and sex-specific exposure prevalence and summary relative risk estimates from meta-analyses were applied to the Levin formula (25) to estimate age- and sex-specific PARs for each UVR risk factor. PAR estimates were applied to Canadian melanoma incidence data for each age and sex category, and the number of attributable cases were summed. The number of attributable cases was divided by the total incident cases in 2015 to obtain overall PARs associated with each UVR risk factor. Monte Carlo simulation methods were used to estimate 95% confidence intervals (CIs) around PAR estimates. The same methods were used to estimate PARs for Canadian provinces.

5.4.3.5 Combined UVR Risk Behaviour PAR Estimation

Given that UVR risk behaviors are strongly related (18,19) and that combined PAR estimates can be underestimated when risk factors are dependent (36), joint exposure distributions of sunburn, sunbathing, and indoor tanning were used to estimate a combined PAR. To estimate a combined UVR risk behavior PAR, joint prevalence distributions of the UVR risk factors in the past year by age and sex were obtained from the NSS2. To obtain a measure of ever exposure within each joint distribution stratum, we used the relationships between the risk factors in the past year and the marginal totals to apply these relationships to our estimated "ever" exposures. Multiplicative relative risks were then applied to each joint distribution prevalence and PAR estimated for a multilevel exposure (37).

5.4.4 Future Burden – Potential Impact Fraction Estimation

5.4.4.1 Prevalence of Exposure Projections

Estimates of future PAR and PIF require an assumed exposure distribution. There are insufficient historical data on the prevalence of UVR risk behaviors necessary to project future trends. Therefore, we assumed stable prevalence of exposure in the future based on the NSS2.

5.4.4.2 Cancer Incidence Projections

The methodology for cancer incidence projections has been published previously (38). Briefly, a decision algorithm to choose the most appropriate model for the projection was used and face validity was evaluated independently of goodness-of-it. Sex-specific incidence for melanoma was projected using a negative-binomial based age-drift-period-cohort model (39).

5.4.4.3 Counterfactuals

To estimate the proportion of melanoma cases associated with UVR risk behaviors that could be avoided in the future, we considered three counterfactual scenarios (10, 25, and 50% reductions by 2037 – assuming a 5 year latency period). These counterfactuals were applied to each UVR risk behavior, as well as to all UVR risk behaviors combined. For the latter, we assumed for each counterfactual scenario that the percentage reduction in exposure would occur equally across joint exposure categories. To estimate the cumulative cases that could be prevented by 2042, we assumed that a constant decrease from current prevalence (2018) to the counterfactual scenario would be achieved by 2037.

5.5 Results

5.5.1 Current Attributable Burden for Ultraviolet Radiation Overall

The PARs and numbers of attributable melanoma cases by age and sex are presented in Table 1. In 2015, we estimated that 62.3% of all melanomas in Canada were attributable to increases in exposure to UVR compared to a 1920 cohort, accounting for 4,276 cases and 2.3% of all cancers. The PAR estimates were higher in men than for women with PARs of 65.8% (2,506 cases) and 57.9% (1,770 cases), respectively. For both sexes, PAR estimates were greatest for the 35-49 age group and smallest for the 65+ age group. Age- and sex-specific PARs and attributable cases for Canadian provinces are presented in Supplemental Table 1.

5.5.2 Current Attributable Burden for Sunburn, Sunbathing, and Combined Modifiable UVR Risk Behaviours

5.5.2.1 Estimated Risk of Melanoma Associated with Sunburn and Sunbathing Relevant to Canada

We identified 3,380 studies in the initial PubMed search (Figure 1). Thirty-four studies from the PubMed search and 86 additional studies identified from previous reviews (3,7,8) underwent full-text review. After full-text screening and applying our exclusion criteria, 10 studies examining the association of sunburn and/or sunbathing on the risk of melanoma were included in the quantitative analysis. The primary reasons for exclusion were a lack of an effect estimate for either of these exposures (n = 37), and a lack of mutual control for the other UVR behaviors included in this study (n = 30) or a lack of control for other important confounders (n = 26). The specific reasons of exclusion for each individual study during the full-text review are presented in Supplemental Table 2 and the characteristics of the included studies are presented in Table 2 (33,40-48). Of the included studies, four studies each reported results for the relationship of sunburn or sunbathing with melanoma risk, while two studies reported risk estimates for both sunburn and sunbathing.

Random effect meta-analyses yielded a pooled relative risk of developing melanoma of 1.28 (95% CI: 1.15, 1.43) associated with ever having a severe sunburn and a relative risk of 1.50 (95% CI: 1.25, 1.81) associated with ever intentionally sunbathing. There was little heterogeneity among relative risk estimates for both the sunburn ($Q = 0.23$; $I^2 = 27.7\%$) and sunbathing ($Q = 0.35$; $I^2 = 9.8\%$) meta-analyses. There was no statistical evidence of publication bias in the meta-analysis of relative risks for ever sunburn ($p = 0.93$). There was suggestion of publication bias for sunbathing ($p = 0.13$; Supplemental Figure 1) and the trim and fill approach implied that there may be two unpublished studies among the sunbathing meta-analysis and yielded a summary relative risk of 1.44 (95% CI: 1.18, 1.76). The trim and fill relative risk estimate for sunbathing

was used in all PAR and PIF analyses. In our previous publication we estimated that a relative risk of 1.38 (1.22, 1.56) for the ever versus never use of an indoor tanning device (26).

5.5.2.2 Prevalence of UVR Exposure Behaviours

Based on the past-year prevalence estimates from the NSS2 survey and applying our conversion factors (Table 3), we estimate that 32.1% of Caucasian Canadians have had a severe sunburn in adulthood, and that 54.5% have intentionally sunbathed at least once in adulthood (Table 3). The prevalence of sunburn in adulthood was higher for men (37.0%) than for women (27.3%). In contrast, the prevalence of intentionally sunbathing in adulthood was higher for women (62.8%) than for men (45.9%) (Table 3). For both men and women the prevalence of ever sunburn and sunbathing was highest for those aged 25-44. The prevalence of sunburn and sunbathing overall and stratified by sex for Canadian provinces are presented in Supplemental Tables 3 and 4.

5.5.2.3 Current Attributable Burden for UVR Behaviours

Estimated age- and sex-specific PARs for sunburn, sunbathing, and combined UVR risk behaviors (including indoor tanning) are presented in Table 4. In 2015, an estimated 29.7% of melanomas (2,040 cases) were attributable to the combination of sunburn, sunbathing, and indoor tanning. Independently, 7.4% of melanomas (509 cases) were attributable to sunburn, while 17.8% (1,225 cases) were attributable to intentional sunbathing. PARs for sunburn were higher for men than for women at all age groups. In contrast, the PARs for intentional sunbathing and for combined modifiable UVR risk behaviors were higher for women than for men in all age groups. The PARs for sunburn, sunbathing and combined modifiable UVR risk behaviors were highest for those aged 30-

49 and lowest for those aged greater than 50. Measures of statistical uncertainty (95% CIs) are presented in Supplemental Table 5. PAR results for Canadian provinces overall and stratified by sex for sunburn, sunbathing, and combined UVR risk behaviors is presented in Supplemental Table 6.

5.5.3 Future Avoidable Burden of Melanoma

We estimated that 10,349 melanoma cases will occur in 2042. If no reductions in modifiable UVR risk behaviors (indoor tanning, sunburn, or intentional sunbathing) occur, we estimate that 3,032 cases will be attributed to these behaviors in 2042. The number of melanoma cases that could be prevented by changing the prevalence of modifiable UVR risk behaviors, both separately and combined are presented in Table 5. If a 50% reduction in the prevalence of these risk behaviors steadily occurs by 2037, 1,242 melanoma cases could be prevented in 2042, with a cumulative total of 11,980 cases by 2042. If reduction of these behaviors were more modest (10-25%) by 2037, we would expect 218-570 cases to be prevented in 2042 and 2,191-5,656 cumulative melanoma cases could be prevented by 2042. Results for Canadian provinces stratified by sex are presented in Supplemental Tables 7 and 8.

5.6 Discussion

Incidence rates of melanoma in Canada have increased by over 50% in both males and females over the last three decades (1). After adjusting for improvements in reporting and changes in the ethnic distribution of Canada, we estimated that 62.3% of melanomas (4,276 cases) in 2015 were attributable to increases in UVR exposure. These estimates account for increases in exposure to solar UVR, but also for the use of indoor devices that were not available for earlier birth cohorts. In addition, we estimated that the combination

of sunburn, intentional sunbathing, and indoor tanning accounted for 29.7% of melanomas, with sunburn, sunbathing, and indoor tanning accounting for 7.4%, 17.8%, and 7.0%(26) of melanoma cases, respectively. PAR estimates for UVR exposure and for sunburn were highest for men, while PARs for sunbathing and for UVR behaviors combined were highest for women. By reducing the prevalence of indoor tanning, adulthood sunburn, and intentional sunbathing by 50%, 11,980 cases of melanomas could be prevented by 2042.

Several studies have used a similar birth cohort comparison to estimate a PAR for UVR. Parkin employed this approach using incidence data from 1960-2010 and a 1903 birth cohort as the referent in a comparison with 2010 incidence data and estimated a PAR of 85.9% for the UK (10). In 2010, Olsen and colleagues compared 2010 Australian melanoma rates to both the UK referent cohort and 1982 incidence data for Australia and estimated PARs of 63.3% and 45.1% respectively. Both the study for France and the world used the UK cohort as the referent and observed PARs of 83% for France and 90% for North America. The higher PAR for the UK, France, and North America is likely a product of not accounting for improvements in the reporting of melanoma, as capture rates for the UK have been historically low (49), and to some extent the use of a referent population that was less exposed to UVR (earlier cohort). The higher PAR in comparison to Australia can be partly explained by our use of earlier incidence data, but also possibly due to changes in exposure as a result of population-wide sun behavior campaigns and the banning of indoor tanning devices.

The method of PAR estimation based on the prevalence of exposure and relative risk estimates for UVR risk behaviors has been employed several times for indoor

tanning (11,50,51), but has rarely been used for sun-related behaviors. Indeed, only one study has estimated a PAR for a sun-related behaviors (51) and no study has sought to quantify a combined PAR across multiple UVR risk behaviors. Gandini and colleagues estimated that 13% of melanoma cases in Italy were attributable to intentional sun exposure, defined as greater than 3 hours in the sun per day. Our estimate of 17.8% of melanomas being attributable to intentional sunbathing is higher, but the estimates are difficult to compare given the disparate methods employed.

Strengths of our risk factor approach relate to estimates of relative risk, exposure estimation, and future burden under different counterfactual scenarios. First, we estimated relative risks for each UVR risk behavior that were generalizable to Canada and adjusted for important confounders. This method for PAR estimation is important given that ambient UVR varies by latitude. Second, we only included estimates that were mutually adjusted for the other UVR risk behaviors to ensure independent relative risks. Third, we used joint prevalence distributions due to the potential dependency of UVR risk behaviors. This point is important given that when risk factors are dependent, combining PARs with the Miettinen-Steenland and Armstrong approach (52,53) can lead to an underestimation (36). In this analysis we did not observe a large difference with the two approaches; the combined PAR was 29.7% when accounting for joint distributions and 29.2% when using the Miettinen-Steenland and Armstrong formula. Finally, our incorporation of PIFs is important for future interventions and policy targeted at these behaviors, and this type of analysis for UVR risk behaviors has only been conducted once before (54).

Our analysis of the prevalence of UVR risk behaviors among Caucasian Canadians show that yearly exposure is highest among the youngest age groups and decreases with age. From a cancer prevention standpoint, interventional strategies should be aimed at young adults, which if successful could lead to a considerably lower lifetime exposure to UVR if modification of behaviors can occur early in life. In addition, among this age group we observed that women were more likely to use indoor tanning devices (26) and sunbathe, while men were more likely to sunburn. These results suggest that prevention strategies should be sex-specific – focusing on reduction of tanning among young women, and on sun protection among young men.

While this study is the first application of the birth cohort approach that accounts for changes in ethnicity and reporting practices, our methods have some limitations. First, we generalized ethnic-specific melanoma incidence rates from the USA to Canada, which likely introduced some misclassification because of the potential differences in diagnosis and reporting. Second, the risk of melanoma associated with UVR exposure for Hispanics and Aboriginals is lower than that for Caucasians, however, the proportion of Hispanics and Aboriginals in Canada has only changed marginally. Third, we applied the rate of under-reporting equally across age groups and sex, which could lead to misclassification if under-reporting is more prevalent in a specific demographic group. Finally, we applied capture rates of Ontario to all of Canada, which may not be nationally representative.

Despite the strengths of our risk factor approach, our analysis has limitations that warrant acknowledgement. Our prevalence estimates were based on self-reported data and social desirability bias could have led to underestimations of exposure. In addition, there is a considerable amount of uncertainty involved in our conversion factor for past-

year exposure to ever exposure that could possibly lead to inaccurate results. Third, age categories were collapsed because of the lack of reliable prevalence estimates from the NSS2 and an appropriate conversion factor for certain categories. Our analysis of modifiable UVR risk behaviors was limited to adult exposures, which could underestimate PARs given that exposure early in life, particularly sunburns have been shown to play a role in the development of melanoma. For our PIF analyses we were unable to include projections of UVR risk behaviors due to insufficient population-based data. Our cohort approach provides some evidence that UVR risk behaviors have decreased in recent cohorts, particularly among younger men, and therefore our PIF estimations could be slight overestimations. Finally, projections of cancer incidence involves several assumptions each of which are associated with some degree of uncertainty, which ultimately influence our estimates of preventable cases.

5.7 Conclusions

To our knowledge, this is the first attempt to estimate the current and future burden of melanoma in Canada attributable to UVR and modifiable UVR risk behaviors. In addition, the methods we have employed can be adapted to derive estimates in other contexts. Given that melanoma rates continue to increase in Canada, preventive strategies aimed at the modifiable UVR behaviors is crucial to reduce the growing burden of melanoma.

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5.10 Conflict of Interests

None declared.

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5.12 Tables and Figures

Table 5.1 Melanoma cases diagnosed in 2015, estimated to be attributable to increases in UVR exposure in Canada

	Melanoma			All cancers*	
Age	**Obs.**	**PAR**	**AC**	**Obs.**	**PAR**
Males					
20-34	105	70.5	74	845	8.8
35-49	405	74.3	301	5355	5.6
50-64	1135	72.0	817	27920	2.9
65+	2165	60.7	1314	60790	2.2
Total	3810	65.8	2506	94910	2.6
Females					
20-34	225	68.0	153	1370	11.2
35-49	540	71.9	388	10300	3.8
50-64	990	66.0	653	29635	2.2
65+	1300	44.3	576	50855	1.1
Total	3055	57.9	1770	92160	1.9
Total	6865	62.3	4276	187070	2.3

*Excludes cases of non-melanoma skin cancer
Abbreviations: AC = Attributable cases due, Obs. = Observed cases, PAR = Population attributable risk

Table 5.2. Characteristics of studies relevant to Canada investigating the association of sunburn and/or sunbathing with the risk of melanoma (n = 10)

Study and Location	Design	Population	Age (range)	% Men	Exposure(s)
Autier, 1994 Europe	Population Case-control 1991-1992	412 cases, 445 controls	20- >60	45	Sunburn
Autier, 1998 Europe	Population Case-control 1991-1992	412 cases, 445 controls	20- >60	45	Sunbathing
Bataille, 2004 United Kingdom	Hospital Based Case-control 1989-1993	413 cases, 416 controls	16-75	not reported	Sunburn
Chen, 1996 Connecticut, USA	Population Case-control 1987-1989	512 cases, 624 controls	> 18	52.8	Sunburn
Han, 2006 USA (Nurses)	Nested Case-control 1989-1998	200 cases, 804 controls	30-79	0	Sunbathing and Sunburn
Kaskel, 2001 Germany	Hospital Based Case-control 1996-1997	271 cases, 271 controls	not reported	not reported	Sunbathing
Nielsen, 2012 Sweden	Prospective cohort 1990-1992	215 cases, 29,305 non-cases	25-64	0	Sunburn and Sunbathing
Walter, 1999 Ontario, Canada	Population Case-control 1984-1986	583 cases, 608 controls	20-69	47.1	Sunburn

Westerdahl, 1994 Sweden	Population Case-control 1988-1990	400 cases, 640 controls	15-75	48.8	Sunbathing
Zaridze, 1992 Russia	Population Case-control not reported	96 cases, 96 controls	not reported	not reported	Sunbathing

Table 5.3. Estimated prevalence of exposure to sunburn and sunbathing among Caucasian Canadians

Age (years)	Prevalence (95% confidence interval)					
	Sunburn			Sunbathing		
	Past year (%)	Conversion Factor	Ever exposed (%)	Past year (%)	Conversion Factor	Ever exposed (%)
Men						
16-24	35.5 (30.1-41.3)	--	35.5 (30.1-41.3)	35.2 (29.9-41.0)	--	35.2 (29.9-41.0)
25-44	27.6 (24.8-30.7)	1.72	47.5 (42.7-52.8)	20.7 (18.1-23.5)	2.75	56.8 (49.8-64.6)
44+	18.1 (15.8-20.6)	1.72	31.1 (27.2-35.4)	15.4 (13.3-17.7)	2.75	42.3 (36.6-48.7)
Total	23.6 (21.8-25.5)	--	37.0 (34.2-40.0)	19.9 (18.3-21.6)	--	45.9 (42.2-49.8)
Women						
16-24	33.7 (28.9-38.9)	--	33.7 (28.9-38.9)	53.0 (47.8-58.2)	--	53.0 (47.8-58.2)
25-44	22.8 (20.5-25.3)	1.72	39.3 (35.2-43.5)	32.9 (30.3-35.6)	2.75	90.5 (83.3-97.9)
44+	11.1 (9.6-12.9)	1.72	19.2 (16.5-22.2)	18.2 (16.3-20.2)	2.75	50.0 (44.8-55.6)
Total	17.7 (16.4-19.1)	--	27.3 (25.3-29.5)	27.3 (25.7-28.9)	--	62.8 (59.1-66.5)
Overall	20.6 (19.5-21.7)	--	32.1 (30.4-33.8)	23.7 (22.6-24.9)	--	54.5 (52.0-57.3)

*Data from the Second National Sun Survey (2006)
**Conversion factors were estimated by comparing estimates from Walter et al (1999) and The First National Sun Survey
Note: Total and overall prevalence calculated by population weighted averages

Table 5.4. Melanoma cases and proportions estimated to be attributable to sunburn, sunbathing and combined UVR risk behaviors in Canada in 2015

Age at Exposure	Age at Diagnosis	Sunburn			Sunbathing		Combined*	
		Obs.	PAR	AC	PAR	AC	PAR	AC
Men								
16-24	20-29	40	10.0	4	12.5	5	27.2	11
25-44	30-49	470	11.7	55	19.8	93	34.7	163
45+	>=50	3300	7.9	261	15.6	513	25.9	855
Total	Total	3810	8.4	320	16.0	611	27.0	1029
Women								
16-24	20-29	110	8.2	9	19.1	21	39.0	43
25-44	30-49	655	9.8	64	28.2	185	45.4	301
45+	>=50	2290	5.1	116	17.8	408	28.8	667
Total	Total	3055	6.2	189	20.1	614	32.7	1011
Total								
16-24	20-29	150	8.7	13	17.3	26	36.0	54
25-44	30-49	1125	10.6	119	24.7	278	41.2	464
45+	>=50	5590	6.7	377	16.4	921	27.2	1522
Total	Total	6865	7.4	509	17.8	1225	29.7	2040

*Includes joint distributions for indoor tanning (O'Sullivan et al., 2019), sunburn, and sunbathing
Abbreviations: AC = Attributable cases, Obs. = Observed cases, PAR = Population attributable risk

Table 5.5. Projected melanoma cases and proportions estimated to be attributable to modifiable UVR risk behaviors and proportion of melanoma cases that could be prevented in 2042 with various changes in the prevalence of modifiable UVR risk behaviors in Canada

Sex	Statistic	CTF	Indoor Tanning	Sunburn	Sunbathing	Combined
Men	Projected Cases	Base	5299	5299	5299	5299
	PAR (%)		4.6	8.3	15.9	26.6
	AC		242	439	841	1409
Women	Projected Cases		5050	5050	5050	5050
	PAR (%)		9.9	6.0	19.6	32.1
	AC		499	304	990	1623
Total	Projected Cases		10349	10349	10349	10349
	PAR (%)		7.2	7.2	17.7	29.3
	AC		741	743	1831	3032
Men	Projected Cases	50% reduction by 2037	5178	5079	4879	4704
	PIF (%)		2.3	4.2	7.9	11.2
	Prevented Cases		121	220	420	595
	Cumulative Cases		1187	2158	4133	5841
Women	Projected Cases		4800	4898	4555	4403
	PIF (%)		5.0	3.0	9.8	12.8
	Prevented Cases		250	152	495	647
	Cumulative Cases		2401	1462	4759	6139
Total	Projected Cases		9978	9977	9434	9107
	PIF (%)		3.6	3.6	8.8	12.0
	Prevented Cases		371	372	915	1242
	Cumulative Cases		3588	3620	8892	11980
Men	Projected Cases	25% reduction by 2037	5239	5189	5089	5023
	PIF (%)		1.1	2.1	4.0	5.2
	Prevented Cases		60	110	210	276
	Cumulative Cases		594	1079	2036	2779
Women	Projected Cases		4925	4974	4802	4756
	PIF (%)		2.5	1.5	5.2	5.8
	Prevented Cases		125	76	248	294
	Cumulative Cases		1201	831	2380	2877

Total	Projected Cases	10% reduction by 2037	10164	10163	9891	9779
	PIF (%)		1.8	1.8	4.4	5.5
	Prevented Cases		185	186	458	570
	Cumulative Cases		1795	1910	4416	5656
Men	Projected Cases		5275	5255	5215	5193
	PIF (%)		0.5	0.8	1.6	2.0
	Prevented Cases		24	44	84	106
	Cumulative Cases		237	432	827	1081
Women	Projected Cases		5000	5019	4951	4938
	PIF (%)		1.0	0.6	2.0	2.2
	Prevented Cases		50	31	99	112
	Cumulative Cases		480	292	952	1109
Total	Projected Cases		10275	10274	10166	10131
	PIF (%)		0.7	0.7	1.8	2.1
	Prevented Cases		74	75	183	218
	Cumulative Cases		717	724	1779	2191

Abbreviations: AC = Attributable cases, CTF = Counterfactual scenario, PIF = Potential impact fraction

