INCIDENCE AND PROFILE OF SKIN CANCER IN PATIENTS UNDERGOING ULTRAVIOLET-B PHOTOTHERAPY

by

Elle (Yueqiao) Wang

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, a thesis entitled:

Incidence and profile of skin cancer in patients undergoing ultraviolet-B phototherapy

submitted by Elle (Yueqiao) Wang in partial fulfillment of the requirements for

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in Experimental Medicine

Examining Committee:

Dr. Sunil Kalia, Associate Professor, Dermatology and Skin Science

Supervisor

Dr. Harvey Lui, Professor, Dermatology and Skin Science

Supervisory Committee Member

Dr. Tim K. Lee, Associate Professor, Dermatology and Skin Science

Supervisory Committee Member

Additional Examiner

Additional Supervisory Committee Members:

Supervisory Committee Member

Supervisory Committee Member

Abstract

Background: Ultraviolet (UV) phototherapy is an important treatment option in Canada for skin diseases. However, the long-term risk of skin cancer, has not been adequately studied and quantified in the published literature.

Objectives: The objectives include i) to create an electronic database for patients receiving phototherapy at the Psoriasis and Phototherapy Clinic, Skin Care Center, Vancouver; ii) to explore incidence of skin cancers including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma in patients with UVB therapy; iii) to evaluate skin cancers by anatomical distribution and skin type; iv) to compare incidence rate of skin cancers in patients with phototherapy and British Columbia general population; v) to correlate total treatment session, cumulative dosage with skin cancer risk; vi) to estimate correlation between skin type and narrow-band UVB (NB-UVB) minimal erythemal dose.

Methods: A retrospective chart review was conducted on patients receiving UV therapy from May 1977 to November 2018. These patients were identified via medical charts at the Psoriasis and Phototherapy Clinic. Pathological ascertainment of basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma for these patients was verified through linkage with an interhospital pathology database for the British Columbia Lower Mainland regional health authorities.

Results: A total of 3,506 patients (1,999 male and 1,507 female) were analyzed for an average of 7.1 years. A total of 170 new skin cancers developed in 79 patients after receiving UVB phototherapy without systemic psoralen plus UVA. Male patients had significantly lower BCC

incidence compared to BC general population (Z scores<0, p<0.05). Sub-analysis of multivariate logistic regression and survival analysis indicated no statistically significant correlations between cumulative dosage and the risk of skin cancer. Odds ratios of developing skin cancer for the upper *vs* lower tercile group for broad-band UVB and narrow-band UVB cumulative dosages were 0.82 (p=0.80) and 0.64 (p=0.57). In addition, there was no dose-related correlation for UVB treatment dosage and skin cancer development.

Conclusion: No increasing skin cancer incidence and risk was found in UVB phototherapy patients compared to general population. Regular UVB treatment might even protect patients from keratinocyte carcinoma, especially BCC, development.

Lay Summary

Ultraviolet (UV) phototherapy is an important treatment option for skin diseases such as psoriasis and atopic dermatitis. It is known that UV exposure from sunlight is a major environmental risk factor for the development of skin cancer in the general population. However, the risk of skin cancer in patients being treated with UVB therapy remain unclear. In this project, a large cohort with a long follow-up duration is evaluated. We found there was no increasing skin cancer incidence and risk for patients with UVB phototherapy compared to general population. Regular UVB treatment might even protect patients from keratinocyte carcinoma, especially basal cell carcinoma, development. Head and neck, the sun-exposed locations, had a tendency of lower keratinocyte carcinoma incidence compared to general population. Total treatment session and cumulative dosage were not statistically correlated with skin cancer risk. Therefore, UVB phototherapy may be a safe treatment options for skin diseases.

Preface

This study was approved and followed the policies and guidelines of the UBC Clinical Research Ethics Board (CREB H17-03410, #). Hardcopies of patient medical charts, specifically those that have received UV therapy were accessed on site at the Psoriasis and Phototherapy Clinic - The VGH Skin Care Centre, Vancouver, Canada. Printed data collection forms including handwritten PHNs will then be used to link patient data to Sunset database for pathological data. All research data were securely stored in the Research Pavilion at the Vancouver General Hospital.

The research idea was brought up by Dr. Sunil Kalia (my supervisor) and designed together by Dr. Sunil Kalia, Dr. Richard Crawford (professor in Department of Pathology and Laboratory, UBC), Yi Ariel Liu (resident in Department of Pathology and Laboratory, UBC), Dr. Harvey Lui and Dr. Tim Lee (my supervisory committee members), and myself.