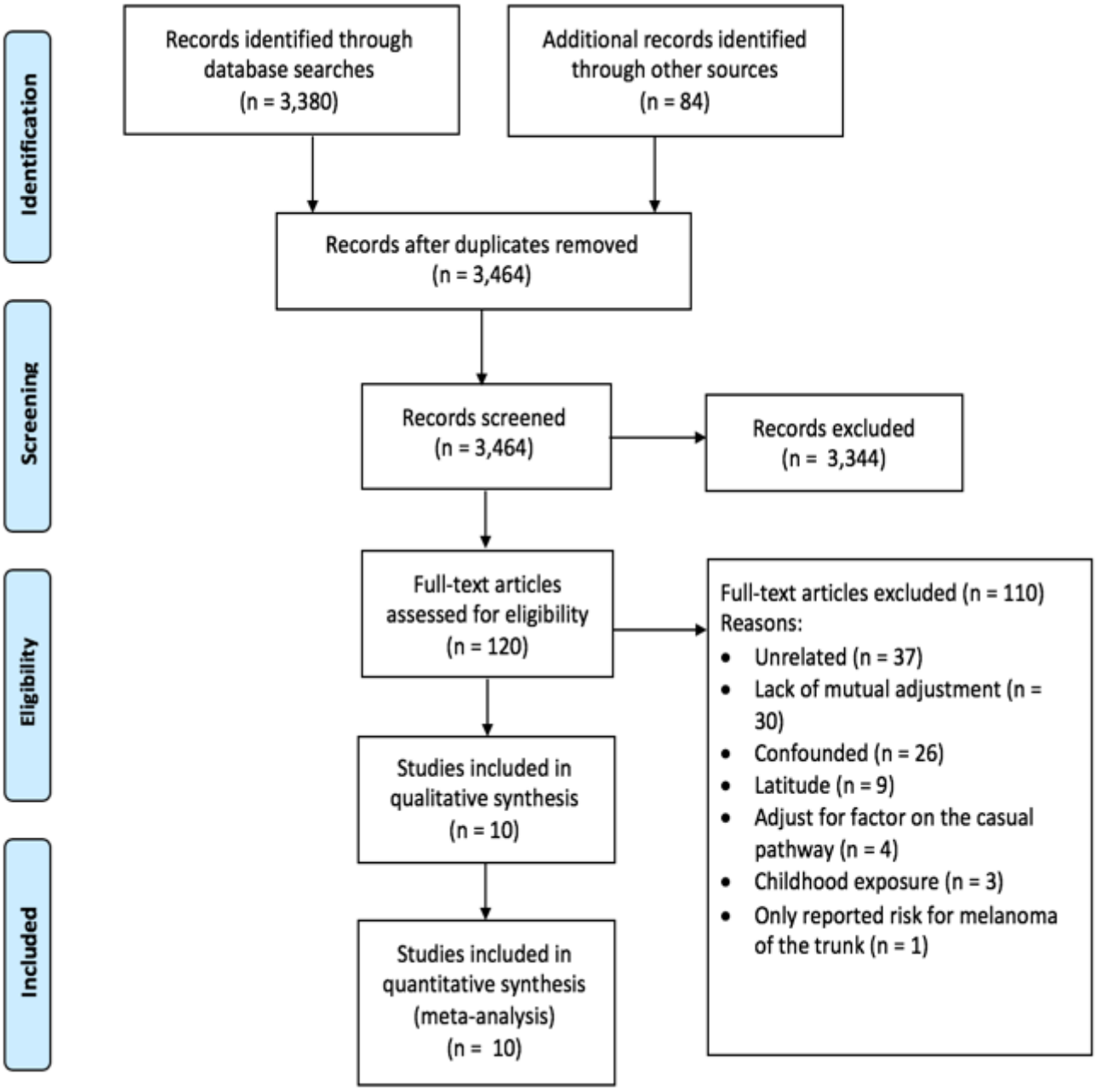

Figure 5.1. Flow diagram of the selection procedure of studies relevant to Canada assessing the relationship of sunburn or sunbathing with the risk of melanoma

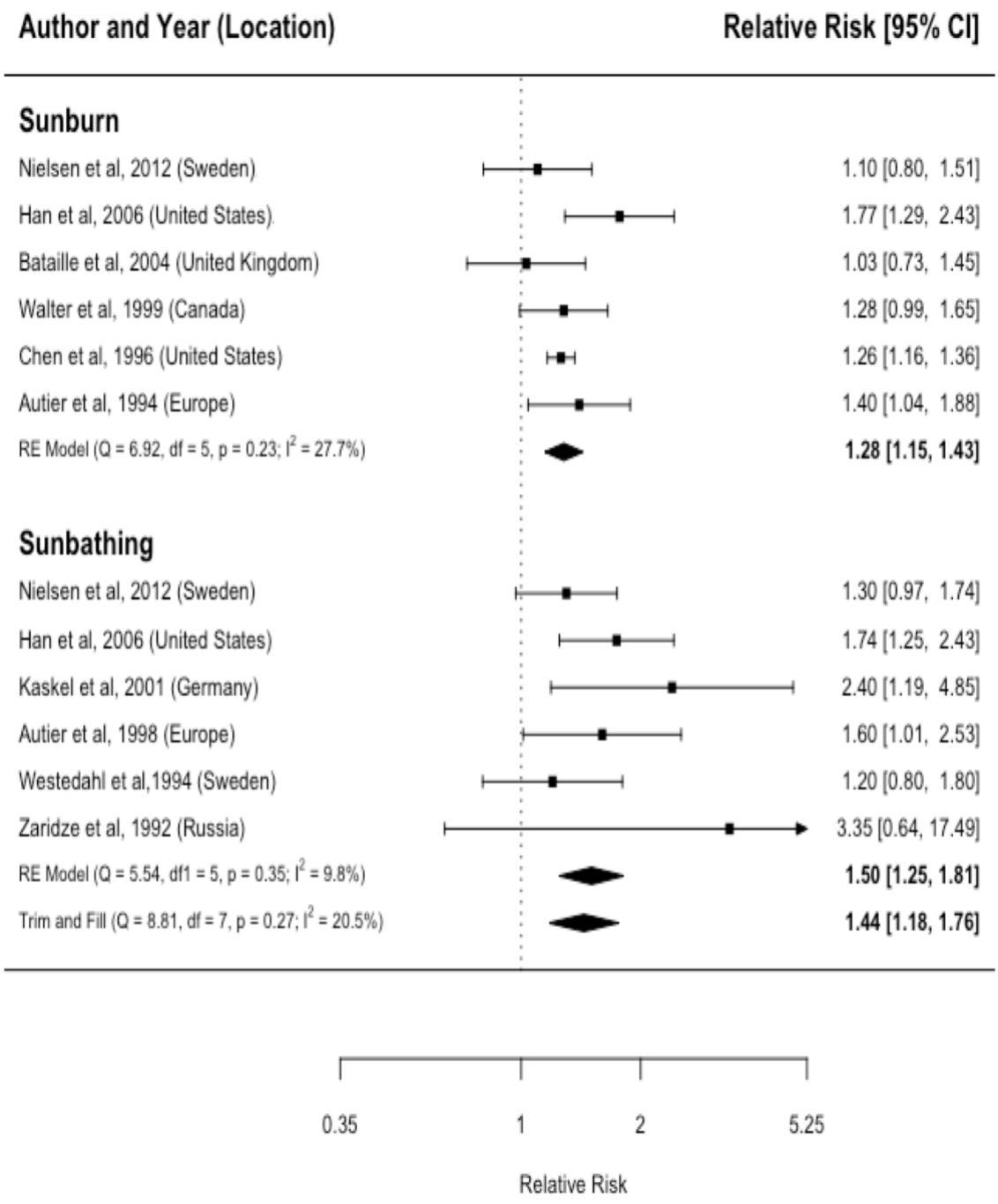

Figure 5.2. Estimated relative risk of melanoma for sunburn and sunbathing that are generalizable to Canada.

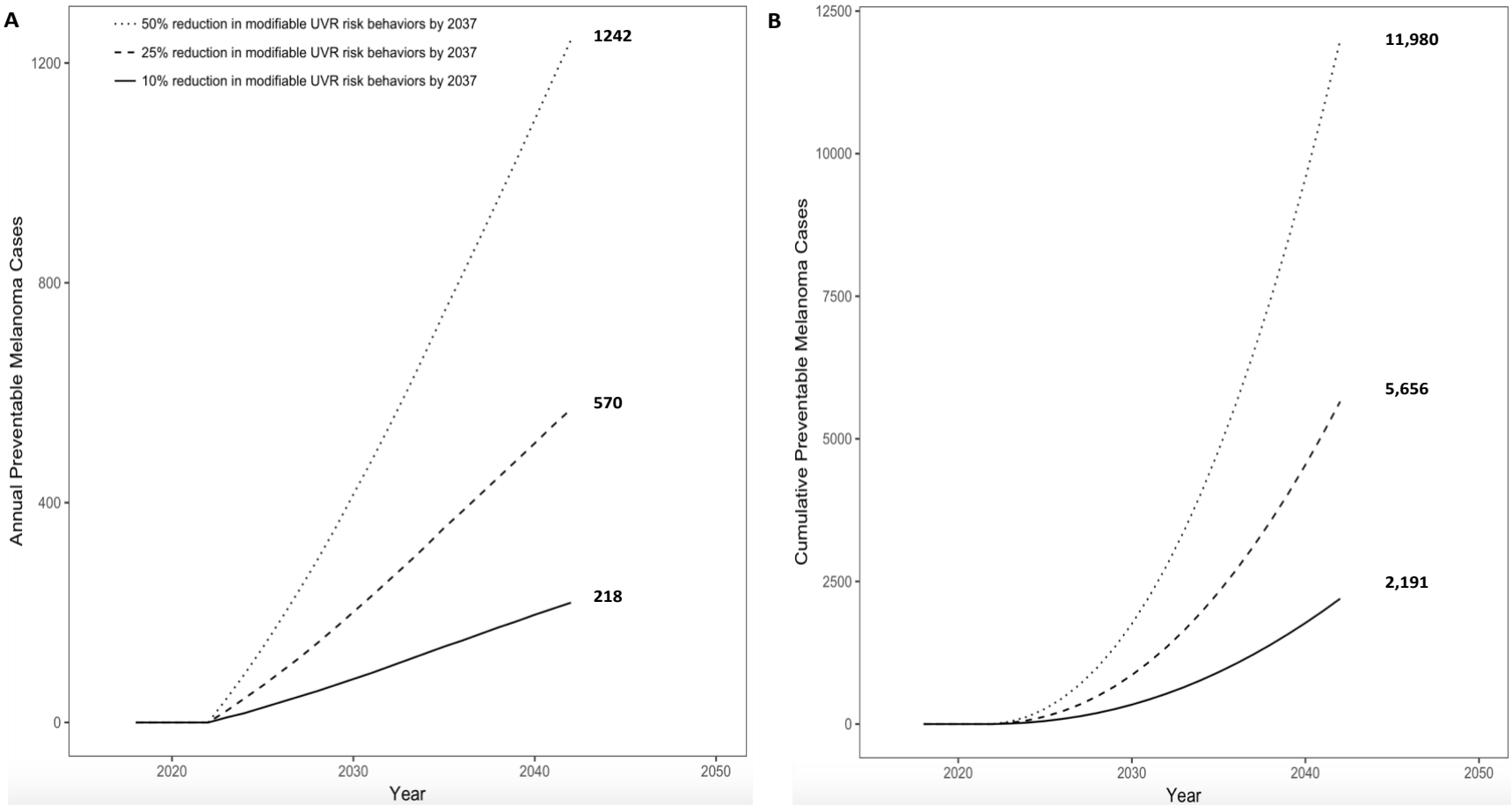

Figure 5.3. A) Projected annual preventable melanoma cases attributable to modifiable UVR risk behaviors by applying 3 counterfactual scenarios; B) Projected cumulative preventable melanoma cases attributable UVR risk behaviors by applying 3 counterfactual scenario.

Chapter 6

The current burden of non-melanoma skin cancer attributable to ultraviolet radiation and related risk behaviours in Canada

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6.1 Abstract

Background: Ultraviolet radiation (UVR) is an established cause of non-melanoma skin cancer (NMSC) – basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). The aim of this study was to estimate the current burden of BCC and SCC associated with UVR and modifiable UVR risk behaviours (sunburn, sunbathing, and indoor tanning) in Canada in 2015.

Methods: The current burden for UVR was estimated by comparing current incidence rates (2015) with rates of less exposed body sites (trunk and legs) after adjusting for estimated surface areas of the sites. The burden for modifiable UVR risk behaviors was estimated by using prevalence estimates among Caucasians from the Second National Sun Survey, and relative risks that are generalizable to Canadians from conducting meta-analyses of relevant studies.

Results: We estimated that 80.5% of BCCs and 83.0% of SCCs were attributable to UVR. Adult sunburn was associated with relative risks of 1.85 (95% CI: 1.15-3.00) for BCC and 1.41 (95% CI: 0.91-2.18) for SCC, while adult sunbathing was associated with relative risks of 1.82 (95% CI: 1.52-2.17) for BCC and 1.14 (95% CI: 0.53-1.70) for SCC. We estimated that 18.5% of BCCs and 9.9% of SCCs were attributable to adult sunburn, while 28.0% of BCCs were attributable to adult sunbathing. We estimated that 46.0% of BCCs and 17.4% of SCCs were attributable to modifiable UVR risk behaviours combined.

Conclusions: Our results provide quantifiable estimates of the potentially avoidable burden of NMSCs among Canadians.

Impact: These estimates can be used to motivate prevention efforts and programming in Canada.

6.2 Introduction

Non-melanoma skin cancer (NMSC) accounts for approximately 40% of cancer diagnoses in Canada (1) and is the most common cancer among Caucasian populations (2). In 2015, it was estimated that 78,300 cases of NMSC occurred in Canada (3). NMSC is comprised of two distinct subtypes, where basal cell carcinoma (BCC) accounts for approximately 77% of NMSC cases and squamous cell carcinoma (SCC) accounts for the remaining 23% of cases in Canada (1). BCC has a high survival rate (100% 5-year relative survival) and tends to occur more commonly in younger individuals, while SCC has a greater propensity to metastasize and typically occurs in older adults (4). People who that develop NMSCs tend to subsequently have multiple lesions throughout their lifetime and are at increased risk of melanoma and non-cutaneous cancers (5). Although rarely fatal, the high incidence of NMSC results in a considerable burden of disease in terms of morbidity, social impact and health care costs. Indeed, the Global Burden of Disease project estimated that NMSC was responsible for 1.3 million disability adjusted life years lost in 2017 (6). It was estimated that the economic burden of skin cancer in Canada in 2004 was $532 million (7).

The relative risks associated with different patterns of exposure to solar ultraviolet radiation (UVR) differ for the subtypes of NMSC. BCC is most strongly related to a history of sunburn and measures of intermittent exposure to the sun, such as sunbathing and beach vacations (8). SCC, on the other hand, is most strongly associated with continuous patterns of sun exposure, including occupational exposures (9). A weak relation between occupational sun exposure and BCC has also been observed (9). The relation between solar UVR exposure and NMSC is dependent on latitude with stronger associations being observed closer to the equator. The relation of different sun exposure

patterns and NMSC subtypes at different latitudes has not been explored in a systematic review or meta-analysis, but relationships are hypothesized to vary by latitude. In terms of exposure to artificial tanning devices, increased risks have been demonstrated for both NMSC subtypes (10).

Few studies have estimated the proportion or number of NMSCs attributable to exposure to UVR. Indeed, only Olsen et al. (2015) has estimated a population attributable risk (PAR) for UVR and NMSC, and did so by comparing NMSC incidence rates in Australia to incidence rates in Nordic countries (11). This PAR is difficult to interpret, since it largely accounts for differences in ambient UVR rather than behaviours, which is not modifiable. The most common PAR approaches for UVR estimate the difference between skin cancer incidence in a target population and a theoretical 'unexposed' population. The two most common variants of this approach use incidence rates in an earlier birth cohort (12) or incidence rates on body sites not usually exposed to the sun as the theoretical unexposed population (13). However, these approaches require routinely collected incidence data for the former and incidence by anatomical location for the latter, but most cancer registries do not capture the corresponding data for NMSC. To our knowledge, no previous study on NMSC has estimated a PAR for UVR exposure using one of the above approaches. There have been two previous studies on NMSC that have estimated PARs associated with indoor tanning in Europe (10), the United States (10), and Canada (14), but there have been no previous studies that have estimated PARs for NMSC associated sun behaviours, such as sunburn and sunbathing. Several studies have estimated PARs for NMSC associated with occupational UVR exposure (15-17), including a recent study in Canada (18). The purpose of this study was therefore to

estimate the burden of NMSC in the Canadian population in 2015 that were attributed to UVR and to non-occupational UVR risk behaviours (sunburn, sunbathing, and indoor tanning).

6.3 Materials and Methods

This analysis was part of the Canadian Population Attributable Risk of Cancer (ComPARe) study, and the methods for this study has been previously summarized (19). Methods for estimating the PARs for UVR exposure and melanoma have been previously published (20). We have adapted these methods to this paper.

6.3.1 Body Site Distribution Comparison

Armstrong and Kricker (13) developed an approach to estimate the proportion of skin cancer attributable to UVR exposure based on the anatomical location of the lesions. They assumed that if skin cancers were not related to UVR exposure that they would be evenly distributed across the body. In other words, the rate of skin cancer per unit area of skin is similar to the rate at other sites with varying UVR exposure. This approach assumes that skin cancers on exposed body parts are attributable to UVR exposure, while unexposed body parts are not, and therefore the latter can be used as the non-exposed rate. This method requires knowledge of the anatomical site of the neoplastic lesions and uses the direct method of PAR estimation:

$$PAR = \frac{Incidence_{population} - Incidence_{non-exposed}}{Incidence_{population}}$$

Where Incidence $_{population}$ represented the incidence rate of NMSC in the Canadian population, and Incidence $_{non\text{-}exposed}$ was the incidence rate of the body site deemed as having low exposure to UVR. Using the International Classification of Diseases for Oncology Third Edition (ICD-O-3) codes we were able to categorize body sites into four broad categories: head and neck (C44.0, C44.1, C44.2, C44.3, C44.4), trunk (C44.5), upper limbs (C44.6), and lower limbs (C44.7). The non-exposed body site for this analysis was the combination of trunk and legs. The non-exposed rate was adjusted for surface area of those sites (trunk/legs) where the incidence rate was calculated as:

$$Incidence\ rate\ non\ exposed = \frac{\%\ of\ cases \times Incidence_{population}}{Proportion\ of\ skin\ surface\ area}$$

% of cases = proportion of cases occurring on trunk/legs

The proportion of skin surface area for the non-exposed site (trunk/legs) was estimated using data from Neaman et al. 2011, which provides estimates that are sex and body mass index (BMI) specific (21). Given that body site specific surface areas vary by BMI (normal/overweight versus obese), for each age and sex group we calculated proportion of skin surface area with a weighted average by the proportion of adults that were normal/overweight and obese from the Canadian Health Measures Survey that were adjusted for self-reporting (22). In summary, the non-exposed rate was the incidence of NMSC that would be observed on the whole body if the incidence per unit area of the non-exposed site were to apply to the whole body.

The body site distribution of NMSC cases in Canada was obtained from the 2014 Canadian Cancer Statistics report (1), which was based on data from five Canadian

provinces (Alberta, Manitoba, Quebec, New Brunswick and Newfoundland). Age, sex, and histological subtype distributions were estimated from NMSC data obtained from the Manitoba Cancer Registry and were applied to the total number of NMSC cases estimated by the 2015 Canadian Cancer Statistics report (3). While the risk of NMSC associated with UVR exposure varies by ethnicity (8), we assumed that this would be captured by the site distribution of NMSC. We therefore did not take into account ethnicity and the PAR estimate applied to all of Canada.

6.3.2 The UVR risk factor approach

The proportion of NMSCs cases in Canada in 2015 that was attributable to different UVR risk behaviours (indoor tanning, sunburn, and sunbathing) was estimated using the traditional risk factor approach that applies summary relative risk and population prevalence estimates to the Levin formula (23). The methods for estimating PARs for indoor tanning and the results for that analysis in relation to NMSC have been previously published (14).

6.3.2.1 Estimating Relative Risks Relevant in Canada

To determine relative risks for NMSC subtypes for each UVR risk behavior, including sunburn, sunbathing, and time spent in the sun, we conducted a systematic review and meta-analysis of the current literature. A full-text review of all studies included in the most recent review for the risk of NMSC associated with solar UVR behaviors (24), as well as a systematic review of studies published after 2007 were conducted. The literature search was conducted in PubMed using the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). All studies published between January 2008 and December 2018 were reviewed using the

following search terms: “sun” or “sunbathing” or “sunburn” or “sunlight” or “solar ultraviolet” or “sunbed” or “indoor tanning” or “artificial ultraviolet” and “basal cell carcinoma” or “squamous cell carcinoma” or “non-melanoma skin cancer”. The terms relevant to indoor tanning were included to capture studies that include sunburn or sunbathing as secondary analyses. Inclusion of a study in the meta-analysis was determined according to the criteria applied by O’Sullivan et al. (2019) (20), and eligibility was assessed independently by DO’S and WK. Briefly, studies needed to be conducted at a latitude similar to Canada, adequately control for confounding (host characteristics and other UVR-related behaviours), contain an appropriate control group, report an effect estimate for adult or lifetime exposure, and report effect estimates for BCC and SCC separately. If two studies reported findings for the same population, the study with the larger sample size or with the most relevant exposure was included.

For studies that met our inclusion criteria we extracted the adjusted effect estimates for “ever” being exposed to the UVR risk factor. Some studies included in this analysis reported effect estimates for different levels of exposure rather than for “ever” being exposed. To obtain an “ever” exposed metric to match our prevalence estimates, effect estimates for exposure levels were combined using inverse variance weighting. The standard error for this estimate was computed using crude data to adjust for the degree of covariance among the exposure categories (25).

For the purposes of this study, hazard ratios and odds ratios were assumed to be approximations of relative risk. DerSimonian and Laird random-effect models were used in all analyses (26). The degree of heterogeneity was estimated using the Q-test and the I^2 statistics (27). To assess for publication bias we inspected funnel plots and employed

both Egger's weighted linear regression (28) and Begg's rank correlation tests (29). Where there was evidence of publication bias, the trim and fill approach was employed to obtain a summary relative risk estimate. All analyses were performed using the R computing framework (www.r-project.org).

6.3.2.2 Estimating Prevalence of Exposure

The prevalence of ever sunburn in adulthood, ever sunbathing in adulthood, and ever indoor tanning in lifetime in Canada have been previously estimated and have been used for these analyses (30,31).

6.3.2.3 Cancer Incidence and Target Population

The estimated numbers of newly diagnosed NMSC cases in Canada 2015 was obtained from the Canadian Cancer Statistics report (3). These estimates were based on incidence data from the four provincial registries that currently collect data on NMSC (Alberta, Manitoba, New Brunswick and Newfoundland) and the pooled rates were applied to Canada to estimate absolute number of cases. Age, sex, and histological subtype distributions were estimated from NMSC data obtained from the Manitoba Cancer Registry and were applied to the total number of NMSC cases estimated by the 2015 Canadian Cancer Statistics report.