I was responsible for literature review, creation of cohorts, data collection, data manipulation and analysis, result interpretation, writing and revision of the manuscript. Yi Ariel Liu ascertained pathological results of skin cancers from Sunset database and Dr. Richard Crawford confirmed the results. Dr. Sunil Kalia, Dr. Harvey Lui and Dr. Tim Lee gave guidance of data analysis and reviewed this document.

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List of Abbreviations

AD	Atopic dermatitis
ASIR	Age-standardized incidence rate
BB-UVB	Broad-band ultraviolet-B
BC	British Columbia
BCC	Basal cell carcinoma
CI	Confidence interval
CIR	Crude incidence rate
IR	Incidence rate
KC	Keratinocyte carcinoma
MED	Minimal erythemal dose
MM	Melanoma
NB-UVB	Narrow-band ultraviolet-B
NMSC	Non-melanoma skin cancer
PHN	Personal Health Number
PPCD	Psoriasis and Phototherapy Clinic Database
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
PUVA	Psoralen combined with UVA
p-y	Person-year
SCC	Squamous cell carcinoma
SD	Standard deviation
SE	Standard error

SIR	Standardized incidence rate ratio
SPUVA	Systemic PUVA
US	United States
UV	Ultraviolet
VGH	Vancouver General Hospital

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I would like to thank all nurses in Psoriasis and Phototherapy Clinic - The VGH Skin Care Centre. Thank you all for helping me get access to patients' charts. I also appreciate Dr. Richard Crawford and Yi Ariel Liu for providing pathological confirmation. This project would not be possible without their support.

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Dedication

To my parents and family. (致我的父母和家人)

Chapter 1: Introduction

1.1 Overview of Project and Thesis

1.1.1 Rationality and Objectives

UVB phototherapy is an important treatment option for skin diseases such as psoriasis and atopic dermatitis. On the other hand, it is known that UV exposure from sunlight is a major environmental risk factor for the development of skin cancer in the general population. However, the incidence of skin cancer in patients being treated with UVB therapy remains unclear. Studies with an adequate number of patients that have an adequate long follow up time are limited. We have conducted a literature review and meta-analysis of the correlation between UVB phototherapy and incidence of skin cancer. A retrospective review was performed using clinical records of patients receiving UVB phototherapy in the Psoriasis and Phototherapy Clinic – VGH Skin Care Center, BC, Canada. Incidence and profile of skin cancer in patients undergoing UVB phototherapy was characterized.

The study design is shown in Figure 1.1. Our objectives include:

1) Literature review of UVB phototherapy and risk of skin cancer and meta-analysis of NB-UVB and incidence rate of skin cancer.
2) Electronic Psoriasis and Phototherapy Clinic Database (PPCD) creation of patients receiving phototherapy in Psoriasis and Phototherapy Clinic – Skin Care Center, Vancouver General Hospital, BC, Canada.
3) Correlation analysis between skin type and NB-UVB minimal erythemal dose.

4) Incidence of skin cancer and anatomical distribution of patients with UVB phototherapy.
5) Comparison of skin cancer incidence of patients with UVB phototherapy and general population.
6) Sub-analysis for correlation of number of total treatment sessions and cumulative dosage with skin cancer risk.