The relative risks for UVR risk behaviors are derived from studies that only include Caucasians, and the majority of NMSCs in Canada occur among Caucasians, therefore our PAR estimates only apply to this subgroup. To apply our approach exclusively to Caucasians, UVR risk behavior prevalence for Caucasians was ascertained from the NSS2. To estimate the number of attributable cases, the Caucasian-specific PARs were then applied to 98.9% of NMSC cases in Canada (14). While it has been

shown that 98.9% of melanoma cases in Canada occur among Caucasians, similar estimates do not exist for NMSC (32). Given that NMSC predominantly occurs among Caucasians to a similar magnitude as melanoma (8), we used this to estimate the number NMSC cases in Canada occurring among Caucasians.

6.3.2.4 Population Attributable Risk

Age- and sex-specific exposure prevalence and summary relative risk estimates from meta-analyses were applied to the Levin formula (23) to estimate age- and sex-specific PARs for each UVR risk factor. PAR estimates were applied to both BCC and SCC incidence data for each age and sex category, and the number of attributable cases were summed for each subtype (BCC and SCC) separately. The number of attributable cases was divided by the total incident cases in 2015 to obtain overall PARs associated with each UVR risk factor for each subtype. The method used in O'Sullivan et al., 2019 (20) was utilized to estimate a combined UVR risk behaviour PAR. Specifically, we estimated joint exposure distributions and assumed independent and multiplicative relative risks.

6.4 Results

In the approach based on a contrast of incidence by anatomical site, we estimate that 81.1% of all BCC cases in men and 79.7% in women could be attributable to UVR exposure in Canada in 2015, leading to a PAR of 80.5% (Table 1). Similarly, we estimate that 88.3% of all SCC cases in men and 73.5% in women are a consequence of UVR exposure, resulting in an overall PAR of 83.0% (Table 1). The PAR estimates were higher for men than women and increased with age.

We identified 36 studies from a previous review conducted by IARC and identified 5,115 studies in the PubMed search of studies published after the IARC review (Figure 1). Eighty-nine studies underwent full-text review. After full-text screening, six studies met the inclusion criteria for the relation of sunburn and/or sunbathing on the risk of one or both of the NMSC subtypes (33-38). The primary reasons for exclusion were the lack of mutual adjustment of UVR risk behaviours (n = 25) or lack of control of an important confounder (n = 23). The characteristics of the included studies are presented in Table 2.

Random effect meta-analyses yielded pooled relative risks of 2.24 (95% CI: 1.37-3.36) and 1.41 (95% CI: 0.91-2.18) for BCC and cutaneous SCC associated with ever having a severe sunburn in adulthood (Figure 2). There was significant heterogeneity among relative risk estimates for both BCC ($Q < 0.001$; $I^2 = 81.1\%$) and cutaneous SCC ($Q = 0.07$; $I^2 = 68.8\%$). There was evidence of publication bias for BCC (Eggers: $p < 0.001$), but not cutaneous SCC (Eggers: $p = 1.0$). The trim and fill approach imputed one study in the sunburn and BCC meta-analysis (Supplemental Figure 1) and yielded a pooled relative risk of 1.85 (95% 1.15-3.00). Despite the cutaneous SCC meta-analysis not reaching statistical significance, subsequent estimations of PARs included sunburn for SCC, since statistical power for this analysis was limited and a previous systematic review has identified sunburn as a risk factor for SCC (8).

Random effect meta-analyses yielded pooled relative risks of 1.82 (95% CI: 1.52-2.17) and 1.14 (95% CI: 0.53-2.46) for BCC and cutaneous SCC associated with sunbathing (Figure 2). There was considerable heterogeneity among the relative risk estimates for cutaneous SCC ($Q < 0.001$; $I^2 = 91.7\%$), but not BCC ($Q = 0.90$; $I^2 = 0.0\%$).

There was no evidence of publication bias for either of the meta-analyses (Eggers: BCC: $p = 0.93$; SCC: $p = 1.0$). In our previous publication (14) we estimated relative risks of 1.29 (95% CI: 1.23-1.36) and 1.49 (95% CI: 1.23-1.80) associated with the ever use of an indoor tanning device for BCC and cutaneous SCC, respectively.

Estimated age- and sex-specific PARs for sunburn, sunbathing, and combined UVR risk behaviours (including indoor tanning) associated with BCC are presented in Table 3. 18.5% of BCCs (10,701 cases) in 2015 were attributable to ever sunburn in adulthood, while 28.0% (16,175 cases) were attributable to ever sunbathing in adulthood. Collectively, an estimated 46.0% of BCCs (26,636 cases) in 2015 were attributable to the combination of sunburn, sunbathing, and ever indoor tanning during lifetime. For both sexes, PARs were highest among the age group 25-44 years for ever sunburn and sunbathing in adulthood, respectively.

The estimated age- and sex-specific PARs for sunburn and combined UVR risk behaviours (sunburn and indoor tanning) for SCC are presented in Table 5. An estimated 9.9% (2,028 cases) of cutaneous SCCs in 2015 were attributable to ever sunburn in adulthood, while 17.4% of cutaneous SCCs (3,553) were attributable to the combination of ever sunburn in adulthood and ever indoor tanning during lifetime. Similar to BCC, PARs for sunburn and the combination of sunburn and indoor tanning were highest among the age group 25-44 years for both men and women, respectively.

6.5 Discussion

In this study, we estimated that 80.5% of BCCs (46,565 cases), and 83.0% of SCCs (16,947 cases) in 2015 were attributable to regular exposure to UVR, which includes both occupational and recreational exposures. In meta-analyses relevant to

exposure in Canada, ever sunburn in adulthood was associated with increased risks of 1.85 (95% CI: 1.15-3.00) for BCC and 1.41 (95% CI: 0.91, 2.18) for cutaneous SCC, while ever sunbathing in adulthood was associated with risks of 1.82 (95% CI: 1.52-2.17) for BCC and 1.14 (95% CI: 0.53-2.46) for cutaneous SCC. We estimated that 18.5% of BCCs and 9.9% of SCCs were attributable to sunburn in adulthood, while 28.0% of BCCs were attributable to sunbathing in adulthood. Additionally, we estimated that the combination of sunburn, sunbathing, and indoor tanning accounted for 46.0% of BCCs and 17.4% of cutaneous SCCs, respectively. PARs were highest for women and the middle age group (24-44) for both sexes.

Only one previous study has estimated a PAR for UVR exposure and NMSC (11). Olsen and colleagues estimated that in Australia that 99.4% of NMSC cases were attributable to higher ambient UVR by comparing incidence rates to Nordic countries. Given that ambient UVR could only be modified through substantial geographic migration, we sought to estimate PARs associated with exposure to body sites usually exposed to the sun. In a previous estimation of the attributable burden of melanoma in Canada associated with UVR, we used a birth cohort comparison approach, but this method requires reliable historical incidence data. Only the province of Manitoba has routinely collected incidence data for NMSC, but it is consistently under-reported and it is difficult to know how its incidence varied over time. Instead, for NMSC we used a body site distribution comparison of NMSC on sun exposed versus typically unexposed areas with the assumption that underreporting occurs equally across different body sites.

Previous studies that have used the body site distribution approach on a smaller scale for melanoma (13,39) and have ascertained detailed anatomical locations of the

melanomas through pathology reports. In these studies, unexposed body parts (buttocks for both sexes, and scalp for women) were used as the referent category, leading to PAR estimations of 97% for Australia and 95% for Nordic countries, respectively. These estimates were then interpreted as the absolute proportion of melanoma cases that were attributable to UVR exposure. In our study, access to pathology reports was not feasible and thus we had to rely on broader and less detailed anatomical locations — as provided by ICD-0-3 codes. From these codes we were able to categorize body sites into four groups of mixed UVR exposure: head, arms, legs, and trunk. We used a combination of the trunk and legs as the least exposed rate. Given these broader categories we likely underestimated the 'true' fraction of NMSCs attributable to UVR exposure. This underestimation occurred because our referent body sites are not completely unexposed to UVR, but are only less exposed than the face or arms. Indeed, the trunk is particularly susceptible to intermittent sun exposure—an exposure pattern associated with BCC. The PAR that was derived from this approach can be interpreted as the proportion of NMSC cases that could be reduced if our entire bodies were exposed to UVR to the same degree as the trunk/legs. While this PAR is not necessarily a modifiable PAR, it could represent the proportion of NMSC cases that are attributed to regular UVR exposure (recreationally and from occupation), and thus may reflect the proportion of cases that could be reduced if long and consistent durations in the sun were minimized. All body site distribution studies to date, as well as PAR projects using this method have estimated the proportional surface area of body sites using the data of Lund and Browder (40) for major parts of the body and using the data of Pearl and Scott (41) for smaller sub-sites. While these data sources provide reasonable estimates for normal weight individuals, they can misclassify

the distribution of body surface area for individuals suffering from obesity, and they are not sex-specific (21). A strength of this investigation is that we applied sex and BMI-specific body surface areas (21) to the demographics to Canada, which should reduce potential misclassification.

The risk behaviour PAR approach that incorporates prevalence of exposure and relative risk estimates for a specific behaviour has been conducted for indoor tanning and NMSC in several geographic regions (14,42), but has never been used for sun-related exposures or for a combined modifiable UVR risk behaviour PAR. Use of this method requires up-to-date relative risk estimates for each behaviour that are generalizable to the population of interest. There has only been one previous meta-analysis for UVR risk behaviours and subtypes of NMSC (8). In that study, Armstrong and Kricker estimated that sunburns were associated with relative risks of 1.40 (95% CI: 1.29, 1.51) for BCC and 1.23 (95% CI: 0.90, 1.69) for cutaneous SCC based on studies published prior to 2001. In contrast, we estimated relative risks of 1.85 (95% CI: 1.15, 3.00) for BCC and 1.41 (95% CI: 0.91, 2.18) for cutaneous SCC, respectively based on an up-to-date systematic review and meta-analysis. The higher relative risks found in this study could be due to our restriction to studies that controlled for host characteristics and other UVR-related behaviours. Armstrong and Kricker, in contrast, included studies that only controlled for age and sex. Given their broader inclusion, Armstrong and Kricker concluded that the effect for SCC was likely a product of residual confounding from sun sensitivity. Our study, however, controlled for these additional factors and provide evidence that there may be a relationship between sunburn and cutaneous SCC. Molecular studies have shown that TP53 gene mutations are common in cutaneous SCCs

and that mutations of this gene is strongly related with sunburns (43), which provides some biologic plausibility for this relationship. For intermittent sun exposure, such as sunbathing, our estimate for BCC was higher than Armstrong and Kricker's, which is likely due to our analysis only including studies that mutually control for sun behaviours and host characteristics. Indeed, individuals with lighter skin pigmentation are at increased risk for BCC, but are also less likely to partake in sunbathing activities, which could lead to confounding that biases effect estimates towards the null. For cutaneous SCC we observed a null relationship for sunbathing, which is consistent with previous literature.

Our estimate of the proportion of cases attributable to modifiable UVR risk behaviours was considerably larger for BCC than for cutaneous SCC. This estimate is largely due to BCC being strongly associated with sunburn and sunbathing, while evidence suggests that SCC is only moderately associated with sunburn and is not related to sunbathing at all. Cutaneous SCC, on the other hand, is most strongly related with continuous or consistent exposure to the sun, such as outdoor occupational work. A recent study estimated that 9.2% of cutaneous SCCs are attributable to occupational sun exposure (18), which leaves a considerable portion of SCCs that are likely attributable to consistent non-occupational sun exposure. In this study, we sought to estimate PARs for SCC associated with typical time spent in the sun during summer months, however, there were no studies with these exposure metrics that met our inclusion criteria, and therefore we were unable to obtain an appropriate effect estimate. Given that there is literature emerging for possible protective effects of moderate amounts of time spent in the sun with some non-cutaneous cancer sites (44), it is important to determine the association of

time spent in the sun for BCC and SCC to adequately inform population and individual sun-related behavioural changes aimed at reducing the risk of developing cancer.

Our risk behaviour approach identified age group 24-44 years as having the highest PARs for sun-related behaviours, which makes immediate interventions important for reducing the growing burden of NMSC in Canada. Given the absolute number of NMSC cases attributable to UVR, the implementation of population interventions that reduce the prevalence of exposure to modifiable UVR risk behaviours is imperative. If these types of interventions were implemented a considerable impact on population health could be achieved and costs associated with treatment for NMSC controlled. In addition, while the direct mechanisms remain unclear, the occurrence of NMSC is associated with increased risk of several non-cutaneous cancers (5), and therefore the reduction in NMSC may lead to an overall reduction in other cancers as well.

Our risk behaviour approach had a number of strengths and limitations that have been detailed elsewhere (20). Briefly, strengths include obtaining relative risk estimates that are generalizable to Canada, our approach to joint exposure estimation, and incorporation of future burden under different counterfactual scenarios. Limitations include use of self-reported exposure information, conversion of past-year exposure to ever exposure, and the inability to project the future prevalence of UVR risk behaviours due to insufficient data on historical UVR exposure levels. In addition, there are limitations of this study that are inherent to the quality of data on the incidence of NMSC. First, Canada does not have a national surveillance system and thus we had to rely on data from only select provinces for our body site approach. Second, many NMSC cases

are diagnosed and treated outside of a hospital setting and without confirmatory biopsies, which likely led to underestimations of the absolute number of cases attributed to exposure to UVR and UVR risk behaviours. Third, individuals that develop NMSC cases tend to develop multiple lesions, which could also be due to exposure to UVR, but we lack data at this level. Finally, we were unable to estimate potential impact fractions associated with potential interventions, since that would require reliable historical prevalence and incidence data, which is not available for Canada.

6.6 Conclusion

This study is the first to estimate the current burden of NMSC in Canada attributable to UVR and the first study to estimate PARs for NMSC associated with modifiable UVR risk behaviours. Estimates indicate that a considerable proportion of BCCs are attributed to modifiable UVR behaviours, while cutaneous SCCs are primarily a product of general exposure to the sun. Prevention efforts aimed at high-risk patterns of exposure are required to reduce the large and potentially increasing burden of NMSC in Canada.

6.7 Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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6.10 Tables and Figures

Table 6.1 Estimated non-melanoma skin cancer cases diagnosed in 2015, estimated to be attributable to ultraviolet radiation in Canada

Age	Basal cell carcinoma			Cutaneous squamous cell carcinoma		
	Obs.	PAR	AC	Obs.	PAR	AC
Men						
<50	2751	78.8	2168	260	63.5	165
50-69	13651	77.8	10617	3530	82.2	2900
70+	14823	84.6	12538	9285	91.3	8475
Total	31225	81.1	25323	13075	88.3	11540
Women						
<50	3758	72.7	2732	248	47.6	118
50-69	10481	76.8	8046	1713	61.6	1055
70+	12408	84.3	10464	5393	78.5	4234
Total	26647	79.7	21242	7354	73.5	5407
Total						
<50	6509	75.3	4900	508	55.7	283
50-69	24132	77.3	18663	5243	75.4	3955
70+	27231	84.5	23002	14678	86.6	12709
Total	57872	80.5	46565	20429	83.0	16947

*PAR was calculated with the body site distribution direct approach with the trunk/leg as the least-exposed rate

**Incidence rate for the trunk/leg was calculated by multiplying the proportion of cases in those body sites by the incidence rate in the population, which was then divided by the proportion of skin surface area for those body site

Abbreviations: AC = Attributable cases due, Obs. = Observed cases, PAR = Population attributable risk

Table 6.2. Characteristics of studies relevant to Canada investigating the association of sunburn and/or sunbathing with the risk of basal cell carcinoma or cutaneous squamous cell carcinoma (n = 6)

Study and Location	Design	Population	Age (range)	% Men	Exposure(s)
Dessinioti, 2011 Greece	Case-control (relative based) 2006-2009	199 BCCs, 200 controls	54.2*	51.4	Sunbathing
Han, 2006 United States	Case-control (nested) 1991-1992	200 BCCs, SCCs, 804 controls	30-79	0.0	Sunburn and Sunbathing
Kaskel, 2015 Germany	Case-control (hospital based) 1997-1999	212 BCCs, 329 controls	27-92	49.4	Sunburn
Rosso, 1998 Europe	Case-control (population based) 1989-1993	420 BCCs, 419 controls	not reported	not reported	Sunbathing and Sunburn
Walther, 2004 Germany	Case-control (hospital) 1997-1999	214 BCCs, 411 controls	69 for BCC, 58 for controls**	48.1	Sunburn
Zanetti, 2006 Europe and Argentina	Case-control (hospital) 2001-2002	215 BCCs, 139 SCCs, 349 controls	20-75	100.0	Sunbathing and Sunburn

*Mean age
**Median age

Table 6.3. Basal cell carcinoma cases and proportions estimated to be attributable to sunburn, sunbathing and combined UVR risk behaviors in Canada in 2015

Age at Exposure	Age at Diagnosis	Sunburn			Sunbathing		Combined*	
		Obs.	PAR	AC	PAR	AC	PAR	AC
Men								
16-24	20-29	170	22.9	39	22.4	38	43.5	74
25-44	30-49	2626	28.5	747	31.4	825	53.1	1393
45+	≥50	28429	20.7	5878	25.5	7244	44.4	12611
Total	Total	31225	21.3	6664	26.0	8107	45.1	14078
Women								
16-24	20-29	223	22.0	49	30.0	67	52.5	117
25-44	30-49	3004	24.8	744	42.1	1266	62.2	1868
45+	≥50	23420	13.9	3244	28.8	6735	45.1	10573
Total	Total	26647	15.2	4037	30.3	8068	47.1	12558
Total								
16-24	20-29	393	22.4	88	26.7	105	48.6	191
25-44	30-49	5630	26.5	1491	37.1	2091	57.9	3261
45+	≥50	51849	17.6	9122	27.0	13979	44.7	23184
Total	Total	57872	18.5	10701	28.0	16175	46.0	26636

*Includes joint distributions for indoor tanning (O'Sullivan et al., 2019), sunburn, and sunbathing
Abbreviations: AC = Attributable cases, Obs. = Observed cases, PAR = Population attributable risk

Table 6.4. Cutaneous squamous cell carcinoma cases and proportions estimated to be attributable to sunburn and combined UVR risk behaviors in Canada in 2015

Age at Exposure	Age at Diagnosis	Sunburn			Combined*	
		Obs.	PAR	AC	PAR	AC
Men						
16-24	20-29	8	12.5	1	25.0	2
25-44	30-49	286	16.1	46	25.5	73
45+	≥50	12781	11.2	1429	16.5	2108
Total	Total	13075	11.3	1476	16.7	2183
Women						
16-24	20-29	19	10.5	2	31.6	6
25-44	30-49	318	13.8	44	31.4	100
45+	≥50	7017	7.2	506	18.0	1264
Total	Total	7354	7.5	552	18.6	1370
Total						
16-24	20-29	27	11.1	3	29.6	8
25-44	30-49	604	14.9	90	28.6	173
45+	≥50	19798	9.8	1935	17.0	3372
Total	Total	20429	9.9	2028	17.4	3553

*Includes joint distributions for indoor tanning (O'Sullivan et al., 2019), sunburn, and sunbathing
Abbreviations: AC = Attributable cases, Obs. = Observed cases, PAR = Population attributable risk

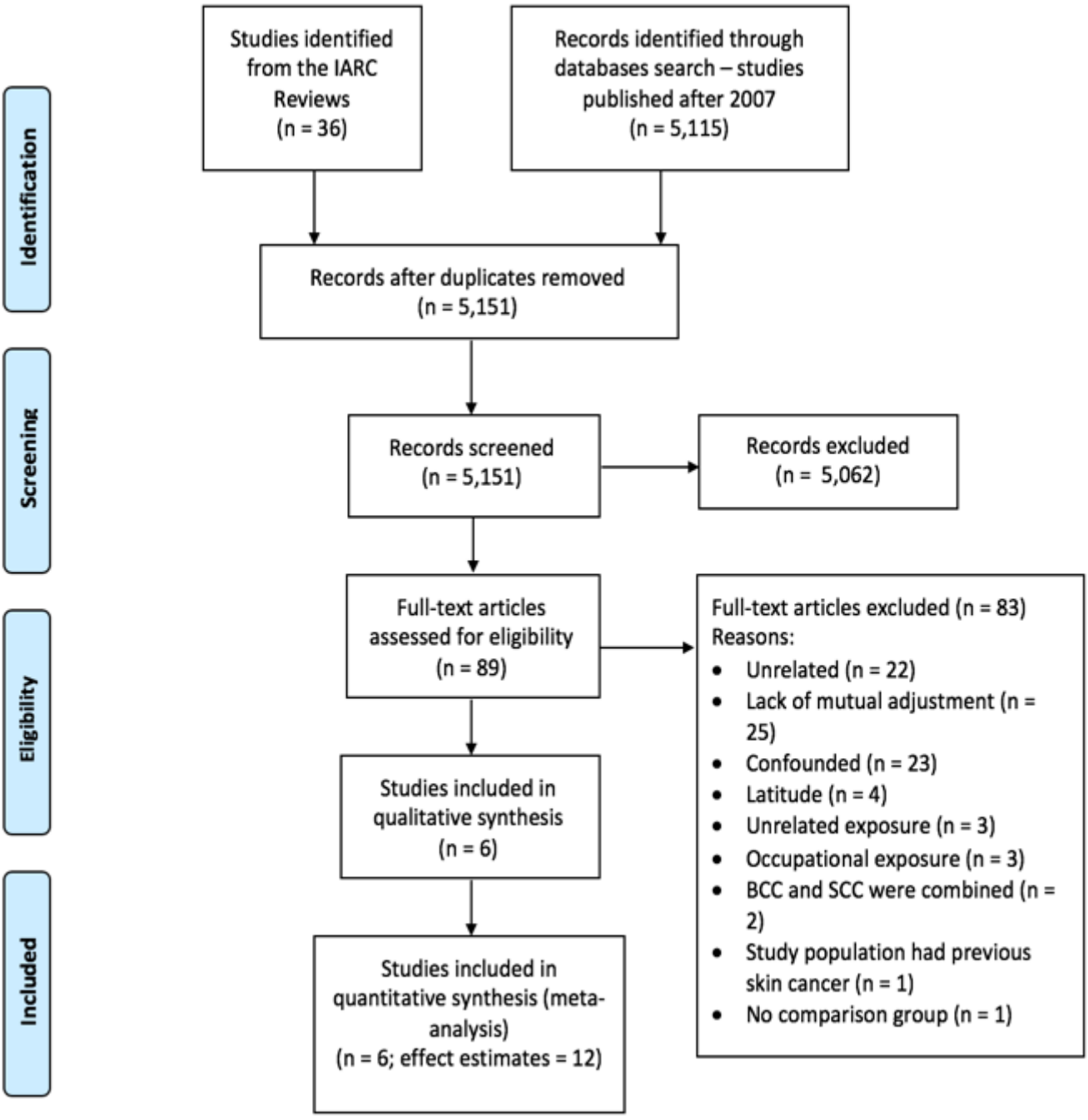

Figure 6.1. Flow diagram of the selection procedure of studies relevant to Canada assessing the relationship of sunburn or sunbathing with the risk of NMSC.

Description: A PRISMA flow diagram that details the inclusion and exclusion of studies considered for this meta-analysis.

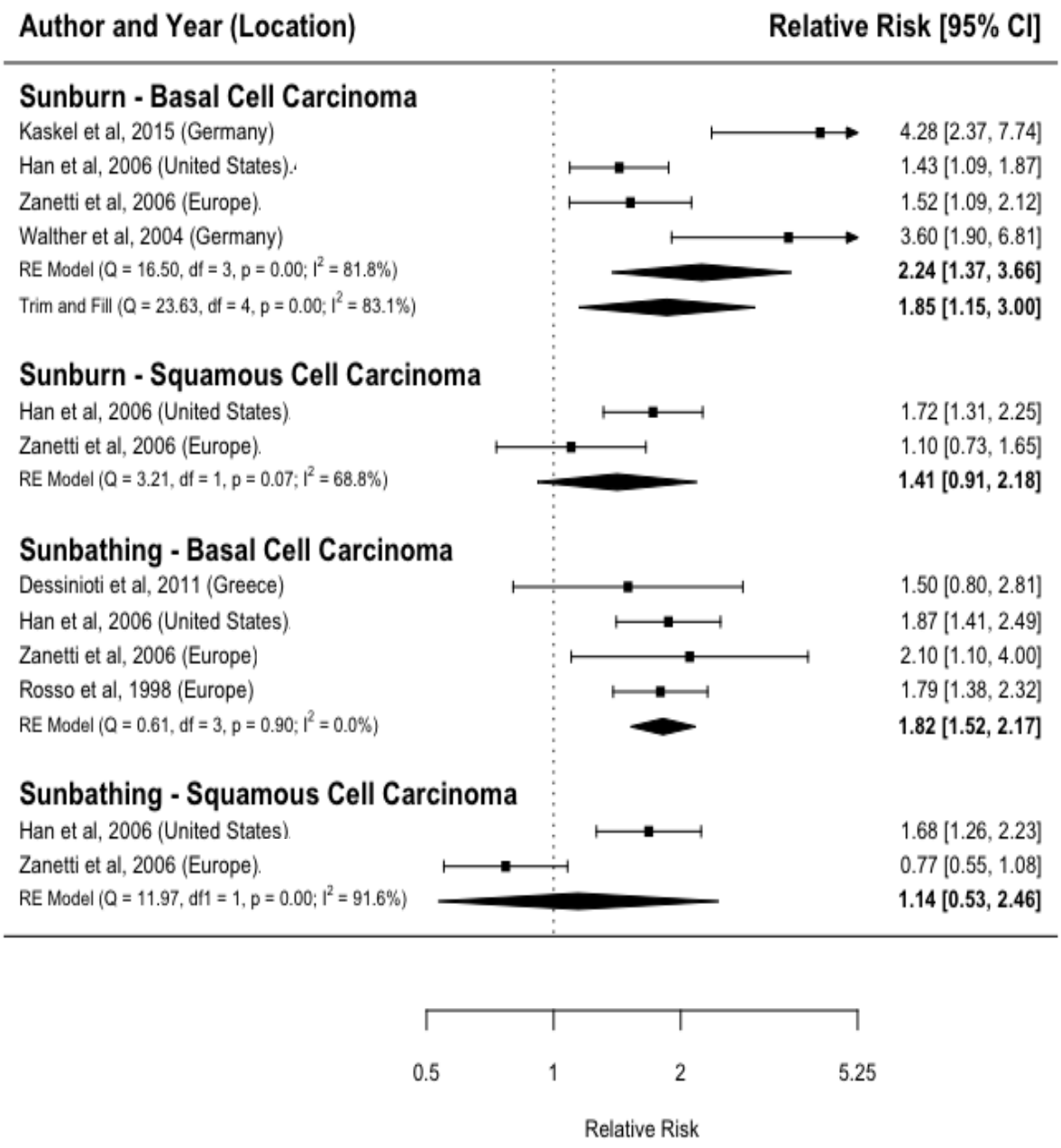

Figure 6.2. Estimated relative risk of basal cell carcinoma and cutaneous squamous cell carcinoma for sunburn and sunbathing that are generalizable to Canada.

Chapter 7

Time spent in the sun and the risk of developing non-Hodgkin lymphoma: A Canadian cohort study

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7.1 Abstract

Background: There is emerging evidence that sun exposure is protective against the development of non-Hodgkin lymphoma (NHL), but few prospective studies have investigated this relationship.

Objectives: To investigate the relationship between time in the sun and risk of NHL in a Canadian prospective cohort and to determine if the relationship varies by sun protection or pattern of exposure.

Methods: Baseline residence and sun behaviour information from Alberta's Tomorrow Project, Quebec's CARTaGENE and Ontario's Health Study were utilized. The relationship of time spent in the sun during summer months with NHL risk was assessed using Cox proportional hazard models with age as the time-scale and adjustment for potential confounders. Cohorts were analyzed separately and hazard ratios (HR) pooled with random effects meta-analysis. Effect modification by protection behaviours was examined with meta-regression for regular versus seldom use of sun protection. Patterns of sun exposure were explored via combinations of weekday and weekend time spent in the sun.

Results: During an average follow-up of 7.6 years, 205 NHL cases occurred among study participants (n=79,803). Compared to < 30 min in the sun, we observed HRs of 0.84 (95% CI: 0.55-1.28) for 30-59 minutes, 0.63 (95% CI: 0.40-0.98) for 1-2 hours, and 0.91 (95% CI: 0.61-1.36) for > 2 hours. The use of sun protection did not modify this association (p = 0.69). Intermittent (< 30 min on weekday and > 2 hours on weekend) and chronic (> 2 hours every day) exposures were not associated with the risk of NHL. Moderate exposure (all other categories) was associated with a lower risk of NHL (HR: 0.63, 95% CI: 0.43-0.92) compared to < 30 min every day.

Discussion: This study provides evidence of a protective effect of moderate time spent in the sun on NHL risk.

7.2 Introduction

Non-Hodgkin lymphoma is a heterogeneous group of malignant neoplasms of the lymphoid tissues, and is the most common hematologic malignancy worldwide (1). Projected to account for 4.6% of all cancers in Canada in 2020, NHL ranks as the 4th and 5th most common cancer among males and females, respectively (2). Between 1983 and 2015 the age-standardized incidence rate of NHL has increased annually by 1.3% (3). Despite continued increases in the incidence of NHL, risk factors explaining this increase are unknown. Older age, being male, Caucasian ethnicity, higher socioeconomic status, a family history of NHL, autoimmune disorders, ionizing radiation, and exposure to certain pesticides are all established causes of NHL (1). Obesity has been associated with an increased risk of NHL, while there is little evidence that physical inactivity is associated with NHL risk (1,4). Alcohol consumption, fruit and vegetable consumption, and sun exposure have been linked to decreased risks of NHL, but associations have not been consistent (1).

The literature on the relationship between sun exposure and the risk of non-Hodgkin lymphoma has been inconsistent. Several studies, including a pooled analysis of 5 published and 5 unpublished case-control studies (5) and a recent meta-analysis have observed statistically significant protective effects of recreational time spent in the sun or sunbathing on NHL risk (6). In contrast, in the pooled analysis there was no association with total sun exposure (5) and a meta-analysis of occupational sun exposure observed an

increased risk of NHL associated with occupational sun exposure (7). The majority of studies on recreational sun exposure and NHL risk are case-control studies, which are potentially subject to recall and selection bias (6). Only two prospective cohort studies have been conducted on this relationship with one study observing no association between time in the sun and NHL risk (8), while the other study found no association with sunbathing and NHL risk (9). In addition to the lack of prospective cohort studies, there is a lack of studies that have examined the shape of the relationship with reproducible categories of time spent in the sun. The use of sun protective measures and the pattern of exposure (consistent or intermittent) could also have an influence on the association of time spent in the sun and risk of NHL, but few studies have examined this. Finally, the nature of exposure to solar ultraviolet radiation (UVR) is highly variable and dependent on geographical location and latitude, which merits an investigation in a Canada population where individuals go long periods without any exposure to UVR during winter months and where ambient UVR is low.

The objective of this study was to investigate the relationship between time in the sun and NHL risk using data from Canadian prospective cohort studies. In addition, a secondary objective of this study was to determine if the relationship of time spent in the sun and NHL risk varied by the use of sun protection and the pattern of sun exposure.

7.3 Methods

The Canadian Partnership for Tomorrow Project (CPTP) is a prospective cohort study created to examine the effect of genetics, behaviours, family history, and the environment on developing chronic diseases, including cancer (10). It consists of five regional prospective cohort studies and is the basis for this study (10). Accrual time

period, study methods, and data elements vary across the cohorts and within phases of individual cohorts. Phases of individual cohorts refer to different recruitment periods within the cohort.

7.3.1 Data Source

In this study, we utilized data from three of the provincial cohorts that are partners of the CPTP, including Alberta's Tomorrow Project (ATP) (11), Quebec's CARTaGENE (CaG) (12), and Ontario's Health Study (OHS) (13). While the data collected by the cohorts are largely harmonized, there are variables where the questionnaire item has varied over time and geography. In particular, for time spent in sun, and for potential NHL risk factors including physical activity and alcohol consumption. In addition, questions on weight and height were not asked on the questionnaire for phase two of ATP, and therefore BMI could not be estimated for that phase. Cancer diagnosis data was also varied by cohort. The ATP and OHS have questionnaire data linked to provincial cancer registry databases through health insurance plan numbers, while incident cancer cases for CaG have been identified through linkage with two administrative databases in Quebec (Med Echo for hospital claims and RAMQ for general physician billing).

7.3.2 Exposures

The primary measure of exposure to ultraviolet radiation in this study was time spent in the sun during summer months. In all of the cohorts and phases except for the first phase of ATP, participants were questioned on the typical amount of time spent in the sun on both weekdays and weekends and could choose one of the following categories: <30 min/day, 30 min-1 hour/day, 1-2 hours/day, 2-3 hours/day, 3-4 hours/day, and > 4 hours/day. For the first phase of ATP, participants were questioned on the typical

amount of time they spent in the sun in the summer and could choose one of the following categories: <30 min/day, 30 min-1 hour/day, 1-2 hours/day, and >2 hours/day. To harmonize the data to the first phase of ATP, a daily measure was estimated by using the mid-points of the categories and weighting weekday and weekend exposures.

The secondary objective of this study was to explore effect modification of sun protection use on the association of time spent in the sun and the risk of NHL. For sun protection, participants were asked how often they used sun protection including sunscreen lotion, hat, or protective clothing when they are in the sun for 30 min or more on weekdays and weekends. Participants could answer: never, rarely, sometimes, often and always. In this study, we considered sun protection for the participants if they answered often or always. For this analysis, the referent group were participants that typically spent less than 30 min in the sun, while the exposure categories were 30 min to 2 hours/day and greater than 2 hours/day. Joint effects of time in the sun and the use of sun protection (yes or no) were examined.

The final objective of this study was to determine if there were differences in the relationship of time spent in the sun and risk of NHL by the pattern of exposure (chronic vs. intermittent). For the pattern of exposure analysis we categorized participants based on their exposure during both weekdays and weekends. The referent category for this analysis was participants that typically spend less than 30 min in the sun on both weekdays and weekends. We estimated the risk of NHL compared to this referent category for any combination with a prevalence in the study population > 5%. To test for statistical differences by patterns of exposure we further classified exposure into three

categories: intermittent (< 30 min on weekday and > 2 hours on weekend), chronic (> 2 hours on weekdays and weekends), and moderate (all other exposure categories).

7.3.3 Covariates

Variables related to the biological effect of exposure to ultraviolet radiation, including ambient UVR and skin tone, were considered as both effect modifiers and potential confounders. Ambient UVR for the highest quarter (3 months) for residence at baseline was obtained by linking 3-digit postal codes to erythemal UVB NASA satellites at a resolution of 0.25 x 0.25 degree latitude and longitude (13 x 24 km). Ambient UVR was tested as an effect modifier by dichotomizing at the median UVR level across all of the cohorts and was put into quartiles when tested as a confounder in the cohort-specific models. In the second phase of ATP and in the other cohorts, skin tone was categorized into two groups based on skin reaction to the sun after spending one hour in the sun without protection after several months of not being in the sun. The light skin tone group consisted of individuals that mildly burned with some tanning, had a severe sunburn for a few days with peeling, or a severe sunburn with blisters. The medium/dark skin tone group consisted of individuals that had no skin reaction to the sun or turned darker without a sunburn. In the first phase of ATP, participants were asked about the untanned skin color of their upper arm and could answer: light (white, fair, ruddy), medium (olive, light brown, medium brown), or dark (dark brown, black). We combined the medium and dark skin tone groups to be consistent with the other cohorts.

Other variables considered as potential confounders included established and suspected risk factors for non-Hodgkin lymphoma. These included sex, a family history of non-Hodgkin lymphoma, household income, body mass index (BMI), physical

activity, alcohol consumption, tobacco smoking status, and fruit and vegetable consumption. We used a backwards elimination approach with a liberal p-value of 0.2 to determine inclusion of potential confounders in the final models (14).

Harmonized variables across cohorts and phases were sex (male/females), family history of non-Hodgkin lymphoma (yes or no), household income (< $50,000, $50,000 to $99,999, and ≥ $100,000), tobacco smoking status (never, former, or current), and fruit and vegetable consumption (under recommendations (4 servings per day) for both fruits and vegetables, meet recommendations for fruit or vegetable consumption, or meet recommendations for both).

Physical activity was measured in all of the cohorts, but different instruments were used. In the first phase of ATP, physical activity was measured with the Past Year Total Physical Activity Questionnaire (PYTPAQ) (15) and was measured with the International Physical Activity Questionnaire (IPAQ) (16) in the other cohorts. Both of the questionnaires are validated with accelerometer data, but the PYTPAQ tends to overestimate (15) and the IPAQ tends to underestimate (16), which makes these measures inappropriate to apply in a combined analysis. For each cohort or phase, physical activity was categorized into quartiles. Alcohol consumption was also measured in all cohorts, but different questions were asked. In the first phase of ATP, drinking status (ever or never) and the number of drinks consumed in a week were quantified. In all of the other cohorts, drinking status and number of times consuming alcohol drinks is a week were quantified. For the first phase of ATP we categorized alcohol consumption as never drinker, former drinker, less than or equal to 1 drink/day, and > 1 drink/day. In all of the other cohorts we categorized alcohol consumption as never drinker, former drinker,

drinks 2 or less times a week, and drinks more than 2 times a week. BMI was included for all of the cohorts except for the second phase of ATP (15.4%), and was categorized according to the World Health Organization classification of normal weight (18 to < 25 kg/m2), overweight (25 to < 30 kg/m2), and obese (≥30 kg/m2).

7.3.4 Statistical Analysis

Given that there were discrepancies among cohorts with respect to the inclusion of certain potential confounders as well as differences in the measurement of other potential confounders, we analyzed each cohort or phase separately. Phases of cohorts refer to different recruitment periods within the cohort. OHS and CaG were pooled together since the cohorts had the same data elements and OHS was too small to analyze on its own.

Cox proportional hazards regression models using age as the time-scale were used to estimate HRs and 95% confidence intervals (CI) for the risk of developing NHL associated with time spent in the sun (17). Participants were censored at NHL diagnosis, other cancer diagnosis, if they moved out of the province of their respective cohort, or at the date of the last cancer linkage. Potential confounders for each cohort or phase of a cohort were identified using a backwards selection with a liberal p-value of 0.20. The proportional hazard assumption was tested using the cumulative sums of martingale-based residuals method (18). Risk estimates for each exposure category were pooled using a random effects meta-analysis model to yield summary estimates. Heterogeneity of among effect estimates were quantified with the I^2 test statistic.

For the exploratory sun protection analysis, a meta-regression was used to test for an interaction between the use of sun protection methods and each of the exposure

categories (19). That is, data from each strata were treated as separate datasets and the meta-regression provided the test for interaction. For the exploratory pattern of exposure analysis, compared to participants that spend < 30 min in the sun on both weekdays and weekends, effect estimates for each weekday and weekend combination with > 5% of participants are presented. To test for statistical difference determine by patterns of exposure, we further classified exposure into three categories: high intermittent (< 30 min on weekday and > 2 hours on weekend), high continuous (> 2 hours on weekdays and weekends), and moderate (all other exposure categories). Meta-regression was performed to determine if there were statistical differences in these patterns of exposure and the risk of developing NHL. All analyses were performed using the R computing framework (www.r-project.org).

7.4 Results

The cohort and demographic characteristics of the participants included in this study are presented in Table 1. The study population included a total of 79,803 participants with an average follow-up of 7.6 years, where 205 NHL cases occurred in 603,994 person years of observation. Among the participants, the average age at enrollment was 53.1 years of age and 58.1% of the study population was female. Approximately one-third of the study population belonged in each of the household income categories and 1.3% had a family history of NHL.

Table 2 presents the results for the main analysis of average time spent in the sun during summer months and the risk of developing NHL. Compared to < 30 min in the sun, we observed HRs of 0.84 (95% CI: 0.55-1.28) for 30-59 minutes, 0.63 (95% CI: 0.40-0.98) for 1-2 hours, and 0.91 (95% CI: 0.61-1.36) for > 2 hours. There was no

heterogeneity across cohorts for any of the exposure categories (Supplemental Figure 1; I_2 = 0%).

Table 3 presents the joint effect results of the exploratory analysis of the interaction of sun protection behaviours on the relationship of average time spent in the sun during summer months the risk of developing NHL. Overall, there was not a significant interaction between time spent in the sun and the use of sun protection methods on the risk of developing NHL (p-value meta-regression = 0.69). Among participants who typically spent 30 min to 2 hours/day in the sun, the risk of developing NHL compared to participants who typically spent < 30 min/day was similar among participants that regularly used sun protection (HR: 0.72; 95% CI: 0.43-1.21) and participants that did not (HR: 0.70; 95% CI: 0.43-1.21) (p-value meta-regression = 0.94). Among participants who typically spent > 2 hours/day in the sun, the risk of developing NHL compared to participants that typically spent < 30 min/day was lower for participants who regularly used sun protection (HR: 0.66; 95% CI: 0.38-1.14) than participants that did not (HR: 1.01; 95% CI: 0.59-1.73), but was not statistically significant (p-value meta-regression = 0.27). There was no heterogeniety among any of the exposure categories (I_2 = 0%). Neither skin tone nor ambient UVR were significant effect modifiers (p-value meta-regression = 0.72 and 0.71, respectively).

Table 4 presents the results for the analysis of patterns of time spent in the sun during summer months and the risk of developing NHL, as well as the proportions of participants in each category. When examining patterns of exposure, intermittent (< 30 min on weekday and > 2 hours on weekend) and chronic (> 2 hours on weekdays and weekends) were not associated with the risk of developing NHL. Moderate exposure (all

other categories) was associated with a reduced risk of NHL (HR: 0.63, 95% CI: 0.43-0.92) compared to individuals spending < 30 min in the sun during weekdays and weekends. However, the lower risk for the moderate exposure group was not significantly different from the intermittent or chronic exposure groups (meta-regression p-values: 0.36 and 0.40). There was no heterogeneity across cohorts for any of the exposure categories (I_2 = 0%).

7.5 Discussion

In this large Canadian prospective cohort study of 79,803 participants and 205 NHL cases, we observed a potential U-shaped relationship of time spent in the sun with the risk of NHL. In particular, we found a significantly lower risk of NHL associated with spending 1-2 hours in the sun per day in summer months compared to < 30 min. There was suggestive evidence that spending greater than 2 hours in the sun per day was protective against the development of NHL with the use of sun protection, but not without it. The use of sun protection did not modify the overall relationship between time spent in the sun and NHL risk. When examining different patterns of exposure, high intermittent (< 30 min on weekday and > 2 hours on weekend) and high continuous (> 2 hours on weekdays and weekends) exposures were not associated with NHL risk, while moderate exposure regardless of patterns was associated with a decreased risk of NHL.

Our observations of a protective effect of moderate time in the sun on the risk of developing NHL is consistent with several case-control studies, but a potential U-shaped relationship has not previously been reported. Three case-control studies (20-22) and a pooled analysis of 10 case-control studies (5) observed significant protective effects for the highest recreational sun exposure category and downward linear trends across

categories. In the pooled analysis, total sun exposure, including working days, was significantly associated with a lower risk of NHL, but only for 10 years prior to diagnosis. In contrast, one study observed a lower risk of NHL associated with recreational sun exposure during teenage years (23). Two studies observed suggestive decreased risk associated with time spent in the sun (24,25), while two other studies found no evidence of a relationship (26,27). In contrast, a study of women in Connecticut and a case-control study of Israelis and Palestinians observed higher risks of NHL with longer durations of a suntan and higher levels of time spent in the sun, respectively (28,29). The higher risk in the Connecticut study could be due to the exposure metric - of duration of suntan - which might be capturing repeated intermittent exposures, rather than consistent moderate exposure, which could have different biologic effects. The higher risk observed in Kleinstern et al., 2017 is difficult to compare to our study since it was among a non-Caucasian population at a latitude much lower than Canada. The overall shape of the relationship among the literature is difficult to discern since the majority of studies used study-defined groups.

There is biological plausibility for a U-shaped relationship of time spent in the sun with the risk of NHL. Moderate levels of sun exposure have been shown to enhance immune function, promote vitamin D synthesis, and possibly help to maintain normal circadian rhythm patterns. Moderate exposure to solar UVR have been shown to enhance T-cell motility (30) and upregulate TH-2 cells, which are required for humoral immunity against tumor associated antigens and help to regulate anti-inflammatory responses (31). Exposure to the sun leads to vitamin D synthesis, which regulates cellular proliferation and differentiation, and can induce apoptosis and inhibit angiogenesis. However, dietary

vitamin D intake and serum/plasma 25-hydroxyvitamin D levels have not been shown to be protective against the development of NHL (6). Moderate levels of sun exposure can also promote circadian rhythm maintenance through regulation of melatonin and serotonin – both of which have been shown to have antiproliferative effects (32). On the other hand, higher levels of exposure could negate these beneficial mechanisms through immune suppression, inflammation, oxidative stress and alterations to the epigenome. High levels of UVR exposure can induce systemic suppression of the immune system's ability to detect and attack malignant cells (33). Immune suppression through other pathways, such as infectious agents or treatments that weaken immune function are strongly linked to the risk of hematologic malignancies (34). In addition, UVR can induce pro-inflammatory cytokine production (35), which has been linked to an increased risk of a number of cancer sites, including NHL (36). Alterations to the DNA methylome can occur through degradation of folate (dysregulation of methyl donation in one-carbon metabolism) or indirectly from oxidative stress (reactive oxygen species) (37). Aberrant DNA methylation in the blood has been linked to several cancer sites including NHL (38).