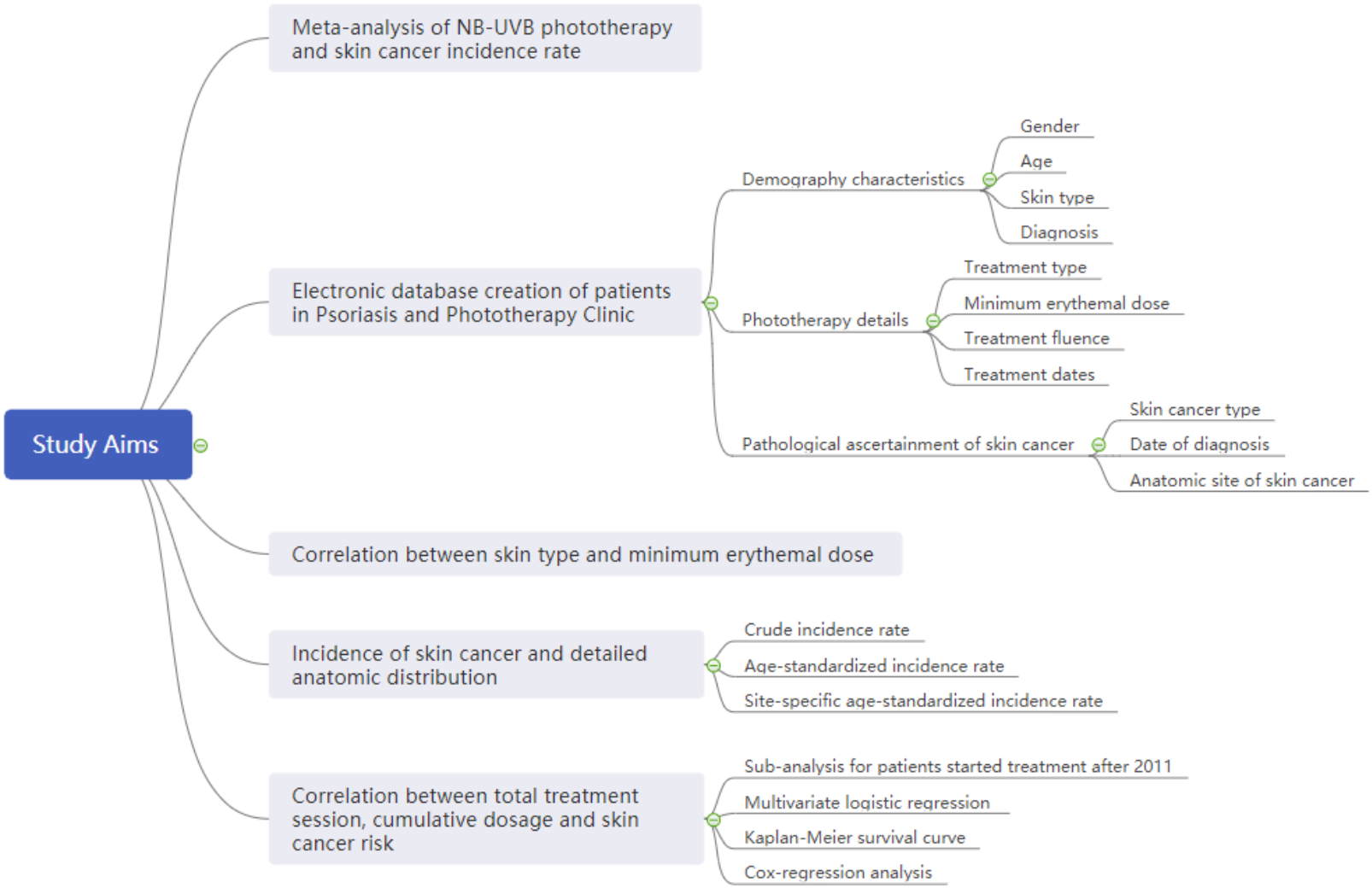

Figure 1.1 Study Design Flowchart

Our primary objectives include: i) to explore the incidence of skin cancer in patients receiving UVB phototherapy in the Psoriasis and Phototherapy Clinic – VGH Skin Care Center, BC, Canada. Skin cancer incidence profile will be estimated in anatomical distribution, skin type, age and treatment type. Comparison of skin cancer incidence rates in patients undergoing UVB phototherapy to rates in the BC general population will be performed; ii) to estimate the correlation between total number of treatment sessions, cumulative dosage and skin cancer risk by sub-analysis for patients starting treatment after 2011.

Our secondary objective is evaluating correlation between minimal erythemal dose (MED) for narrow-band UVB (NB-UVB) and phototypes.

1.1.2 Hypothesis

UV exposure is recognized as a risk for skin cancer [1]. Previous studies assessing psoralen combined with UVA (PUVA) phototherapy and indoor tanning suggest a dose-response correlation with skin cancer risk [2, 3]. Therefore, we hypothesize that patients undergoing UVB phototherapy will have higher incidence of skin cancer compared to the general population and that patients with higher number of treatment sessions will have higher risk of developing skin cancer.

1.1.3 Structure of Thesis

Chapter 1. Give a review of i) project and thesis; ii) ultraviolet phototherapy; iii) skin cancer.

Chapter 2. Summarize publications assessing UVB phototherapy and skin cancer and conducted meta-analysis of NB-UVB on skin cancer incidence rate.

Chapter 3. Introduce methods of electronic database creation including data source and database structure.

Chapter 4. Provide results of skin cancer incidence in UVB phototherapy patients including demographic information, crude skin cancer incidence, individual-based and case-based skin cancer age-standardized incidence and anatomical distribution.

Chapter 5. Provide sub-analysis results for assessing correlation between total number of treatment session, or cumulative dosage and skin cancer development by multivariate logistic regression analysis, Cox-regression analysis and Kaplan-Meier survival analysis.

Chapter 6. Summarize key findings and discuss true risk of skin cancer in UVB phototherapy patients based on our results.

1.2 Ultraviolet Phototherapy

The use of sunlight for the treatment of skin diseases dates back to 2000 B.C. in Egypt and India [4]. However, because of the varying intensity and availability of sunlight, artificial ultraviolet (UV) phototherapy was developed as a treatment for skin conditions in the early 1900s to overcome limitations of natural sunlight [5].