This is the first study to examine the influence of sun protection behaviours on the relationship of time spent in the sun on the risk of NHL. There was some evidence that spending greater than 2 hours in the sun per day was protective against the development of NHL with the use of sun protection, but not without it. This analysis was limited by a small sample size, since it only included 139 cases, and therefore effect modification by sun protection should be explored in future studies. We also tested the potential interaction of time spent in the sun with ambient UVR and skin tone, but neither were

significant effect modifiers. These analyses were limited due to a lack of statistical power, and the ambient UVR analysis was further limited by low variation across the study population. Finally, vitamin D from diet or supplementation may also modify this relationship, but we were unable to test this since only a small proportion of the study population had data vitamin D intake.

This is also the first study to examine the combination of weekday and weekend time spent in the sun on the risk of NHL. Previous studies that have examined different patterns of time in the sun with the risk of developing NHL have done so by examining the risk associated with weekday and weekend exposures separately. These studies have observed a lower risk of NHL with time spent in the sun on non-working days, but not for working days (20-22). These results are difficult to interpret, however, since exposure on non-working days could simply be capturing individuals with lower overall exposure. It is imperative to incorporate combinations of working and non-working days, since different combinations could have different biological effects. In this study, we observed a lower risk of NHL associated with moderate exposure, but not with high intermittent or high continuous exposure. While we had low power to detect statistically significant differences between these exposure groups (118 cases), there is biological plausibility of a protective effect for moderate exposure and not for high intermittent and high continuous exposures. While high intermittent exposure would result in moderate weekly exposure, the lack of exposure during weekdays would result in low levels of melanin, making individuals more susceptible to the damaging effects of the sun. For high continuous exposure the positive benefits could be negated by the detrimental effects of too much sun exposure, such as chronic inflammation and oxidative stress. Moderate

exposure during weekdays and weekend could afford individuals the beneficial effects of the sun and build up melanin to protect against the potential detrimental effects of the sun.

This is one of the first studies to comprehensively examine the relationship of time spent in the sun, sun protection behaviours and risk of NHL. In particular, examining the shape of the relationship, incorporating ambient UVR and skin tone, examining effect modification by sun protection use, and examining combined weekday and weekend patterns of exposure. Other strengths of this study include the prospective design, complete follow-up through generally high quality outcome databases, and little missing data. This study has limitations that must be acknowledged. First, exposure was only measured at baseline and may not accurately capture average lifetime exposure. Given the prospective nature of the study, this would likely lead to non-differential misclassification, which could have an unpredictable influence on the effect estimates since the exposure was not dichotomous (14). We were unable to control for some established risk factors including autoimmune disorders, type II diabetes, immunosuppression therapy, HIV/AIDS, Hepatitis C, Epstein-Barr virus, and occupations with high exposure to pesticides or benzene. However, most of these risk factors tend to be extremely rare in the general Canadian population, rendering uncontrolled confounding unlikely. In addition, residual confounding is a potential concern. In particular, alcohol consumption was quantified as the number of times a participant drink on an average week, but this does not take into account the number of drinks consumed, which could have led to residual confounding. Our analyses were not sufficiently powered to examine effect modification by sun protection and different

patterns of time spent in the sun. Outcome data for CaG was derived from hospital claims and physician billing, which has been shown to lead to false positives due to lower specificity compared to registries (39,40). This would have led to some non-differential misclassification, but is likely to have a minimal effect on the results of this study as demonstrated by a bias analysis (Supplemental Table 1). Finally, the results of this study can only be generalizable to Caucasians residing at northern latitudes, since the majority of the study population was Caucasian (~92%) and the study was conducted in Canada.

In conclusion this is the largest prospective cohort study and first Canadian study to examine the association between time spent in the sun and the risk of developing NHL. We observed a U-shaped relationship - with moderate exposure to the sun (1-2 hours/day) being protective against developing NHL. In addition, it is one of the first studies to investigate the influence of sun protection and patterns of exposure on this relationship. Overall, this study adds to the several case-control studies that have observed protective effects of moderate sun exposure on the risk of NHL. Future studies should focus on specific patterns of exposure to further clarify the relationship of time spent in the sun and the risk of developing NHL.

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7.9 Tables

Table 7.1. Cohort and demographic characteristics of participants included in this study from Alberta's Tomorrow Project, Quebec's CARTaGENE and Ontario's Health Study

Variable	Population n (%)	Events n (%)
Cohort/Phase		
Phase 1 Alberta's Tomorrow Project	22,610 (28.3)	87 (42.4)
Phase 2 Alberta's Tomorrow Project	12,290 (15.4)	36 (17.6)
Quebec's CARTaGENE	39,051 (48.9)	71 (34.6)
Ontario's Health Study	5,852 (7.3)	11 (5.4)
Total	79,803 (100.0)	205 (100.0)
Age at baseline		
Mean (SD)	53.1 (8.7)	57.0 (8.7)
Follow-up time		
Mean (SD)	7.6 (2.2)	4.5 (2.8)
Sex		
Male	33,411 (41.9)	113 (55.1)
Female	46,392 (58.1)	92 (44.9)
Household Income		
< $50,000	26,669 (33.8)	69 (34.3)
$50,000 to $99,999	28,673 (36.3)	83 (41.3)
> $100,000	23,569 (29.9)	49 (24.4)
Family History of non-Hodgkin lymphoma		
Yes	1,011 (1.3)	2 (1.0)
No	78,590 (98.7)	203 (99.0)

Abbreviations: SD = standard deviation

Table 7.2 Time spent in the sun during summer months and the risk of developing NHL

	Events	Person-years	Combined HR (95% CI)
Time in sun			
< 30 min	40	97,307	ref (1.0)
30 to 59 min	49	153,767	0.84 (0.55-1.28)
1 hour to 2 hours	40	168,390	0.63 (0.40-0.98)
> 2 hours	76	184,530	0.91 (0.61-1.36)

*For the first and second phase of ATP only sex was included in the model after backwards selection ($p < 0.2$). For CaG and OHS, sex and alcohol consumption were included in the model after backwards selection ($p < 0.2$).
**Abbreviations: CI = confidence interval; HR = hazard ratio

Table 7.3. The joint effect of time spent in the sun during summer months and the use of sun protections methods on the risk of developing NHL

	Events	Person-years	Combined HR (95% CI)	Meta-regression P-value
Time in sun and sun protection				0.69
< 30 min	30	59,884	ref (1.0)	
30 to 2 hours protected	32	97,372	0.72 (0.43-1.21)	0.94
30 to 2 hours unprotected	29	84,402	0.70 (0.42-1.18)	
> 2 hours protected	21	57,449	0.66 (0.38-1.14)	0.27
> 2 hours unprotected	27	45,837	1.01 (0.59-1.73)	

*For the first and second phase of ATP only sex was included in the model after backwards selection ($p < 0.2$). For CaG and OHS, sex and alcohol consumption were included in the model after backwards selection ($p < 0.2$).
**Abbreviations: CI = confidence interval; HR = hazard ratio

Table 7.4. Patterns of time spent in the sun during summer months and the risk of developing NHL (118 cases)

	Weekend		
Weekday	**< 30 min**	**30 min to 2 hours**	**> 2 hours**
< 30 min	(13.8%) **ref.**	(14.7%) **0.63 (95% CI: 0.30-1.30)**	(8.0%) **0.95 (95% CI: 0.43-2.12)**
30 min to 2 hours	(4.5%) **NA**	(22.4%) **0.70 (95% CI: 0.40-1.22)**	(16.6%) **0.54 (95% CI: 0.27-1.11)**
> 2 hours	(0.2%) **NA**	(1.3%) **NA**	(18.5%) **0.84 (95% CI: 0.48-1.48)**

*Percentages refer to prevalence of study participants in each exposure category.
**For the second phase of ATP only sex was included in the model after backwards selection ($p < 0.2$). For CaG and OHS, sex and alcohol consumption were included in the model after backwards selection ($p < 0.2$).
***Effect estimates presented are hazard ratios
****Abbreviations: CI = confidence interval

Chapter 8

Discussion

8.1 Summary of Thesis

The overall goal of this thesis was to inform efforts to reduce the burden of cancer in Canada associated with exposure to ultraviolet radiation (UVR). The first component of this thesis focused on the examination of an established UVR-cancer relationship (melanoma and non-melanoma skin cancer (NMSC)), while the second component focused on a novel, unestablished UVR-cancer relationship (non-Hodgkin lymphoma). Specifically, the first component estimated Canadian-specific population attributable risks (PAR) and potential impact fractions (PIF) for UVR and UVR risk behaviours (indoor tanning, sunburn, and sunbathing). The second component examined the relationship of time spent in the sun with the risk of NHL and tested the influence of sun protection and patterns of exposure on this relationship.

8.2 Component 1 – Population Attributable Risk

8.2.1 Summary of Main Findings

The primary goals of component 1 of this thesis (manuscripts 1, 2, and 3) were to expand upon previous PAR methods for UVR and to provide the first PAR and PIF estimates associated with UVR exposure and modifiable UVR behaviours in Canada. Specifically, we performed meta-analyses for UVR risk behaviours (indoor tanning, sunburn, and sunbathing) and each skin cancer type that were relevant to Canada – restricted to studies of high quality and with exposure similar to Canada – and this methodology is novel. In addition, we estimated the lifetime prevalence of indoor tanning

in Canada to be 20%, and the adulthood prevalence of sunburn and sunbathing to be 32.1% and 54.5%, respectively. Overall, we estimated that 62.3% of melanomas, 80.5% of basal cell carcinomas (BCC), and 83.0% of cutaneous squamous cell carcinomas (SCC) were attributable to UVR exposure in 2015. It was also estimated that 29.7% of melanomas, 47.0% of BCCs, and 17.4% of SCCs were attributable to modifiable UVR behaviours. Of the modifiable UVR risk behaviours, sunbathing contributed the most to the burden of melanoma and BCC, while sunburns contributed the most to SCC. A 50% reduction in these behaviours by 2037 could cumulatively avoid an estimated 11,980 melanomas. PIFs were not estimated for NMSC due to unreliable data.

8.2.2 Methodologic Considerations: Current Burden of Skin Cancer Attributable to UVR

To estimate a PAR for UVR and melanoma we used the cohort approach where current rates of melanoma (2015) were compared to estimated rates of an earlier birth cohort (1920 cohort) (1). Methodologic considerations for this approach include predicting rates in the 1920 cohort, under-reporting of melanoma, and population level ethnic distributions. For NMSC we used the body site distribution approach where current rates of NMSC were compared to rates on typically unexposed body sites (trunk and legs) after adjusting for skin surface area (2). Methodologic considerations for this approach include the body sites utilized for comparison, under-reporting of NMSC, and ethnicity.

8.2.2.1 Cohort Approach and Melanoma

The validity of the cohort approach to estimate a PAR rests on the assumption that all other risk factors and system levels factors, such as reporting and diagnosis practices

are relatively constant between the earlier cohort and the current rates. Since we did not have incidence data for every age group in the 1920 birth cohort we needed to estimate rates in the cohort by using a log normal age-cohort model. Since predicting incidence rates to the past involves a degree of error, the rates of the 1920 cohort could be either an underestimation or overestimation of the true rate of melanoma. This would have led to some bias in our PAR estimate, since we did not need to predict current incidence rates of melanoma – creating a discrepancy between the two rates in terms of accuracy.

Given that melanoma is often treated outside of hospital settings, there is potential for under-reporting to cancer registries. Evidence from studies in Ontario provide evidence that under-reporting has increased over time and therefore this is an important consideration for the cohort approach (3,4). To account for under-reporting of melanoma, we inflated melanoma rates by the degree of under-reporting for both the 1920 cohort and for current rates (2015) using estimates of under-reporting in Ontario in 1976 (3) and 1993-2009 (4). To do this we used a logistic regression model to extrapolate under-reporting to the years without data. For the current rates of melanoma the possibility of error was low given that extrapolation was only occurring over 6 years and because the majority of melanoma cases were being captured in Canadian Cancer Registries (5). Our estimate for under-reporting of melanoma for the 1920 birth cohort would have a higher degree of error since we had to extrapolate well beyond our data for some of the older age groups. If the real trend in reporting deviates from a logistic model then there would be some inaccuracy of the rates for the 1920 cohort. Additionally, we applied under-reporting equally across age groups and sex, which could lead to biased rates if under reporting is more prevalent among specific demographic groups. Finally, changes in

reporting were ascertained from studies in Ontario, which may not be representative of Canada as a whole. Overall, the direction of bias for the incidence rates of the 1920 birth cohort is difficult to discern, but the magnitude is likely small.

Since melanoma rates differ by ethnicity (20 times high among Caucasians compared to Blacks and Asians) (6) and the ethnic diversity of Canada has increased over time, it is important to adjust for ethnicity when using this approach. To account for ethnicity, we restricted this analysis by only applying this approach to Caucasians, Hispanics and Aboriginals. To do this, we removed cases of melanoma occurring among Blacks and Asians by applying incidence rates from the United States Surveillance, Epidemiology, and End Results Program to the proportion of Blacks and Asians in Canada in both the 1920 cohort and in 2015. We then divided these cases by the number of Caucasians, Hispanics, and Aboriginals for both the 1920 cohort and 2015 to derive rates. This could have induced some misclassification if there are differences in diagnosis and reporting in the USA.

8.2.2.2 Body Site Distribution Approach and Non-Melanoma Skin Cancer

Since we did not have access to pathology reports we used the trunk and legs as the least exposed body sites. Given that these broad categories for the unexposed group are not truly unexposed to UVR, our PAR was likely an underestimation of the true PAR. Additionally, there is evidence that skin cancer can manifest in body site locations distal of localized UVR, suggesting a systemic effect (7). The systemic effect of UVR could lead to an underestimation of the PAR if some cases occurring in the low exposed body sites are a result on UVR at commonly exposed body sites. Given that under-reporting is a concern for NMSC, there is potential that under-reporting could have biased our

estimates if NMSC is differentially reported by body site. It is possible that NMSC on the face is more likely to be reported since it has a greater cosmetic burden, but there is a lack of data on under-reporting for NMSC in Canada, so it is difficult to discern. Since we did not have access to body site distribution by ethnicity we did not account for it in this analysis. However, this likely had a minimal influence on the PAR estimates given that skin cancers tend to occur on non-exposed body sites of Blacks and Asians. Therefore, the lower risk for Blacks and Asians associated with UVR exposure would be reflected in the PAR.

8.2.3 Methodologic Considerations: Current and Future Burden of Skin Cancer Attributable to Modifiable UVR Behaviours

Methodologic considerations for the current and future burden of skin cancer attributable to UVR risk behaviours include methods affecting the validity of individual studies used to determine relative risks (RR), the validity of the prevalence of exposure, and the validity of outcome data. For individual studies, selection bias, information bias, non-differential misclassification of the exposure, and confounding are discussed below. For prevalence of the exposure, social desirability bias and generalizability to the general Canadian population are discussed. For the future burden of skin cancer, issues related to exposure projections, incidence projections, and counterfactual scenarios are discussed. Finally, given the strong interaction between UVR exposure and ethnicity, methods to account for ethnicity are also discussed for the current and future burden of skin cancer associated with UVR risk behaviours. Figure 8.1 provides a visual summary of the various inputs and associated sources of bias for estimating PARs for UVR risk behaviours in this thesis.

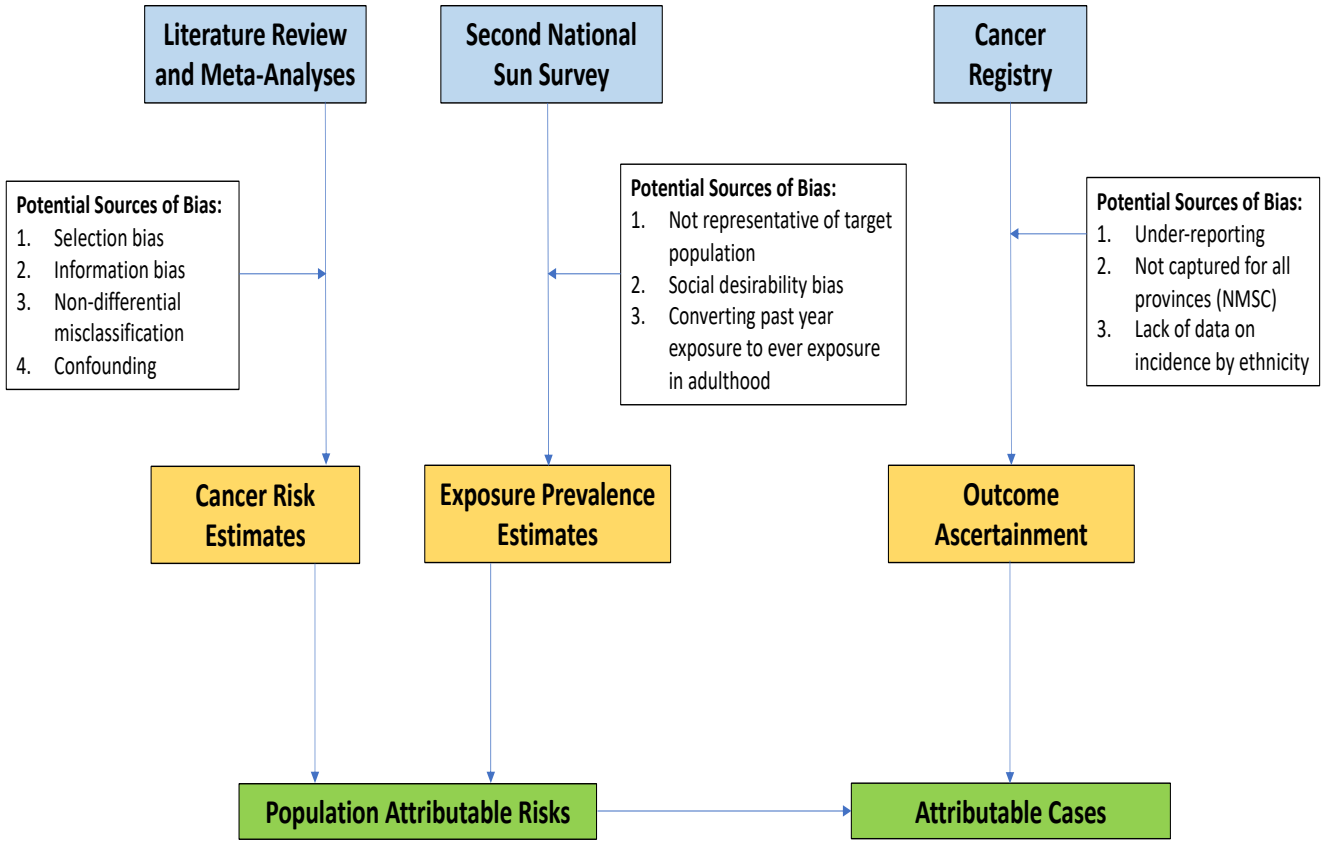

Figure 8.1 Flow diagram of the inputs and the associated biases in population attributable risk estimates for UVR risk behaviours

*NMSC = Non-melanoma skin cancer

8.2.3.1 Relative Risk

Meta-analyses relevant to Canada were conducted to obtain relative risk for each skin cancer type associated with modifiable UVR risk behaviours. The relative risks resulting from these meta-analyses are subject to biases from individual studies. Given that these meta-analyses largely relied on case-control studies, selection bias and information bias are of concern. In addition, non-differential misclassification and confounding are concerns in this area of literature.

8.2.3.1.1 Selection Bias

Selection bias is a potential source of bias in case-control studies, since being a case or control that participates in the study could be related to the exposure of interest. Among hospital-based case-control studies we only included studies where the controls did not have a condition that was related to the exposure. For case-controls studies – both hospital and population-based – selection bias is a concern when there is low and differential response rates between cases and controls. The majority of studies included in the meta-analyses were case-control studies and the response rates by outcome status for each study is presented in Table 8.1. Overall, studies tended to have a higher response rate among cases and therefore are susceptible to selection bias. If controls that participate in the study are more likely to have the exposure than individuals that refused to participate then this would bias estimates towards the null. If the opposite was true then controls would be over represented by individuals without the exposure and would bias away from the null.

8.2.3.1.2 Information Bias

Information bias can occur when participants respond differentially to questions related to the exposure of interest based on their outcome status. Since the majority of

studies included in the meta-analyses were case-control studies there is a possibility that differential misclassification biased the RR estimates. Information bias tends to have a higher probability when the hypothesized relationship is known by the broader public. Since the relationship between UVR behaviours and skin cancer is intuitive, it is possible that cases could overestimate their exposure, which would bias RRs away from the null. For the meta-analyses on UVR risk behaviours and melanoma, study design (case-control vs. cohort) was not a source of heterogeniety, which provides some evidence of minimal selection and information bias. For the non-melanoma skin cancer meta-analyses, there were not enough studies to test the influence of study design and therefore it is difficult to discern the magnitude of this potential bias for those estimates.

8.2.3.1.3 Non-differential misclassification

Among the studies included in the meta-analyses, participants were questioned on ever engaging in a UVR risk behaviour or on the number of times that they engaged in the behaviour during adulthood. For studies that simply asked participants if they have ever engaged in a behaviour, non-differential misclassification would likely be low since it is likely not a difficult exposure to recall. For studies where participants were asked about the number of times they engaged in the behaviour, there is likely a moderate amount of non-differential misclassification because it is difficult to recall the number of times that one engaged in a certain behaviour over their entire adulthood. Given that we needed to collapse RRs for multiple exposure categories for these studies to obtain a common metric of ever exposure, this non-differential misclassification would have little effect on our summary effect estimate of ever engaging in the UVR risk behaviour.

The use of such a broad exposure category does carry the limitation that a RR from one study may not be comparable to one from another study due to differences in the duration and frequency of exposure within this ever exposure category. In our meta-analyses we restricted to studies that had a similar prevalence of exposure to Canada, assuming that overall prevalence is highly correlated with duration of exposure. The generalizability of these risk estimates to Canada depend on the validity of this assumption.

8.2.3.1.4 Confounding

A potential source of bias for the RR estimates included in a PAR is inadequate control for confounding. In this component, studies were only included in a meta-analysis if important confounders were adjusted for including age, sex, sun sensitivity, host characteristics, and other UVR risk behaviours. In addition, we excluded studies that controlled for factors on the causal pathway including dysplastic nevi for melanoma. While this ensured a low probability of uncontrolled confounding there is still a possibility of residual confounding for the RR estimates included in our meta-analyses.