1.2.1 The Type of Ultraviolet Light and Phototherapy

There are two major sources of UV radiation: solar exposure and human-made UV lamps. UV radiation ranges from 100–400 nm, which can be categorized in three types: UVA (315–400 nm), UVB (280–315 nm) and UVC (100–280 nm) [6].

Phototherapy is an effective treatment option for common skin disorders such as psoriasis, atopic dermatitis (AD), vitiligo, and pruritus. It is most commonly used in psoriasis patients. Types of phototherapy include, broad-band UVB (BB-UVB, 280-320 nm), narrow-band UVB (NB-UVB, 311-313 nm), UVA-1 (340-400 nm) and photochemotherapy (PUVA). The treatments involve exposing target areas of skin or the whole body to UV light.

UVB phototherapy is most common treatment option, especially for psoriasis patients. In 1925, the combination of BB-UVB and crude coal tar, also known as Goeckerman therapy, was applied to psoriasis patients [7]. BB-UVB was used to treat AD patients from the 1940s [8]. After discovery that UVB was most effective at about 310 nm, NB-UVB phototherapy was introduced in the 1980s for the treatment of psoriasis [9].

1.2.2 Dosage and Therapeutic Protocols

Among all types of phototherapy, UVB treatment is used most frequently. Treatment begins with an initial dose and increases progressively during each phototherapy session. The initial dose is determined in relation to Fitzpatrick skin type [10], or minimal erythema dose (MED) by phototesting [11]. MED is the lowest UV dose that produces the first perceptible erythema with defined borders in the field of UV exposure, 24 hours after UV exposure. Multiple treatment regimens exist. A common treatment protocol using MED phototesting involves using an initial dose of 70% of the MED with 10% - 20% increments in the fluence at successive treatment sessions provided no adverse erythema is experienced [12]. In cases of erythemal responses, dose increments are reduced or halted depending on the regimen. [13]. For psoriasis, UVB treatment is recommended at a frequency of 3-5 sessions per week, up to 2-3 months [11]. However, psoriasis is a lifelong chronic inflammatory disease and there is no cure for psoriasis yet. Phototherapy is

an option to get relief from psoriasis symptoms and help patients to enter psoriasis remission, having no visible symptoms for a period of time. But psoriasis may come back after stopping treatment [14]. For AD, UVB treatment usually requires at least 2–5 sessions per week, up to 2–3 months [15].

For all patients receiving phototherapy in the Psoriasis and Phototherapy Clinic-Skin Care Center, Vancouver General Hospital, starting dose is determined by a patient's Fitzpatrick skin phototype. When in doubt regarding skin phototype or initial dosing, a phototest is done to establish the patient's MED and the starting dose is set as 70% of the MED. Patients are recommended to receive treatment 2-3 times per week. With each subsequent dose, 10% dosage increments are given if no erythema or pain is experienced with the previous exposure. If a patient shows moderate erythema or adverse effects, dosage increments are decreased, or treatment is held until resolution of symptoms. If a patient has a break during treatment, the dose is adjusted according to the break duration as set out in the local protocol. If the break in treatment is more than 28 days, the treatment is started over at the baseline. Details of protocol used in Psoriasis and Phototherapy Clinic-Vancouver General Hospital is attached in Appendixes (Appendix 1.1).

1.2.3 Adverse Effects of Phototherapy

Short-term adverse effects of phototherapy include erythema, blisters, tanning and xerosis. For UVB phototherapy, long-term photodamage may be observed [15]. Carcinogenic risk has not been adequately quantified. For patients receiving systemic PUVA treatment, the risk of developing skin cancers has been shown to be increased [16].

1.3 Skin Cancer

1.3.1 Type of Skin Cancers

Skin cancer is commonly classified as cutaneous malignant melanoma and non-melanoma skin cancers (NMSC). The major subtypes of NMSC are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), also known as keratinocyte carcinomas (KC) collectively.

1.3.2 Multiplicity of Skin Cancers

The incidence of skin cancers may be underestimated due to the possibility of the occurrence of multiple primary tumor sites within an individual [17]. Multiple skin cancers are different from recurrence of skin cancers. Definition of a recurrence is a skin cancer that reappears at the same site after removing it by surgery or other methods [18]. However, multiple skin cancers are defined as skin cancers found at different sites and/or after a delay in time [18]. Although it is difficult to identify recurrence of skin cancer, it is possible to track multiple skin cancers. However, methods of dealing with patients with multiple skin cancers are not consistent in different studies.

1.3.3 Anatomical Distribution of Skin Cancers

According to the recommendation of the Surveillance, Epidemiology and End Results program, skin cancers should be reported with a site-specific code. The primary sites include head, lip, eyelid/canthus, external ear/auditory canal, face (cheek, chin, forehead, jaw, nose and temple), scalp, neck, upper trunk, lower trunk, arm/shoulder, leg/hip, and vulva/penis/scrotum [19]. Studies have suggested that facial subsites have a higher incidence of skin cancers [17, 20, 21].

1.3.4 Epidemiology of Skin Cancers in British Columbia, Canada

The incidence of skin cancers shows regional difference. In Canada, there are many challenges identifying and tracking skin cancers, since counts of cancer incidence are kept by various provincial/territorial cancer registries [22]. Due to high incidence rate with high rate of treatment, few cancer registries track KCs and even if KCs are recorded, only the first diagnosis is included [23].

The average crude incidence and mortality rate of cutaneous malignant melanoma across Canadian provinces during 1992-2010 was 12.29 (95% CI: 12.20-12.38) cases per 100,000 individuals and year and 2.41(95% CI: 2.37-2.45) cases per 100,000 individuals and year, respectively [24]. The incidence (15.41 cases per 100,000 individuals and year) and mortality (2.58 cases per 100,000 individuals and year) rates in BC were higher than the Canadian average [25].

The latest research reporting incidence rate of KCs in BC was published in 2012 by McLean *et al.*[26]. They suggested the prevalence of skin cancers increased from 1973 to 2003 for both genders in BC. In 2003, age-standardized incidence rate (ASIR) of BCC, SCC and melanoma was 188.9, 52.5 and 16.1 per 100,000 individuals for male, and was 131.9, 28.2 and 12.2 per 100,000 individuals for female. In addition, they reported incidence rate by anatomic subsite (head and neck, truck, upper limbs, and lower limbs). They also described code rules for multiple skin cancer in BC cancer registry. A special code was used for multiple sites of same skin cancer type, but only the date of the first diagnosis was recorded. However, if a patient developed multiple different type of skin cancers, separate records were recorded on the registry. Multiple primary melanomas within an individual were always recorded as separate tumors. Only case-based incidence rates were reported in this study.

1.3.5 Risk Factors of Skin Cancers

The most important environmental risk factor for all types of skin cancer is solar UVR exposure. One strong evidence for the relation between skin cancer and sun exposure is the geographic variation in incidence of skin cancer [27]. The risk of skin cancer increases in fair skin individuals who reside within year-round high irradiance solar exposure and those who spend a lot of time outdoors [28]. Skin type is an important phenotype trait for developing skin cancer [27]. Due to photoprotection provided by increase epidermal melanin in higher number of skin type, incidence of skin cancer is lower in darker skinned groups [29].

Other well-established risk factors include age [30], genetic factors such as family history of skin cancers [27], and immunosuppression [31].

1.3.6 Skin Type, Minimal Erythemal Dose and Skin Cancer

Fitzpatrick skin type was developed in 1975 by Fitzpatrick as a method to assess the response of different types of skin to UV light [32]. Skin type classification shows in Table 1.1, whereas skin types is categorized by the ability to burn or tan [33].

Table 1.1 Fitzpatrick Skin Type Classification

Skin Type	Effect
I	Always burns, never tans
II	Always burns, sometimes tans
III	Sometimes burns, always tans

IV	Minimally burns, always tans
V	Rarely burns, tans very easily, moderately pigmented, including: Mongoloids, American Indians, Asiatic, Mexicans, Puerto, Ricans, etc.
VI	Never burns, African Americans

Skin type is used to estimate the MED for initial dose in phototherapy [34]. Initial dosage determination based on skin type for different treatment type shows in Table 1.2. Studies show a positive correlation between MED and skin type [29, 35, 36].

Table 1.2 Initial Dosage Determination

Skin Type	NB-UVB Dosage	BB-UVB Dosage	UVA Dosage
I	130 mJ/cm^2	30 mJ/cm^2	0.5 Joules/cm^2
II	220 mJ/cm^2	30 mJ/cm^2	1.0 Joules/cm^2
III	260 mJ/cm^2	30 mJ/cm^2	1.5 Joules/cm^2
IV	330 mJ/cm^2	40 mJ/cm^2	2.0 Joules/cm^2
V	350 mJ/cm^2	50 mJ/cm^2	2.5 Joules/cm^2
VI	400 mJ/cm^2	60 mJ/cm^2	3.0 Joules/cm^2

Skin type is also applied as predictor of skin cancer risk. Many studies confirmed that skin type I and II are highest risk group of developing skin cancer [36-39].