8.2.3.2 Prevalence of Exposure

For PAR estimates to be valid, they require an estimate of exposure prevalence in the target population. The response-rate for the Second National Sun Survey (NSS2) was 63% and the sample was over-representative of Caucasians (88% versus 85% for the 2006 census), Canadian-born (83% versus 76% for the 2006 census), and individuals with a university degree (27% versus 18% for the 2006 census). Since our analyses were restricted to Caucasians, the over-representation of Caucasians would not have biased our prevalence estimates. Given that education may be related to sun behaviours, we applied

sample weights to ensure that our estimates were not biased by an over-representation of university educated Canadians in this sample. The NSS2 did not include individuals living in the territories, full-time residents of institutions (nursing homes, penal institutions, group homes, etc. 1.7% of Canadians), residents not fluent in one of Canada's official languages (1.7% of Canadians), and residents without any telephone service (1.2% of Canadian households). Therefore, our prevalence estimates were not completely representative of the entire Canadian population.

In any survey there is always a possibility of social desirability bias, where respondents are more likely to underestimate their exposure. Given the causal link between sun exposure and skin cancer, it is possible that respondents underestimate their exposure to UVR risk behaviours due to social desirability bias. A larger potential source of bias in our estimate of prevalence was the conversion from past year exposure to ever exposure. Past year exposure can be highly variable and therefore difficult to determine an appropriate conversion factor to ever exposure. It is therefore difficult to discern the magnitude of error that would be induced by this methodology. For indoor tanning we were able to provide some validation by evaluating our conversation factors in the context of a Canadian study that measured indoor tanning in the past year and past 5-years on the same individuals (Chapter 4). This comparison provided some evidence that our conversion factors result in prevalence of exposure that are likely within a reasonable range of the true prevalence. Finally, age categories had to be collapsed for the highest age groups due to a lack of reliable prevalence estimates from NSS2 and an appropriate conversion factor for the category.

8.2.3.3 Outcome Ascertainment

For melanoma, high quality incidence data from the Canadian Cancer Registry were utilized, which captures >99% of incident cases (5). Cancer incidence data for Quebec in 2015 were not available, and therefore incidence data from 2010 was extrapolated to 2015. Given that we only had to extrapolate five years of data likely had a minimal effect on the number of attributable melanoma cases. In contrast, NMSC incidence data for 2015 were obtained from Canadian Cancer Statistics, which extrapolated NMSC rates from four provinces (Alberta, Manitoba, New Brunswick, and Newfoundland) to the rest of Canada (8). These provinces tend to engage in UVR risk behaviours more than other Canadian provinces and therefore extrapolating to the rest of Canada may overestimate the number of attributable cases (9). However, NMSC is likely under-reported among these provinces making an underestimation more likely.

To only apply our PAR estimates to Caucasian skin cancer cases in Canada we used data from the Canadian Census Health and Environment Cohorts to estimate the proportion of melanoma cases that occur among Caucasians (10). We then applied this proportion to all skin cancer types in our PAR analyses. While this is likely an accurate estimation for melanoma it may have overestimated the number of cases for NMSC since there is some evidence that there is a smaller difference in the incidence of NMSC between Caucasian and non-Caucasians than for melanoma (11). This evidence, however, comes from studies conducted in the southern United States where ambient UVR is stronger, which makes it difficult to generalize to Canada.

8.2.3.4 Future Burden of Skin Cancer Attributable to UVR

PIF estimates require RRs, prevalence of exposure projections, cancer incidence projections, and counterfactual exposure scenarios. The biases for RRs acknowledged

previously would have an influence on PIF estimates in the same way. To appropriately project exposure prevalence requires consistent historical prevalence data that is comparable across time (similar questions and sampling methods). In Canada there is a lack of historical prevalence data on UVR risk behaviours and therefore we had to assume a stable exposure prevalence from 2006. The results from our cohort approach indicate that exposure to UVR may have decreased in recent cohorts, particularly among younger men (Chapter 2). Therefore, our lack of ability to project future exposure could have led to PIF estimates that were slight overestimations. For cancer incidence projections to 2042 we used high quality incidence data from the Canadian Cancer Registry, which captures > 99% of incident cases (5). For Quebec we had to extrapolate incidence from 2010 to 2011 and 2012, but this would likely have little influence on our projections. Despite the use of high-quality cancer incidence data, projecting cancer incidence 30 years into the future involves uncertainty. The projections depend on the assumption that trends in both cancer incidence and population demographics will continue at a similar trend in the future. To ensure the most accurate model, we utilized Canproj, which combines a mixture of projection models and uses a decision tree to select the best-fitted model (12). In addition, the models that were chosen included an element of expert review from Drs. Will King and Stephen Walter to ensure realistic projection models based on the data. The ideal counterfactual scenarios for a PIF estimate are exposure reductions related to proven population-based interventions. Data on proven interventions related to UVR exposure primarily exist for Australia (13). Since Australia has much higher rates of skin cancer and higher ambient UVR, it is difficult to generalize the results from those interventions to Canada. Therefore, our PIF estimates were based

on fixed prevalence reductions, which are useful, but are less tangible for public health professionals and policy makers.

8.2.4 Strengths

Despite the limitations, this study has several strengths. In our estimation of the current burden of melanoma attributed to UVR we adjusted for changes in reporting and ethnicity when using the cohort approach, which hasn't been done previously. In our estimation of the current burden of NMSC attributed to UVR, we applied the body site distribution to cancer registry data and adjusted for the prevalence of obesity in Canada when calculating body surface area – both of which are novel applications of the approach. The application of the risk factor approach for multiple UVR risk behaviours and skin cancer is novel. Within this risk factor approach we estimated RRs for each UVR risk behaviour that were generalizable to Canada and adjusted for important confounders. Furthermore, we only included estimates that were mutually adjusted for the other UVR risk behaviours to ensure independent RRs. For the combined UVR risk behaviour PAR we used joint prevalence distributions and multiplicative RRs, due to the potential dependency of UVR risk behaviours. This is an important component of this work, since not accounting for joint distributions when exposures are related could lead to an underestimation of the PAR (14). Finally, our incorporation of PIFs for melanoma is important for future interventions and policy targeted at these behaviours.

8.2.5 Generalizability

While biological relationships can typically be generalizable across populations, PARs can only be generalizable to the population of interest since it considers prevalence of exposure. In addition, since behaviours are modifiable, the prevalence of exposure can

change over time, and therefore PARs are also time-specific. Therefore, the PAR and PIF estimates in this thesis are only generalizable to Canada in 2015. However, the relative risk estimates that were derived from the meta-analyses of UVR behaviours could be generalizable to countries at a similar latitude and with similar exposure patterns.

8.3 Component 2 – Prospective Cohort Study

8.3.1 Summary of Main Findings

The purpose of component 2 of this thesis (manuscript 4) was to build on the previous literature for solar UVR and the risk of NHL by examining the relationship of time spent in the sun with the risk of NHL and the influence of sun protection and pattern of exposures on this relationship in Canadian prospective cohort studies. During an average follow-up of 7.6 years, 205 NHL cases occurred among study participants (n=79,803). Compared to individuals spending < 30 min/day in the sun the risk of developing NHL was 0.84 (95% CI: 0.55-1.28) for 30-59 minutes, 0.63 (95% CI: 0.40-0.98) for 1-2 hours, and 0.91 (95% CI: 0.61-1.36) for > 2 hours. The use of sun protection did not appear to modify the relationship between time spent in the sun and NHL risk. Intermittent (< 30 min on weekday and > 2 hours on weekend) and chronic (> 2 hours every day) exposures were not associated with the risk of NHL, while moderate exposure (all other categories) was associated with a lower risk of NHL (HR: 0.63, 95% CI: 0.43-0.92) compared to < 30 min every day.

8.3.2 Methodological considerations

Methodological considerations relating to the results of this prospective cohort study on time in the sun and the risk of NHL include choosing a referent exposure category, exposure misclassification, outcome misclassification due to ascertainment and

censoring, confounding, and study power. Issues relating to non-differential misclassification and selection bias were not discussed, since these biases were unlikely to occur due to the prospective nature of the data. Finally, this section will discuss the strengths of this investigation in comparison to previous literature on solar UVR and non-cutaneous cancer risk.

8.3.2.1 Exposure Referent Category

For this study, < 30 min time spent in the sun per day during the summer months was used as the referent category. This exposure category was chosen as the referent since a considerable proportion of the study population belonged in this category (approximately 20%) and because it allowed for the assessment of the shape of the relationship between time in the sun and the risk of developing NHL. There is some concern that this referent group is systematically different in that it could represent a mixture of individuals with comorbidities, have light skin tone, and are inactive. However, our analyses adjusted for many of these factors and the 30-59 min group did not have a significantly different risk of NHL compared to this referent group. If this referent group was systematically different, it would be expected that the risk of NHL would be significantly different from the next exposure category.

8.3.2.2 Exposure Misclassification

Given the difficulty in estimating typical time spent in the sun, non-differential misclassification of the exposure is a likely possibility in this study. While non-differential misclassification biases the RR for a dichotomous exposure towards the null (15), the primary analysis included four exposure categories. When the exposure is more

than two categories, non-differential misclassification can bias estimates in both directions (15).

A limitation of this study that must be acknowledged is that we only used baseline data and therefore do not capture lifetime exposure to solar UVR. These analyses assumed that baseline data represents average adult time spent in the sun, but behaviours are modifiable and therefore it may not represent average adult exposure for some participants. Non-differential misclassification could bias the estimates in an unpredictable way depending on the distribution of misclassification across categories. That said, there is some evidence that exposure later in life is a particularly important exposure window in this relationship (16), which our baseline exposure would capture given the age distribution in this study.

8.3.2.3 Outcome Misclassification

While outcome data for ATP and Ontario's Health Study (OHS) came from high quality cancer registries (capture > 99% of cases) (5), outcome data for Quebec's CARTaGENE (CaG) came from medical billing data, which has a higher probability of misclassification(17-19). In particular, benign or precursor cancers, without proper pathologic confirmation can be classified as incident cancer cases. To minimize this possibility, we examined multiple claims and changing outcome statuses to remove any possible false positive cases. However, the higher case rate (1.65 times greater) among CaG compared to the other cohorts provides evidence that a proportion of cases in CaG are false positives, which is due to lower specificity when using administration data (18,19). If these false positive cases are related to time spent in the sun, it could bias our estimates, but this is unlikely. If false positive cases are not related to time spent in the

sun, then this misclassification would bias effect estimates towards the null. The magnitude of this bias and the influence that this would have on the results of the main analysis for CaG and for the cohorts combined is presented in Table 8.2 and Table 8.3, respectively. As demonstrated, this misclassification biases estimates towards the null for CaG. For the pooled results, this didn't bias towards the null for 1-2 hours or > 2 hours due to the reduced weighting of the results from CaG from a lower case count. Overall, the bias from the outcome misclassification of CaG had a minimal influence on the results of this study and does not alter any findings or conclusions.

In prospective cohort studies, bias can also occur due to improper censoring. ATP and OHS both lacked a death clearance and therefore a person could die during follow-up, but contribute person-years until the study end (last cancer linkage). If survival during follow-up is related to time spent in the sun, a lack of a death clearance could bias effect estimates. It's possible that the benefits of time spent in the sun (vitamin D) could influence other diseases and thus survival. This could lead to person-years of observation being artificially higher in the referent group, which would lower the rates of NHL in this group. If a lack of time spent in the sun is associated with mortality, and this is not captured, the effect estimates would be biased toward the null in comparison to the referent. However, the magnitude of this is likely low given the relatively short follow-up period. Moreover, CaG had a death clearance and there was no heterogeneity in effect estimates across cohorts, providing evidence that the magnitude of this was low. CaG didn't capture information on individuals moving out of Quebec during follow-up. This is problematic if individuals moving out of Quebec develop the outcome since it wouldn't be captured in the administrative database. If moving out of the province is related to

time spent in the sun it could bias effect estimates, although this is highly unlikely. We censored individuals that developed another cancer during follow-up (excluding NMSC), since treatments for cancer (chemotherapy and radiation) are associated with increased risk of NHL. This is important given that time spent in the sun could be related to the development of other cancer sites and therefore not censoring these participants could bias effect estimates. However, censoring of false positives of other cancer sites in CaG would bias effect estimates towards the null. Overall, death, migration, and false positives of other cancer sites in CaG during follow-up likely only occurs in a small proportion of participants and is therefore unlikely to have a major influence on the results of this study.

8.3.2.4 Confounding

In this study, there is a possibility of both uncontrolled and residual confounding. While the majority of known potential confounders were controlled for, we were unable to adjust for some established risk factors including autoimmune disorders, type II diabetes, immunosuppression therapy, HIV/AIDS, Hepatitis C, Epstein-Barr virus, and exposure to pesticides or benzene. In particular, a lack of control for occupational exposure to pesticides or benzene may have confounded the results for the highest exposure of time spent in the sun (> 2 hours). That is, to spend > 2 hours in the sun per day likely requires some form of outdoor work and some of these occupations, such as farming, would be exposed to pesticides and benzene. The increased risk of NHL associated with these exposures may have biased the effect estimates of the highest exposure category toward the null. Despite not being able to control for those other risk factors, the majority are quite rare in the population, and likely uncommon among

participants included in this study. It is possible that some of these factors are related to time spent in the sun, but because they are quite rare, the magnitude of uncontrolled confounding in this study is likely very low.

Given that there were some discrepancies in variables across cohorts and phases of cohorts, we sought to minimize the potential for residual confounding by using a meta-analysis approach instead of pooling the studies and making concessions on variables to common exposure categories. While this allowed us to minimize within-cohort residual confounding by using the most appropriate variables for each cohort, there were instances where residual confounding is a possibility. First, in all of the analyses except for the first phase of ATP, alcohol consumption was in the form of number of times drinking per week, rather than number of drinks per week. Since the risk of NHL is more related to number of drinks per week, there could be residual confounding by alcohol in this study. BMI was examined as a confounder in all analyses except for the second phase of ATP. While BMI was not acting as a confounder in the other analyses it is possible that it could have confounded in the second phase of ATP and thereby result in residual confounding by BMI. We were only able to test the potential confounding of meat consumption, sleep duration, and vitamin D in some of the analyses. While these covariates are not strong risk factors for NHL and they did not confound in the analyses in which they were included, the possibility of residual confounding by these factors is a possibility – albeit unlikely. Finally, misclassification of confounders could have led to some residual confounding in this study. In particular, data for each confounder was only available at baseline. For many potential confounders baseline data may inadequately represent lifetime exposure and therefore residual confounding would be present for those

variables. Moreover, residual confounding could occur from only having baseline data if the relationship of the confounder and exposure change over time. For instance, educational attainment has been shown to be related to sun behaviour habits (20), but it was not a predictor of time spent in the sun or a confounder in this study. This could potentially be the result of education being a stronger predictor of sun behaviours in early adulthood and therefore would result in residual confounding.

8.3.2.5 Study Power

This study was slightly underpowered to detect effect estimates that have been observed in previous case-control studies on this relationship (RRs of 0.70s to 0.80s) (16,21). Based on quartile exposure categories, 80% power, and an alpha level of 0.05 the minimum detectable effects for this study was 0.62 and 1.60. In addition, this study was insufficiently powered for analyses involving the influence of sun protection and patterns of exposure. The insufficient power for these secondary analyses were due to lower case counts and due to the increased power that interaction analyses require. Despite this low power, the results of these analyses were in the hypothesized direction and should be explored in future studies. For the final submission of this study, participants from Atlantic's Partnership for Tomorrow's Health will be added to this analysis and will contribute an estimated 25 cases and 64,000 person years to all of the analyses. However, this will have a minimal influence on study power, since it only changes the minimum detectable effect from 0.62 to 0.63 for the main analysis. The addition of this cohort will have a greater influence of the secondary analyses depending on exposure distribution.

8.3.3 Strengths

This is the first study on solar UVR and the risk of NHL in Canada and is only the second prospective cohort study to examine the relationship of time spent in the sun and NHL risk. In addition, it is the only study that has examined the influence of sun protection and different patterns of exposure on this relationship. Beyond the prospective design, this study had complete follow-up through high quality outcomes sources and little missing data. This is particularly important since the majority of prospective cohort studies on time spent in the sun and non-cutaneous cancer risk come from studies that use follow-up surveys to ascertain outcome status. Finally, we were able to limit the potential for confounding by adjusting for several emerging risk factors for NHL.

8.3.4 Prospective cohort study vs. Case-control study

The prospective nature of the data used in this study had the strength that the results were not subject to recall or selection bias. Prospective cohort studies are not subject to recall bias since the exposure is ascertained prior to the development of the outcome. Selection bias is a possibility in cohort studies if the outcome is ascertained through a follow-up questionnaire or if exposures are captured using both baseline and follow-up surveys. Since outcome status was determined with data linkages and because we only used baseline data there was no possibility of selection bias in this study. While the use of baseline data protects against potential selection bias it comes with several limitations. First, the use of only baseline data may not represent lifetime exposure and this could lead to non-differential misclassification that would bias the effect estimates in this study. There is evidence that sun behaviours tend to decrease with age (22) and therefore this would lead to considerable misclassification. Second, the use of only baseline data could lead to residual confounding since several potential confounders

could vary over participants' lifetime. Since case-control studies typically ascertain full exposure histories, the effect estimates are subject to less non-differential exposure misclassification and residual confounding. Finally, case-control studies typically have more study power for main analyses and interactions, since case-control studies do not need to wait long periods for the development of adequate number of cases. Given the different strengths and limitations of prospective cohort studies compared to case-control studies it is important for both study designs to examine the relationship of UVR and the risk of NHL to determine if a true relationship exists.

8.3.5 Generalizability

The biologic effect of exposure to the sun is dependent on both ambient UVR and skin pigmentation. Since the study on time spent in the sun and NHL risk was conducted in Canada and the majority of the study participants were Caucasians, the results of this study can only be generalizable to Caucasians living at northern latitudes.

8.4 Implications and future directions

The results of this thesis have implications for cancer prevention related to UVR and public health messaging. First, we found that approximately one fifth of Canadians have used an indoor tanning device in their lifetime and that this use is responsible for more than 5% of all skin cancer cases in Canada (Chapter 4). At the same time, use of indoor tanning devices does not reduce the risk of other cancer sites and potentially increases the risk of hematologic malignancies (23). Indoor tanning is one of the risk factors for skin cancer that is most amenable to change through policies that limit or restrict use. Strategies aimed at reducing use should be increased and a total ban or restrictions on use and UV-intensity should be considered by health regulators in Canada.

Second, we estimated the proportion of skin cancer cases attributable to the combination of UVR risk behaviours (indoor tanning, sunburn, and sunbathing), which can be mobilized by decision-makers and public health practitioners to inform the general population of Canada (Chapter 5 and 6). In addition, these estimates can be utilized to evaluate the potential costs and benefits of interventions aimed at reducing the prevalence of these risk behaviours.

On the other hand, the results from the prospective cohort study (Chapter 7) indicate that moderate exposure (1-2 hours/day) to the sun may reduce the risk of NHL. In addition, we found that consistent moderate exposure to the sun was protective, while chronically high levels or intermittent exposure (high weekend exposure only) was not associated with a reduced risk of NHL. Our group has also demonstrated a potential reduced risk of breast cancer associated with moderate exposure to the sun in a recent meta-analysis (24). In addition, a systematic review postulates that exposure to the sun could also reduce the risk of colorectal cancer and prostate cancer (25).

As a whole, the results of this research suggest that complete avoidance of the sun may be detrimental for non-cutaneous cancer prevention. In addition, the results also suggest that intermittent exposures are detrimental for all cancer types, while consistent moderate exposure could be protective for NHL and other non-cutaneous cancers through a variety of potential biologic mechanisms. More studies on time spent in the sun and non-cutaneous cancers, particularly studies examining patterns of exposure, are required before this work can be incorporated into public health messaging around sun exposure. In addition, future research should investigate the competing increased risk of skin cancer and the potential reductions in NHL and other non-cutaneous cancer sites associated with

moderate amounts of time spent in the sun. The goal of this research would be to determine whether it is possible to reduce the risk of NHL and other non-cutaneous cancer sites, without increasing the risk of skin cancer.

8.5 Conclusion

This is the first study to estimate the current and future burden of skin cancer in Canada attributable to both UVR and UVR risk behaviours. The methodology employed have expanded on previous PAR work and could be adapted to derive estimates in other geographical contexts. The estimates from this work have also been included in a special edition of *Preventive Medicine* and the Canadian Cancer Society has been using them to frame messaging around skin cancer risk reduction in relation to solar UVR and indoor tanning devices. This thesis also adds to the literature on exposure to UVR and the risk of developing non-cutaneous cancers. Beyond observing a potential U-shaped relationship of time spent in the sun and risk of NHL, this study is one of the only cohort studies that has comprehensively examined this relationship by exploring the influence of sun protection and patterns of exposure. Methods employed in this study can be utilized in future investigations of exposure to solar UVR and non-cutaneous cancer risk.

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8.7 Tables and Figures

Table 8.1. Response rates by outcome status of case-control studies included in meta-analyses for UVR risk behaviours and skin cancer

Study	Response Rate	
	Cases	**Controls**
Indoor Tanning		
Melanoma		
Bataille, 2004	61.0%	95.0%
Chen, 1998	75.0%	70.0%
Clough-Gorr, 2008	77.0%	61.0%
Cust, 2011	76.0%	42.0%
Swerdlow, 1988	NR	NR
Walter, 1999	90.1%	81.0%
Westerdahl, 1994	78.6%	70.1%
Basal cell carcinoma		
Badjik, 1996	72.0%	71.0%
Karagas, 2002	78.0%	66.0%
Squamous cell carcinoma		
Badjik, 1996	80.0%	71.0%
Sunburn		
Melanoma		
Autier, 1994	97.0%	78.0%
Bataille, 2004	61.0%	95.0%
Chen, 1996	75.0%	70.0%
Walter, 1999	90.1%	81.0%
Basal cell carcinoma		
Kaskel, 2015	NR	NR
Walther, 2004	NR	NR
Zanetti, 2006	80.6%	92.8%
Squamous cell carcinoma		
Zanetti, 2006	80.6%	92.8%

Sunbathing		
Melanoma		
Autier, 1998	97.0%	78.0%
Kaskel, 2001	NR	NR
Westerdahl, 1994	78.6%	70.1%
Zardize, 1992	NR	NR
Basal cell carcinoma		
Dessinioti, 2011	NR	NR
Rosso, 1998	83.0%	67.0%
Zanetti, 2006	80.6%	92.8%
Squamous cell carcinoma		
Zanetti, 2006	80.6%	92.8%

*NR = not reported

Table 8.2. Quantitative bias analysis for non-differential misclassification of the outcome in the CARTaGENE cohort.