Chapter 2: Literature Review and Meta-Analysis of UVB Phototherapy and Incidence of Skin Cancer

2.1 Literature Review on Correlation between UVB Phototherapy and Skin Cancer

There is an increasing risk of skin cancer in patients receiving PUVA treatment, shown by both prospective studies [40-44] and retrospective studies [45-47]. Although it is clearly demonstrated that PUVA therapy increases the risk of developing skin cancer, there are limited studies exploring the risk of skin cancer with UVB therapy, especially NB-UVB. In addition, the maximum limit for cumulative dosage or number of sessions has not been well established. Studies assessing the risk of skin cancer in patients with UVB therapy are summarized in Table 2.1.

Table 2.1 Summary of Studies Assessing UVB Phototherapy and Skin Cancer Risk

Study [Ref.]	Year	Country	Sample Size	Mean Age	Mean Follow-up (Years)	Treatment	Study Type	Reported Estimate	Comparison Group	Findings	Limitations
Maughan *et al.* [48]	1980	USA	305	NR	25	Goeckerman and UVB	1	Case number; Expected case number	No	No significantly increased incidence of skin cancer	1;3;4;5
Pittelkow *et al.* [49]	1981	USA	260	NR	25	Goeckerman and UVB	1	Case number; Expected case number	No	No significantly increased incidence of skin cancer	1;3;4;5
Halprin *et al.* [50]	1982	USA	95	62	6.8	Goeckerman and UVB	2	Case number; RR	Age-, gender-matched	No significantly increased incidence of skin cancer	1;2;3;4;5
Larko *et al.* [51]	1982	USA	85	NR	16.2	UVB	2	Case number; RR	Age-, gender-matched	No significantly increased incidence of skin cancer	1;3;4;5

Bhate *et al.* [52]	1993	UK	925	41	NR	UVB	2	Case number	Age-, gender-matched	lower incidence of KCs	2;3;4;5
Bajdik *et al.* [53]	1996	Canada	409	NR	NR	UVB and UVA	2	Case number; OR	Age-matched	UV treatment was correlated with a slightly reduced risk for both BCC and SCC	1;2;5;6
Hannuksela-Svahn *et al.* [54]	2000	Finnish	21	NR	NR	UVB	2	IR; RR	Age-, gender-matched	No increased risk of SCC	1;2;3;4;5
Weischer *et al.*[55]	2004	Germany	126	45.5	5.6	BB-UVB; NB-UVB	1	IR	German population	No increased skin cancer risk	1;2;3;4;5
Man *et al.* [56]	2005	Scotland	1908	NR	4*	NB-UVB	1	Case number; Expected case number	Scottish population	Increased incidence of BCC. No increased incidence of SCC and MM.	2;3;4;5
Black et al. [57]	2006	Ireland	484	NR	NR	NB-UVB	1	IR; ASIR	No	No increased skin cancer risk	1;2;4;5

Hearn *et al.*[58]	2008	Scotland	3867	34.0*	5.5	NB-UVB	1	IR; ASIR	Tayside population	No increased skin cancer risk	2;4;5
Jo *et al.*[59]	2011	Korea	445	43.9	2.8	NB-UVB	1	IR; ASIR	Korean population	No increased skin cancer risk	1,2,4,5
Osmancevic *et al.* [60]	2014	Sweden	162	56.0	-	BB-UVB; NB-UVB	3	IR; OR	Within group	The cumulative rate of skin cancer increased with high number of UVB treatments	1;2;5
Maiorino *et al.*[61]	2016	Italy	50	56.0	7.9	NB-UVB	1	IR	No	High positive case number of skin cancer for patients with high-dose NB-UVB treatment	1,3,4
Ortiz-Salvador *et al.*[62]	2018	Spain	474	47.5	5.8	NB-UVB	1	IR; ASIR	Girona population	No increased skin cancer risk	1;2
Raone *et al.*[63]	2018	Italy	375	46.7	6.9	NB-UVB	1	IR; RR	Italian male population	NB-UVB may increase skin cancer risk especially for non-melanoma skin cancer	1;2;3;4

* Reported as median

Abbreviations: Ref: reference; p-y: person-years; IR: incidence rate; ASIR: age-standardized incidence rate ratio; OR: odds ratio; BCC: basal cell carcinoma; SCC: squamous cell carcinoma; MM: melanoma; NR: not reported

Study Type: 1: Retrospective cohort study; 2: Case-control study; 3: Cross-sectional study

Limitations: 1: Sample size <500; 2: Follow-up duration with average less than 7 years or no report of follow-up time; 3: No age-standardized incidence rate; 4: No classification of skin type for region may containing fair, medium and dark skin; 5: No description of statistical analysis on multiple skin cancer sites; 6: self-reported for receiving treatment

2.1.1 Risk of Keratinocyte Carcinoma with BB-UVB Treated Patients

The first article studying the rate of skin cancer in patients with UVB phototherapy combined with coal tar (Goeckerman therapy) was published in 1980 [48]. They found that the incidence of skin cancer was not significantly increased in 305 AD patients in Mayo Clinic, Rochester, USA [48]. In 1981, Pittelkow *et al.* published the study of skin cancer risk and UVB phototherapy combined with coal tar in 260 psoriasis patients also at Mayo Clinic [49]. They found no increase in skin cancer risk from UVB phototherapy in psoriasis patients. These two studies compared the expected case number of KCs in different regions (Dallas-Fort Worth, San-Francisco-Oakland, Minneapolis-St. Paul and Iowa) from the Third National Cancer Survey. Although the authors stated no increased risk of skin cancer, the incidence of skin cancer in AD patients (11 cases) was less than the expected case number of Dallas-Fort Worth (18.8 cases), but higher than expected rates of San-Francisco-Oakland (9.4 cases), Minneapolis-St. Paul (6.7 cases) and Iowa (5.3 cases). For psoriasis patients, the incidence of skin cancer (20 cases) was also higher than the expected case number of Minneapolis-St. Paul (18.7 cases) and Iowa (15.5 cases).

In 1981, Halprin *et al.* studied the risk of skin cancer in 150 psoriasis patients with non-PUVA treatment (Goeckerman therapy and medication treatment) matching against a control group of patients with diabetes. They found that the incidence of skin cancer in the psoriasis group was significantly higher at three times that of the diabetes patients [50]. However, no significantly increased incidence of skin cancer was observed in patients receiving UVB combined with coal tar (95 patients) in this study [50].

Larko and Swanbeck followed 85 psoriasis patients treated with UVB alone in 1982. Compared to the control group, which consisted of 338 people extracted from government official birth and

address registries, there was no significant difference observed in incidence rates [51]. Another study in the UK found a lower incidence of KCs in 925 psoriasis patients with UVB (1.2%) compared to 1322 patients not treated with UVB (1.8%) [52].

The skin cancer risk with UV light has also been estimated by tracing back UV lamps exposure history in patients with KCs. Bajdik *et al.* recruited people diagnosed with KCs and asked if they had ever been exposed to non-solar UV radiation such as fluorescent lighting, sunlamps, and UV lamps [53]. Among 409 KCs individuals, there were 18 patients exposed to UV treatment lamps before diagnosis. After adjusting to age, skin, hair color, and occupational exposure to the sun, exposure to UV radiation was not significantly correlated with skin cancer risk (odds ratio: 0.8 (95% CI:0.4-1.7) and 0.9 (95% CI:0.3-2.5) for BCC and SCC, respectively).

2.1.2 Risk of Keratinocyte Carcinoma with NB-UVB Treated Patients

The risk of skin cancer in patients being treated with NB-UVB has not been adequately studied, with limited studies including systematic reviews [64, 65]. The conclusion about carcinogenic risk of NB-UVB therapy is far from consistent. Previous evidence from animal studies suggested that NB-UVB may have 2-3 times the carcinogenicity compared to BB-UVB [66]. For humans, most published articles suggest that there is no increased risk of skin cancer in patients receiving NB-UVB [55, 59, 62]. In 2008, Hearn *et al.* performed a retrospective study in 3867 patients with 5.5 follow-up years in Scotland assessing the risk of skin cancer in patients receiving NB-UVB treatment [58]. They found no association between NB-UVB treatment and skin cancer. However, age of this study was reported as median value at 34, which suggested participants were in younger adults' group having lower skin cancer risk. One cross-section study suggested that cumulative rate of skin cancer increased with high number of UVB treatments [60] and one study found high

incidence rate in patients with high total session (>200 sessions) of NB-UVB treatment [61]. A recent published study with limited sample size suggested that NB-UVB may increase the risk of KCs [63].

Limitations of each study is summarized in Table 2.1. Most studies had inadequate participants (<500). For BB-UVB studies, only one study reported cumulative dosage and total treatment session [60]. For NB-UVB, Maiorino *et al.*[61] and Raone *et al.*[63] compared skin cancer incidence by total treatment session, however, selection bias may exist in these two retrospective studies due to long study period (1985-2013 and 1998-2013 respectively) but inadequate participants (50 and 375 respectively). Obviously not all patients during the study period were included, and it was unsure if participants were randomly selected. Patients with higher skin cancer risk, such as patients with higher treatment sessions and longer follow-up time, may be chosen subjectively. Although most studies had a mean follow-up time over 5 years, majority of patients were followed up with enough time since the mean value could be skewed to larger number by patients with long follow-up years. In addition, only three studies adjusted incidence of skin cancer to skin type [53, 60, 62]. Three studies described multiple skin cancer development and number of tumors was used to calculate skin cancer incidence rate in their study [61-63]. No study conducted survival analysis or Cox-regression analysis to assess risk of skin cancer in patients with UV phototherapy.