Time spent in the sun	Observed			Truth*		
	Events	Non-events	RR	Events	Non-events	RR
< 30 min (ref)	18	8,096	1.0 (ref)	11	8,103	1.0 (ref)
30-60 min	13	11,346	0.55 (0.27-1.14)	8	11,351	0.37 (0.12-1.12)
1-2 hours	15	9,532	0.68 (0.34-1.38)	9	9,538	0.58 (0.24-1.43)
> 2 hours	25	11,048	0.86 (0.46-1.61)	16	11,057	0.78 (0.35-1.75)
Total	71	40,022		44	40,049	

*Risk estimates based on sensitivity of 100% and specificity of 99.94%, which equates to a 65% increase in events.

Table 8.3. The influence of non-differential misclassification of the outcome in the CARTaGENE cohort on the pooled results

Time spent in the sun	Observed			Truth*		
	Events	Non-events	RR	Events	Non-events	RR
< 30 min (ref)	40	14,075	1.0 (ref)	33	14,082	1.0 (ref)
30-60 min	49	21,390	0.84 (0.55-1.28)	44	21,395	0.87 (0.54-1.41)
1-2 hours	40	20,865	0.63 (0.40-0.98)	34	20,871	0.58 (0.36-0.94)
> 2 hours	76	23,268	0.91 (0.61-1.36)	67	23,277	0.89 (0.58-1.37)
Total	205	79,598		178	79,625	

*Risk estimates based on sensitivity of 100% and specificity of 99.94% for CaG, which equates to a 65% increase in events are pooled with results from the other cohorts (phase 1 ATP, phase 2 ATP, OHS).

Appendix A

Ethics certification and REB approval

PANEL ON RESEARCH ETHICS
Navigating the ethics of human research

TCPS 2: CORE

Certificate of Completion

This document certifies that

Dylan O'Sullivan

has completed the Tri-Council Policy Statement:
Ethical Conduct for Research Involving Humans
Course on Research Ethics (TCPS 2: CORE)

Date of Issue: **13 July, 2017**

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD (HSREB)

HSREB Initial Ethics Clearance

July 25, 2017

Mr. Dylan O'Sullivan
Department of Public Health Sciences
Carruthers Hall
Queen's University

ROMEO/TRAQ: #6021467
Department Code: EPID-585-17
Study Title: Chronic sun exposure and the risk of developing a hematologic malignancy
Co-Investigators: Dr. W. King, Dr. D. Brenner
Review Type: Delegated
Date Ethics Clearance Issued: July 25, 2017
Ethics Clearance Expiry Date: July 25, 2018

Dear Mr. O'Sullivan,

The Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB) has reviewed the application and granted ethics clearance for the documents listed below. Ethics clearance is granted until the expiration date noted above.

- Protocol

Documents Acknowledged:

- CORE Certificate – D. O'Sullivan

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD (HSREB)

HSREB Amendment Acknowledgment/Ethics Clearance

September 21, 2017

Mr. Dylan O'Sullivan
Department of Public Health Sciences
Carruthers Hall
62 Fifth Field Company Lane
Queen's University

ROMEO/TRAQ: #6021467
Department Code: EPID-585-17
Study Title: Exposure to ultraviolet radiation and the risk of hematologic malignancy and other site-specific cancer development
Review Type: Delegated
Date Ethics Clearance Issued: September 21, 2017

Dear Mr. O'Sullivan,

The Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB) has reviewed the amendment application and granted ethics approval/acknowledgement for the following:

- Title change from: "Chronic sun exposure and the risk of developing a hematologic malignancy"
- Revised protocol - adding an exploration of the relationship of exposure to ultraviolet radiation with other cancer sites.
- All cancer incidence data will be requested from ATP, OHS, and CARTaGENE.

Yours sincerely,

Albert J. Clark.
Chair, Health Sciences Research Ethics Board

The HSREB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations, Canadian General Standards Board, and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP). Federalwide Assurance Number: FWA#:00004184, IRB#:00001173

HSREB members involved in the research project do not participate in the review, discussion or decision.

Appendix B

Manuscript 1 Supplemental Material

Supplemental Table 1. Characteristics of excluded studies (n = 47)

Reference	Diagnosis	Reasons for Exclusion
Boyd, 2004	BCC	Only reported mean number of exposures
Herity, 1989	NMSC	Grouped BCC and SCC patients in effect estimate; controls don't represent source population
Hogan, 1991	Skin cancer	Grouped BCC, SCC, and melanoma patients in effect estimate
O'Loughlin,	BCC, SCC	Grouped BCC and SCC patients in effect estimate; controls don't represent source population
Corona, 2001	BCC	Some controls have melanocytic nevi
Ting, 2007	Melanoma	Inappropriate non-case group
Adam, 1981	Melanoma	Did not control for confounding (crude estimate)
Asgari, 2011	SCC	Did not control for confounding (crude estimate)
Ballester, 2012	Melanoma	Did not control for confounding (crude estimate)
Dunn-Lane	Melanoma	Did not control for confounding (crude estimate)
Holly, 1995	Melanoma	Did not control for confounding (crude estimate)
Holman, 1986	Melanoma	Did not control for confounding (crude estimate)
Osterlind, 1988	Melanoma	Did not control for confounding (crude estimate)

Schmitt, 2011	Melanoma	Did not control for confounding (crude estimate), cross-sectional study
Walther, 2004	BCC	Did not control for confounding (crude estimate); Exposure disconnect (>5 time per year)
Zivkovic, 2012	Melanoma	Did not control for confounding (crude estimate); Exposure disconnect (one year)
Autier, 1994	Melanoma	Did not control for sun sensitivity; was not possible to derive adjusted ever use effect estimate
Bakos, 2011	BCC	Did not control for sun sensitivity or sun exposure; could not estimate ever use from data presented
Garbe, 1993	Melanoma	Did not control for sun exposure
Gon and Minelli,	BCC	Did not control for sun exposure
Kaskel, 2001	Melanoma	Did not control for sun sensitivity or sun exposure; could not estimate ever use from data presented
Rosso, 1999	BCC	Did not control for sun exposure
Segatto, 2015	Melanoma	Did not control for sun sensitivity or sun exposure
Wolf, 1998	Melanoma	Did not control for sun sensitivity or sun exposure
Savoye, 2017	Melanoma, BCC, SCC	Did not control for sun exposure
Stenehjem, 2017	Melanoma	Did not control for sun sensitivity or sun exposure
Karagas, 2002	SCC	Controlled for sun exposure with an intermittent measure

Fears, 2011	Melanoma	Controlled for factors on causal pathway (dysplastic nevi)
Landi, 2002	Melanoma	Controlled for factors on causal pathway (dysplastic nevi); did not control for sun exposure
MacKie, 1989	Melanoma	Controlled for factors on causal pathway (dysplastic nevi)
Naldi, 2000	Melanoma	Controlled for factors on the causal pathway
Bataille, 2005	Melanoma	Prevalence of exposure and distribution do not match Canada
Elliot, 2012	Melanoma	Prevalence of exposure and distribution do not match Canada
Ferrucci, 2011	BCC	Prevalence of exposure and distribution do not match Canada
Lazovich, 2010	Melanoma	Prevalence of exposure and distribution do not match Canada
Nielson, 2012	Melanoma	Prevalence of exposure and distribution do not match Canada
Veierod, 2010	Melanoma	Prevalence of exposure and distribution do not match Canada
Veierod, 2014	SCC	Prevalence of exposure and distribution do not match Canada
Westerdahl, 2000	Melanoma	Prevalence of exposure and distribution do not match Canada
Zanetti, 1988	Melanoma	Prevalence of exposure and distribution do not match Canada
Ghiasvand, 2017	Melanoma	Prevalence of exposure and distribution do not match Canada

Aubrey and McGibbon, 1985	SCC	Does not represent contemporary exposure (mercury lamps)
Elwood, 1986	Melanoma	Occupational exposures
Han, 2006	BCC, SCC	Same study population as Zhang et al. 2012
Karagas, 2014	BCC	Same study population as Karagas et al. 2002
Lazovich, 2014	Melanoma	Same study population Lazovich et al. 2010
Lazovich, 2016	Melanoma	Same study population Lazovich et al. 2010

Abbreviations: BCC = basal cell carcinoma, SCC = squamous cell carcinoma

Supplemental Table 2. Estimated prevalence of indoor tanning among Caucasians in Canadian provinces*

Province	Prevalence (95% confidence interval)					
	Men		Women		Total	
	Past year	Ever use	Past year	Ever use	Past year	Ever use
BC	2.2 (1.1-4.1)	5.4 (2.7-10.1)	12.9 (10.3-16.0)	32.0 (25.6-39.7)	7.6 (6.0-9.4)	18.8 (14.8-23.3)
AB	7.7 (5.5-10.8)	19.3 (13.8-27.1)	18.7 (15.7-22.1)	46.2 (38.8-54.6)	13.1 (11.1-15.3)	32.6 (27.6-38.1)
MBSK	7.1 (4.9-9.9)	17.9 (12.4-25.0)	16.5 (13.6-19.9)	41.0 (33.8-49.5)	11.9 (10.0-14.1)	29.6 (24.9-35.1)
ON	6.0 (4.3-8.7)	14.9 (10.7-21.6)	13.1 (10.8-15.8)	31.6 (26.1-38.1)	9.6 (8.1-11.5)	23.5 (19.8-28.2)
QC	6.4 (4.6-9.0)	16.3 (11.7-22.9)	14.2 (11.9-16.9)	35.4 (29.7-42.1)	10.3 (8.7-12.1)	25.9 (21.9-30.4)
AP	6.8 (4.9-9.2)	17.5 (12.6-23.7)	14.9 (12.5-17.6)	37.0 (31.0-43.7)	11.0 (9.4-12.8)	27.5 (23.5-32.0)

*Data the Second National Sun Survey (2006)
Abbreviations: BC = British Columbia, AB = Alberta, MBSK = Manitoba and Saskatchewan, ON = Ontario, QC =Quebec, AP = Atlantic Provinces
Atlantic Provinces include: Newfoundland, Prince Edward Island, New Brunswick, and Nova Scotia
Note: Total and overall prevalence calculated by population weighted averages

Supplemental Table 3. Estimated confidence intervals for the number and proportion of melanoma and non-melanoma skin cancer cases attributable to indoor tanning in Canada in 2015

Age at Diagnosis	Melanoma		Basal cell carcinoma		Squamous cell carcinoma	
	PAR 95% CI	AC 95% CI	PAR 95% CI	AC 95% CI	PAR 95% CI	AC 95% CI
Men						
20-29	2.5-10.0	1-4	3.5-8.8	6-15	0.0-25.0	0-2
30-49	4.5-11.1	21-52	4.5-11.0	117-289	4.5-10.8	13-31
≥50	2.4-6.5	79-214	2.5-6.3	717-1799	2.5-6.3	323-809
Total	2.7-7.1	101-270	2.7-6.7	840-2103	2.6-6.4	336-842
Women						
20-29	10.9-25.5	12-28	11.2-24.7	25-55	10.5-26.3	2-5
30-49	9.6-22.6	63-148	10.1-22.1	303-665	10.1-22.0	32-70
≥50	4.9-12.3	112-282	5.0-12.0	1171-2820	5.0-12.0	351-845
Total	6.1-15.0	187-458	5.6-13.3	1499-3540	5.2-12.5	385-920
Total						
20-29	8.7-21.3	13-32	7.9-17.8	31-70	7.4-25.9	2-7
30-49	7.5-17.8	84-200	7.5-16.9	420-954	7.5-16.7	45-101
≥50	3.4-8.9	191-496	3.6-8.9	1888-4619	3.4-8.4	674-1654
Total	4.2-10.6	288-728	4.0-9.8	2339-5643	3.5-8.6	721-1762

Abbreviations: AC = Attributable cases due to exposure, PAR = Population attributable risk

Supplemental Table 4. Melanoma and non-melanoma skin cancer cases and proportions attributable to indoor tanning in the Canadian provinces in 2015

Province	Sex	Melanoma			Basal cell carcinoma			Squamous cell carcinoma		
		Obs.	PAR	AC	Obs.	PAR	AC	Obs.	PAR	AC
BC	Men	520	1.1	6	4287	0.8	36	1803	1.2	21
	Women	440	10	44	3612	7.6	273	999	11.7	117
	Total	960	5.2	50	7899	3.9	309	2803	4.9	138
AB	Men	385	7.3	28	3194	5.8	186	1306	9.7	127
	Women	320	13.1	42	2600	9.9	258	699	14.7	103
	Total	705	9.9	70	5794	7.7	444	2005	10.6	230
MBSK	Men	195	5.6	11	1979	4.2	84	827	6.7	55
	Women	215	11.2	24	1662	7.8	129	456	11.2	51
	Total	410	8.5	35	3641	5.9	213	1283	8.3	106
ON	Men	1795	4.3	78	11856	3.3	393	4967	5.2	258
	Women	1410	8.8	125	10336	6.4	659	2851	9.7	276
	Total	3205	6.3	203	22192	4.7	1052	7818	6.8	534
QC	Men	560	5.4	30	7605	3.9	297	3196	6.1	195
	Women	370	10.5	39	6457	7	451	1793	10.4	187
	Total	930	7.4	69	14062	5.3	748	4989	7.5	372
AP	Men	355	5.9	21	2305	4.3	100	976	6.8	66
	Women	300	11.3	34	1981	8	159	554	12.3	68
	Total	655	8.4	55	4285	6	259	1529	8.8	134

Abbreviations: AC = Attributable cases due to exposure, Obs. = Total number of observed cases per age and sex group, PAR = Population attributable risk, BC = British Columbia, AB = Alberta, MBSK = Manitoba and Saskatchewan, ON = Ontario, QC = Quebec, AP = Atlantic Provinces (Newfoundland, Prince Edward Island, New Brunswick, and Nova Scotia), MBSK = Manitoba and Saskatchewan.

Appendix C

Manuscript 2 Supplemental Material

Supplemental Table 1. Melanoma cases diagnosed in 2015, estimated to be attributable to contemporary increases in ultraviolet radiation in Canadian Provinces

Age	British Columbia			Alberta			MBSK			Ontario			Quebec			Atlantic Provinces		
	Obs.	PAR	AC	Obs.	PAR	AC	Obs.	PAR	AC	Obs.	PAR	AC	Obs.	PAR	AC	Obs.	PAR	AC
Men																		
20-34	20	70.0	14	20	80.0	16	0	0.0	0	45	60.0	27	10	80.0	8	10	90.0	9
35-49	40	55.0	22	50	78.0	39	20	70.0	14	175	69.1	121	75	85.3	64	45	91.1	41
50-64	165	67.3	111	130	76.9	100	55	67.3	37	510	67.3	343	175	81.7	143	100	83.0	83
65+	295	50.2	148	185	63.2	117	120	65.0	78	1065	57.3	610	300	75.3	226	200	67.5	135
Total	520	56.7	295	385	70.6	272	195	66.2	129	1795	61.3	1101	560	78.8	441	355	75.5	268
Women																		
20-34	25	44.0	11	30	63.3	19	15	73.3	11	100	63.0	63	35	85.7	30	20	95.0	19
35-49	65	56.9	37	65	70.8	46	40	72.5	29	240	68.8	165	75	82.7	62	55	89.1	49
50-64	140	57.9	81	120	68.3	82	70	68.6	48	440	62.5	275	115	70.4	81	105	81.9	86
65+	210	44.8	94	105	38.1	40	90	47.8	43	630	45.2	285	145	34.5	50	120	53.3	64
Total	440	50.7	223	320	58.4	187	215	60.9	131	1410	55.9	788	370	60.3	223	300	72.7	218
Total																		
20-34	45	55.6	25	50	70.0	35	15	73.3	11	145	62.1	90	45	84.4	38	30	93.3	28
35-49	105	56.2	59	115	73.9	85	60	71.7	43	415	68.9	286	150	84.0	126	100	90.0	90
50-64	305	63.0	192	250	72.8	182	125	68.0	85	950	65.1	618	290	77.2	224	205	82.4	169
65+	505	47.9	242	290	54.1	157	210	57.6	121	1695	52.8	895	445	62.0	276	320	62.2	199
Total	960	54.0	518	705	65.1	459	410	63.4	260	3205	58.9	1889	930	71.4	664	655	74.2	486

Abbreviations: AC = Attributable cases, MBSK = Manitoba and Saskatchewan, Obs. = Observed cases

Atlantic Provinces include: Newfoundland, Prince Edward Island, New Brunswick, Nova Scotia

Supplemental Table 2. Primary reasons for exclusion for each study that underwent full-text review

Primary reason for exclusion	Studies
Unrelated (no measure of sunburn or sunbathing)	Gellin (1969), Klepp (1979), Lee (1980), Beral (1982), Lew (1983), Cooke (1984), Graham (1985), Vagero (1986), Swerdlow (1986), Garbe (1989), Weinstck (1989), Pion (1994), White (1994), Goodman (1995), Fritschi (1996), Freedman (1997), Moore (1997), Lock Anderson (1998), Hakansson (2001), Kanetsky (2001), Fears (2002), Titus-Ernstoff (2005), Gogas (2008), Fortes (2011), Fears (2011), Simic (2011), Asgari (2012), Idorn (2013), Vogel (2014), Chiarugi (2015), Ghiasvand (2016), Stick (2016), Ransohoff (2016), Yager (2016), Hernando (2016), Lazovich (2016), Ghiasvand (2017)
Lack of mutual adjustment	MacKie (1982), Sorahan (1985), Elwood (1986), Holly (1987), Osterlind (1988), Dubin (1990), Grob (1990), Weiss (1991), Nelemans (1993), Holly (1995), Rodenas (1996), Berwick (1996), Breibart (1996), Wolf (1998), Zanetti (1992), Rosso (1998), Carli (1999), Naldi (2000), Pfahlberg (2001), Veierod (2003), Cho (2005), Nijsten (2005), de Vries (2005), Naldi (2005), Nikolaou (2008), Nagore (2010), Veierod (2010), de Vries (2012), Kulichova (2014), Wu (2016), Savoye (2018)

Lack of control for other important confounders	Bell (1987), Cristofolini (1987), Kelly (1989), Beitner (1990), Elwood (1990), Dunn-Lane (1993), Dabkowsk (1997), Kolmel (1999), Mastrangelo (2000), Shors (2001), Shen (2003), Wei (2003), Bean Freeman (2003), Kennedy (2003), Zanetti (2006), Lea (2007), Fortes (2007), Clough-Gorr (2008), Newton-Bishop (2011), Vranova (2012), Ballester (2012), Malagoli/Vinceti (2015/2011), Segatto (2015), Muller (2016), Magoni (2018)
Latitude	Green (1985), Holman (1986), Tabenkin (1999), Loria (2001), Bakos (2004), Lasithiotakis (2004), Le Marchand (20006), Park (2012)
Adjusted for a factor on the causal pathway	Mackie (1989), Landi (2001), Fargnoli (2004), Kaskel (2015)
Childhood exposure	Elwood (1984), Cress (1995), Fernandez (2007)
Only reported risk for trunk melanomas	Herzfeld (1993)

Supplemental Table 3. Estimated prevalence of sunburn among Caucasians in Canadian provinces

Province	Prevalence (95% confidence interval)					
	Men		Women		Total	
	Past year	Ever use	Past year	Ever use	Past year	Ever use
BC	23.9 (19.8-28.5)	37.4 (31.0-44.5)	21.3 (18.0-25.1)	33.1 (28.0-38.9)	22.6 (20.0-25.5)	35.3 (31.2-39.8)
AB	33.2 (28.7-38.1)	51.9 (44.8-59.5)	22.9 (19.5-26.7)	35.2 (30.0-41.1)	28.1 (25.2-31.1)	43.8 (39.3-48.5)
MBSK	26.4 (22.2-31.0)	41.0 (34.5-48.2)	22.0 (18.7-25.9)	33.6 (28.6-39.6)	24.2 (21.5-27.1)	37.8 (33.5-42.3)
ON	21.5 (17.9-25.6)	33.4 (27.8-39.8)	12.8 (10.4-15.6)	19.6 (15.9-23.8)	17.0 (14.9-19.4)	26.5 (23.2-30.3)
QC	20.7 (17.2-24.6)	32.5 (27.0-38.6)	16.6 (14.1-19.6)	25.6 (21.7-30.2)	18.6 (16.4-20.9)	29.0 (25.6-32.6)
AP	19.4 (16.2-23.0)	30.4 (25.5-36.1)	15.3 (12.8-18.2)	23.3 (19.6-27.8)	17.3 (15.2-19.5)	27.0 (23.7-30.4)

*Data from the Second National Sun Survey (2006)
Note: Total and overall prevalence calculated by population weighted averages
Atlantic Provinces include: Newfoundland, Prince Edward Island, New Brunswick, Nova Scotia
MBSK = Manitoba and Saskatchewan

Supplemental Table 4. Estimated prevalence of sunbathing among Caucasians in Canadian provinces

Province	Prevalence (95% confidence interval)					
	Men		Women		Total	
	Past year	Ever use	Past year	Ever use	Past year	Ever use
BC	18.8 (15.3-23.1)	42.9 (34.8-52.7)	25.1 (21.6-28.9)	56.5 (48.6-65.2)	22.2 (19.6-24.9)	49.7 (43.9-55.8)
AB	27.3 (23.2-31.9)	61.4 (52.2-71.7)	48.4 (44.2-52.5)	66.6 (60.8-72.3)	37.7 (34.7-40.8)	64.0 (58.9-69.2)
MBSK	19.3 (15.6-23.3)	43.1 (34.8-52.0)	26.3 (22.8-30.2)	60.7 (52.5-69.7)	22.9 (20.4-25.8)	51.9 (46.3-58.5)
ON	20.7 (17.2-24.6)	47.2 (39.2-56.1)	27.9 (24.8-31.4)	62.9 (56.0-70.8)	24.4 (22.0-26.9)	55.3 (49.8-60.9)
QC	16.4 (13.4-20.0)	38.5 (31.4-46.9)	27.1 (24.1-30.4)	62.8 (55.9-70.4)	21.8 (19.6-24.2)	50.8 (45.7-56.3)
AP	18.3 (15.2-21.7)	43.9 (36.4-52.0)	28.0 (24.9-31.3)	65.2 (57.9-72.8)	23.2 (20.9-25.6)	54.6 (49.3-60.3)

*Data from the Second National Sun Survey (2006)

Note: Total and overall prevalence calculated by population weighted averages

Abbreviations: AB = Alberta; AC = Attributable cases; AP = Atlantic Provinces (Newfoundland, Prince Edward Island, New Brunswick, Nova Scotia); BC = British Columbia; MBSK = Manitoba and Saskatchewan; ON = Ontario; QC = Quebec

Supplemental Table 5. Estimated confidence intervals for the UVR behavior PAR estimates

Age at Diagnosis	Sunburn		Sunbathing		Combined	
	PAR 95% CI	AC 95% CI	PAR 95% CI	AC 95% CI	PAR 95% CI	AC 95% CI
Men						
20-29	5.0-15.0	2-6	7.5-20.0	3-8	20.0-40.0	6-16
30-49	6.6-17.0	31-80	9.1-30.2	43-142	19.2-48.7	90-229
>=50	4.3-11.8	141-391	7.2-24.3	236-802	15.0-38.0	449-1253
Total	4.6-12.5	175-478	7.4-25.0	282-954	14.3-39.3	545-1498
Women						
20-29	5.5-13.6	6-15	9.1-28.2	10-31	23.6-52.7	26-58
30-49	5.5-14.5	36-95	14.0-40.8	92-267	27.0-60.1	177-397
>=50	2.8-7.6	63-175	8.1-27.4	186-628	15.4-41.7	353-956
Total	3.5-9.4	106-288	9.5-30.4	289-930	18.2-46.2	556-1411
Total						
20-29	6.7-16.7	10-25	9.3-30.0	14-45	21.3-49.3	32-74
30-49	6.0-15.6	67-175	12.0-36.4	135-409	23.7-55.6	267-626
>=50	3.6-10.1	204-566	7.5-25.6	422-1430	14.4-39.5	802-2209
Total	4.1-11.2	281-766	8.3-27.4	571-1884	16.0-42.4	1101-2909

Abbreviations: AC = Attributable cases, CI = Confidence interval, Obs. = Observed cases, PAR = Population attributable risk

Supplemental Table 6. Melanoma cases and proportions estimated to be attributable to sunburn, sunbathing and combined UVR risk behaviors in Canada provinces in 2015

Province	Sex	Sunburn			Sunbathing		Combined	
		Obs.	PAR	AC	PAR	AC	PAR	AC
BC	Men	520	7.3	38	15.4	80	22.9	119
	Women	440	7.1	31	17.5	77	31.0	124
	Total	960	7.2	69	16.4	157	25.3	243
AB	Men	385	10.1	39	19.5	75	33.5	129
	Women	320	7.8	25	21.6	69	37.2	119
	Total	705	9.1	64	20.4	144	35.2	248
MBSK	Men	195	11.3	22	14.9	29	29.2	57
	Women	215	7.9	17	19.1	41	34.0	73
	Total	410	9.5	39	17.1	70	31.7	130
ON	Men	1795	6.2	112	16.2	290	25.2	452
	Women	1410	4.4	62	21.0	296	31.2	440
	Total	3205	5.4	174	18.3	586	27.8	892
QC	Men	560	6.6	37	14.1	79	24.5	137
	Women	370	6.5	24	20.3	75	33.5	124
	Total	930	6.6	61	16.6	154	28.1	261
AP	Men	355	6.8	24	16.3	58	27.7	96
	Women	300	5.0	15	21.7	65	34.0	102
	Total	655	6.0	39	18.8	123	30.2	198

*Includes joint distributions for indoor tanning (results previously published), sunburn, and sunbathing

Abbreviations: AC = Attributable cases, AP = Atlantic Provinces (Newfoundland, Prince Edward Island, New Brunswick, Nova Scotia), MBSK = Manitoba and Saskatchewan, Obs. = Observed cases

Supplemental Table 7. Projected melanoma cases and proportions estimated to be attributable to modifiable UVR risk behaviors in Canadian provinces in 2038

Province	Sex	Indoor Tanning			Sunburn		Sunbathing		Combined	
		Proj.	PAR	AC	PAR	AC	PAR	AC	PAR	AC
BC	Men	868	0.9	8	7.8	68	15.4	134	23.0	200
	Women	820	9.4	77	6.8	56	17.1	140	30.1	247
	Total	1688	3.3	85	7.3	124	16.2	274	26.5	447
AB	Men	629	7.0	44	9.2	58	19.2	121	32.3	203
	Women	505	11.9	60	7.3	37	20.6	104	35.2	178
	Total	1134	12.7	144	8.4	95	19.8	225	33.6	381
MBSK	Men	234	5.1	12	6.8	16	14.5	34	24.8	58
	Women	158	10.8	17	8.2	13	19.0	30	33.5	53
	Total	392	7.4	29	7.4	29	16.3	64	28.3	111
ON	Men	2747	4.1	113	5.6	154	16.2	445	24.5	673
	Women	1954	8.4	165	4.3	84	20.8	407	30.7	599
	Total	4701	5.9	278	5.1	238	18.1	852	27.1	1272
QC	Men	1009	2.7	27	5.8	58	13.7	138	21.2	214
	Women	1001	7.1	71	6.5	65	20.0	200	30.6	306
	Total	2010	4.9	98	6.1	123	16.8	338	25.9	520
AP	Men	190	5.3	10	19.0	36	16.3	31	36.3	69
	Women	464	10.6	49	5.0	23	21.1	98	33.0	153
	Total	654	9.0	59	9.0	59	19.7	129	33.9	222

Abbreviations: AB = Alberta; AC = attributable cases; AP = Atlantic Provinces (Newfoundland, Prince Edward Island, New Brunswick, Nova Scotia); BC = British Columbia; MBSK = Manitoba and Saskatchewan; ON = Ontario; PAR = Population attributable risk; Proj. = projected cases; QC = Quebec

Supplemental Table 8. Projected melanoma cases and proportion of cases estimated that could be prevented in 2038 with various changes in the prevalence of modifiable UVR risk behaviors in Canadian provinces

Province	Sex	Statistic	CTF	Indoor Tanning	Sunburn	Sunbathing	Combined
BC	Men	Projected Cases	50% reduction by 2033	864	834	801	765
		PIF (%)		0.5	3.9	7.7	11.9
		Prevented Cases		4	34	67	103
	Women	Projected Cases		782	792	750	691
		PIF (%)		4.6	3.4	8.5	15.7
		Prevented Cases		38	28	70	129
	Men	Projected Cases	25% reduction by 2033	866	851	835	816
		PIF (%)		0.2	2.0	3.8	6.0
		Prevented Cases		2	17	33	52
	Women	Projected Cases		801	806	785	753
		PIF (%)		2.3	1.7	4.3	8.2
		Prevented Cases		19	14	35	67
	Men	Projected Cases	10% reduction by 2033	867	861	855	847
		PIF (%)		0.1	0.8	1.5	2.4
		Prevented Cases		1	7	13	21
	Women	Projected Cases		812	814	806	792
		PIF (%)		1.0	0.7	1.7	3.4
		Prevented Cases		8	6	14	28
AB	Men	Projected Cases	50% reduction by 2033	607	600	569	522
		PIF (%)		3.5	4.6	9.5	17.0

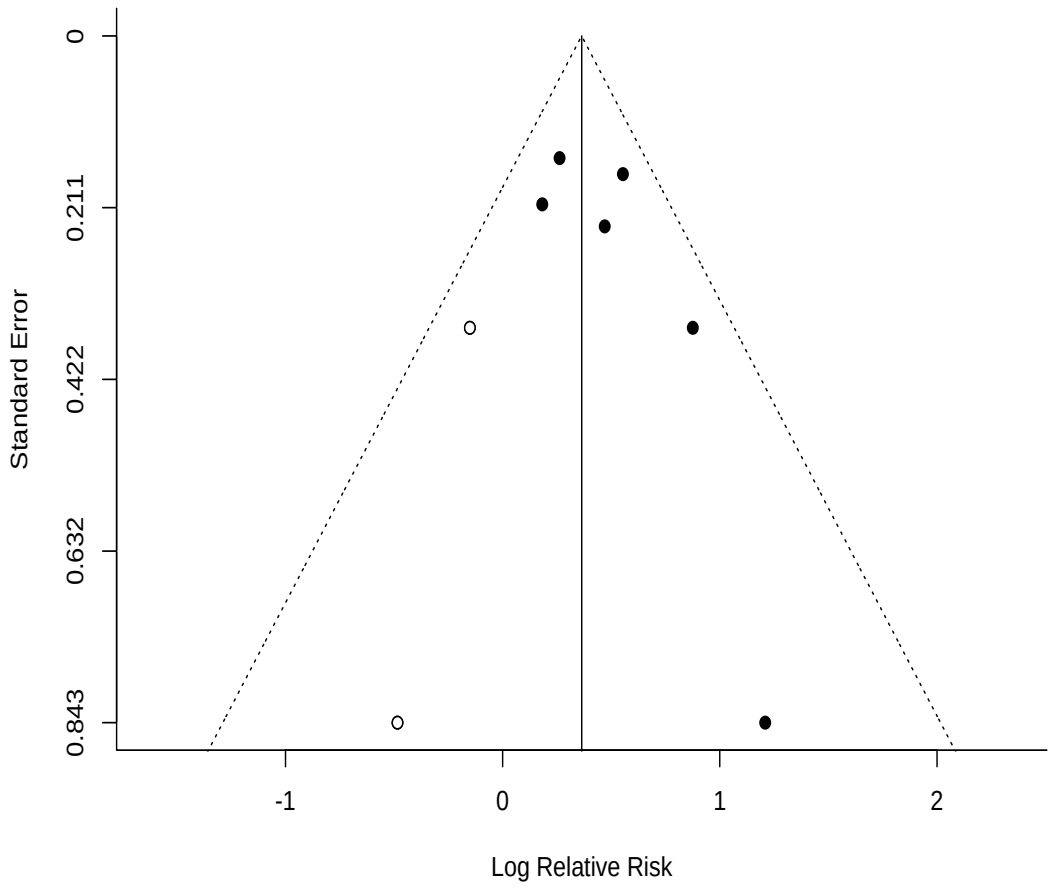
		Prevented Cases		22	29	60	107
		Projected Cases		475	487	453	411
	Women	PIF (%)		5.9	3.6	10.3	18.6
		Prevented Cases		30	18	52	94
		Projected Cases		618	614	599	574
	Men	PIF (%)		1.7	2.4	4.8	8.7
		Prevented Cases	25% reduction	11	15	30	55
		Projected Cases	by 2033	490	496	479	456
	Women	PIF (%)		3.0	1.8	5.2	9.7
		Prevented Cases		15	9	26	49
		Projected Cases		625	623	617	607
	Men	PIF (%)		0.6	1.0	1.9	3.5
		Prevented Cases	10% reduction	4	6	12	22
		Projected Cases	by 2033	499	501	495	485
	Women	PIF (%)		1.2	0.8	2.0	4.0
		Prevented Cases		6	4	10	20
		Projected Cases		228	226	217	204
	Men	PIF (%)		2.6	3.4	7.3	12.8
		Prevented Cases	50% reduction	6	8	17	30
MBSK		Projected Cases	by 2033	150	152	143	131
	Women	PIF (%)		5.1	3.8	9.5	17.7
		Prevented Cases		8	6	15	28
	Men	Projected Cases		231	230	225	218

		PIF (%)	25% reduction by 2033	1.3	1.7	3.9	6.8
		Prevented Cases		3	4	9	16
		Projected Cases		154	155	151	144
	Women	PIF (%)		2.5	1.9	4.4	8.9
		Prevented Cases		4	3	7	14
		Projected Cases	10% reduction by 2033	233	232	230	227
	Men	PIF (%)		0.4	0.9	1.7	3.0
		Prevented Cases		1	2	4	7
		Projected Cases		156	157	155	152
	Women	PIF (%)		1.3	0.6	1.9	3.8
		Prevented Cases		2	1	3	6
ON		Projected Cases	50% reduction by 2033	2690	2670	2525	2397
	Men	PIF (%)		2.1	2.8	8.1	12.7
		Prevented Cases		57	77	222	350
		Projected Cases		1872	1912	1750	1640
	Women	PIF (%)		4.2	2.2	10.4	16.1
		Prevented Cases		82	42	204	314
		Projected Cases	25% reduction by 2033	2719	2709	2636	2572
	Men	PIF (%)		1.0	1.4	4.0	6.4
		Prevented Cases		28	38	111	175
		Projected Cases		1913	1933	1852	1793
	Women	PIF (%)		2.1	1.1	5.2	8.2
		Prevented Cases		41	21	102	161

		Projected Cases		2736	2732	2702	2675
	Men	PIF (%)		0.4	0.6	1.6	2.6
		Prevented Cases	10% reduction	11	15	45	72
		Projected Cases	by 2033	1937	1945	1913	1886
	Women	PIF (%)		0.9	0.5	2.1	3.5
		Prevented Cases		17	9	41	68
		Projected Cases		995	980	940	899
	Men	PIF (%)		1.4	2.9	6.8	10.9
		Prevented Cases	50% reduction	14	29	69	110
		Projected Cases	by 2033	966	968	901	840
	Women	PIF (%)		3.5	3.3	10.0	16.1
		Prevented Cases		35	33	100	161
		Projected Cases		1002	994	974	951
	Men	PIF (%)		0.7	1.5	3.5	5.7
QC		Prevented Cases	25% reduction	7	15	35	58
		Projected Cases	by 2033	983	985	951	919
	Women	PIF (%)		1.8	1.6	5.0	8.2
		Prevented Cases		18	16	50	82
		Projected Cases		1006	1003	995	986
	Men	PIF (%)		0.3	0.6	1.4	2.3
		Prevented Cases	10% reduction	3	6	14	23
		Projected Cases	by 2033	994	994	981	967
	Women	PIF (%)		0.7	0.7	2	3.4

		Prevented Cases		7	7	20	34
AP	Men	Projected Cases	50% reduction by 2033	185	172	175	154
		PIF (%)		2.6	9.5	7.9	18.9
		Prevented Cases		5	18	15	36
	Women	Projected Cases		439	453	415	382
		PIF (%)		5.4	2.4	10.6	17.7
		Prevented Cases		25	11	49	82
	Men	Projected Cases	25% reduction by 2033	187	175	182	164
		PIF (%)		1.6	7.9	4.2	13.2
		Prevented Cases		3	15	8	25
	Women	Projected Cases		452	458	439	422
		PIF (%)		2.6	1.3	5.4	9.1
		Prevented Cases		12	6	25	42
	Men	Projected Cases	10% reduction by 2033	189	186	187	182
		PIF (%)		0.5	2.1	1.6	4.2
		Prevented Cases		1	4	3	8
	Women	Projected Cases		459	462	454	447
		PIF (%)		1.1	0.4	2.2	3.7
		Prevented Cases		5	2	10	17

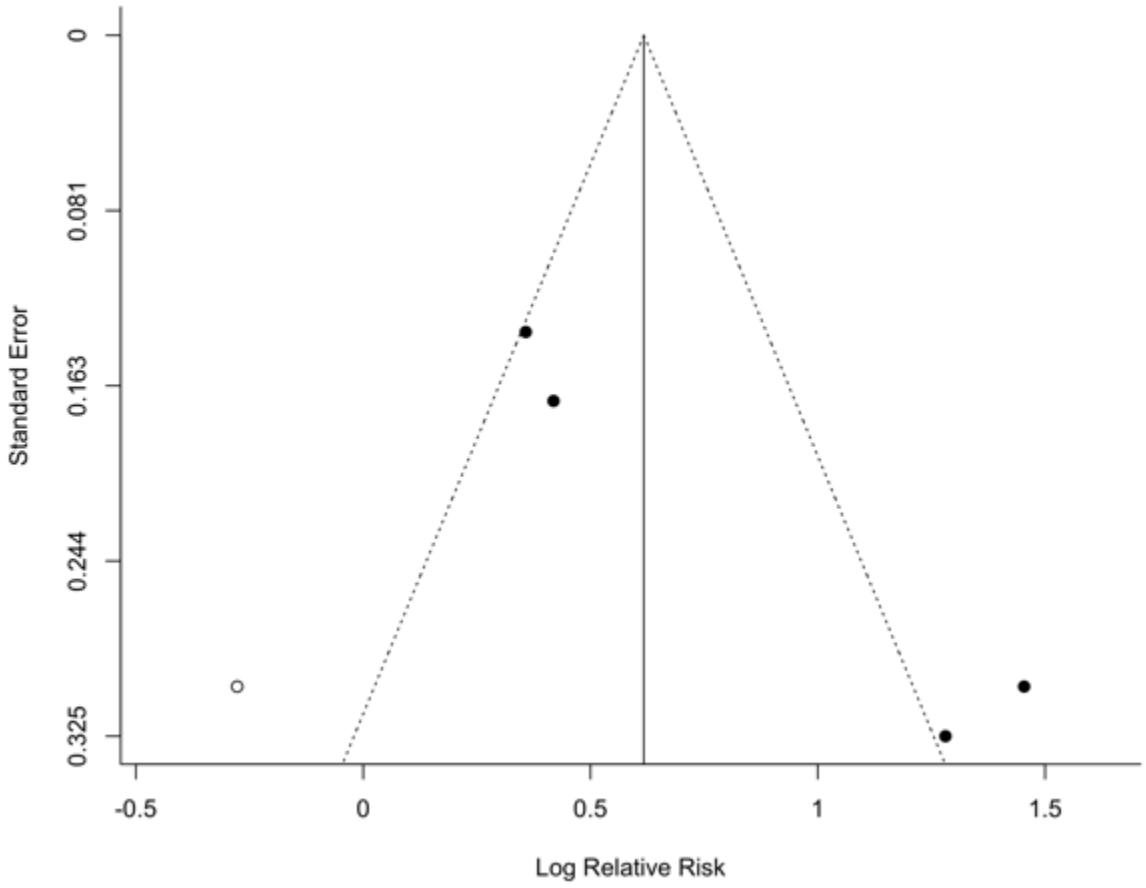
Abbreviations: AB = Alberta; AP = Atlantic Provinces (Newfoundland, Prince Edward Island, New Brunswick, Nova Scotia); BC = British Columbia; CTF = counterfactual scenario; MBSK = Manitoba and Saskatchewan; ON = Ontario; PIF = Potential impact fraction; QC = Quebec



Supplemental Figure 1. Funnel plot of relative risk estimates for melanoma associated with intentional sunbathing in adulthood that is generalizable to Canada.

Appendix D

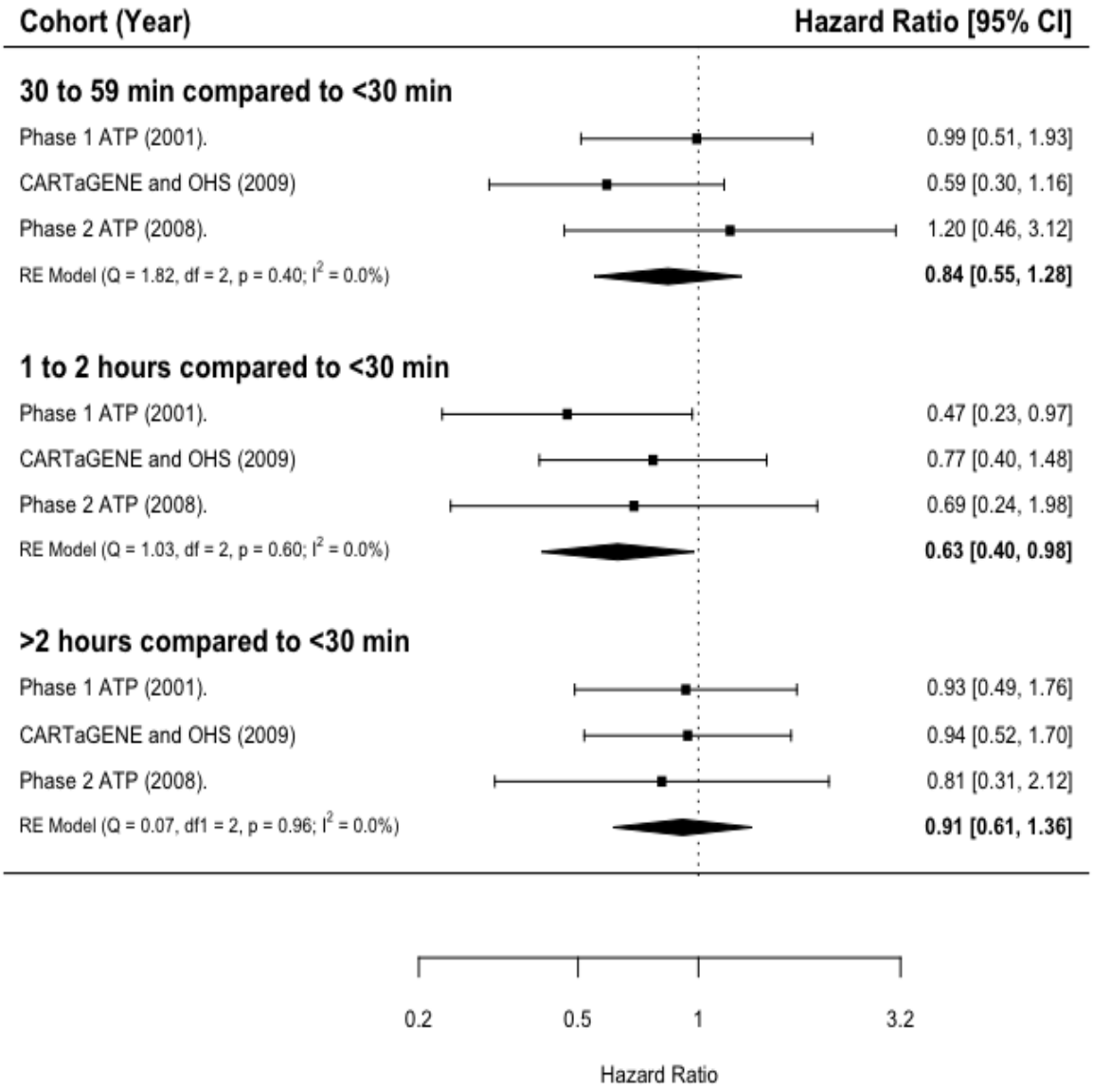
Manuscript 3 Supplemental Material



Supplemental Figure 1. Funnel plot of relative risk estimates for basal cell carcinoma associated with sunburn in adulthood that is generalizable to Canada.

Appendix E

Manuscript 4 Supplemental Material



Supplemental Figure 1. Cohort-specific hazard ratios for time spent in the sun and the risk of developing non-Hodgkin lymphoma

Supplemental Table 1. The influence of non-differential misclassification of the outcome in the CARTaGENE cohort on the pooled results

Time spent in the sun	Observed			Truth*		
	Events	Non-events	RR	Events	Non-events	RR
< 30 min (ref)	40	14,075	1.0 (ref)	33	14,082	1.0 (ref)
30-60 min	49	21,390	0.84 (0.55-1.28)	44	21,395	0.87 (0.54-1.41)
1-2 hours	40	20,865	0.63 (0.40-0.98)	34	20,871	0.58 (0.36-0.94)
> 2 hours	76	23,268	0.91 (0.61-1.36)	67	23,277	0.89 (0.58-1.37)
Total	205	79,598		178	79,625	

*Risk estimates based on sensitivity of 100% and specificity of 99.94% for CaG, which equates to a 65% increase in events, are pooled with results from the other cohorts (phase 1 ATP, phase 2 ATP, OHS).