Overall, the conclusion of whether UVB phototherapy is correlated with the risk of skin cancer remains inconsistent. Dr. John Koo's team completed a comprehensive review on cutaneous carcinogenic risk with phototherapy in 2005 [16] and published an updated article in 2015 [67]. Most of published studies estimating the role of UVB phototherapy in skin cancer had inadequate

sample size and follow-up time, which may not be sufficiently powered to detect an increased risk of cancer if one existed. In addition, most studies compared to historical or national prevalence rates, but since the incidence of skin cancer is increasing with time and has regional difference, it may not be able to draw a generalizable conclusion on whether UVB treatment increases risk of skin cancer or not.

2.2 Meta-analysis on NB-UVB Phototherapy and Skin Cancer Incidence Rate

It was difficult to calculate risk ratio due to lack of a comparable skin cancer incidence rate for general population. Therefore, we mainly aim to evaluate the incidence rate of skin cancer for patients who received NB-UVB treatment by conducting a meta-analysis of published original studies.

2.2.1 Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [68].

2.2.1.1 Search Strategy and Study Selection

Original research and observational studies (including those identified via review articles) published before September 2019, examining the association between NB-UVB phototherapy and skin cancer risk in adults, were selected through English-language literature searches in the MEDLINE, EMBASE, PubMed, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials databases. Combinations of at least two of the following key words were used as search terms: “phototherapy”, “NB-UVB”, “skin neoplasms”, “radiation

induced neoplasm", "exp ultraviolet phototherapy", and "skin cancer", "skin tumor", "melanoma (MM)", "non-melanoma skin cancer (NMSC)", "keratinocyte carcinoma (KC)", "basal cell carcinoma (BCC)", "squamous cell carcinoma (SCC)". In addition, the reference lists of the eligible retrieved articles were used to identify relevant articles that were not extracted through the searching procedure. Abstracts from conferences, reviews, and unpublished dissertations or theses were excluded from analysis. Two independent reviewers (JC and SK) identified potential articles for inclusion. Final selection of articles was then discussed among all authors.

2.2.1.2 Inclusion Criteria

Studies were included if they met the following criteria: (1) original and cohort studies published in an English-language refereed journal; (2) subjects were limited to adults, (3) the exposure of interest was receiving NB-UVB treatment; (4) positive case number and followed-up year were provided; (5) the outcome were incidence rate (IR) and age-standardized incidence rate ratio (SIR) with 95% CI of developing skin cancer (MM; NMSC; BCC; SCC);

2.2.1.3 Data Extraction

The following information was extracted from each study: last name of first author, year of publication, country of origin, time of follow-up in person/years, average and range of follow-up time, cumulative dosage and total treatment session if reported, and number of patients. Although some studies reported cumulative dosage and total treatment session, incidence of skin cancer was not compared based on cumulative dosage. Even if they compared incidence of skin cancer among total treatment session, they categorized total treatment session differently. Therefore, we cannot perform meta-analysis on cumulative dosage and total treatment session. Outcome data was

recorded as cases and corresponding incidence rates (IR) with 95% CI of all skin cancer (MM, KC, BCC, and SCC). Patient demographic data was not collected due to the lack of data in some studies including previous PUVA exposure, number of psoriasis or eczema patients, and Fitzpatrick skin type.

2.2.1.4 Quality Assessment

Newcastle-Ottawa Scale was used to assess the quality of included studies [69]. The specific items were as follows: (1) representativeness of the exposed cohort; (2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at start of study; (5) comparability of cohorts on the basis of the design or analysis; (6) assessment of outcome; (7) follow-up long enough for outcomes to occur; (8) adequacy of follow up of cohorts. For the fifth item, a maximum of two stars can be given. For the other items, a maximum of one star was assigned. The study was defined as having a high quality if the total scores were no less than 6.

2.2.1.5 Data Statistical Analysis

The measure of effect was IR with their corresponding 95% CIs, which was calculated based on developed skin cancer cases and number of follow-up years. Sub-analysis was performed if there were adequate number of articles (at least two articles) reporting SIR. Standard errors were calculated from 95% CIs with a formula [70].

Inverse variance method was used, which incorporated the weight of the different study outcomes. Effect sizes were log transformed if not distributed normally. A continuity correction of 0.5 was employed in all studies to account for studies that reported zero skin cancer events in their patient

population [70]. Statistical heterogeneity that was attributed to studies rather than to chance was examined by Chi-square (assessing the p value) and I^2 test [71]. If high heterogeneity was detected ($p < 0.10$ and $I^2 > 50\%$), the random effect model (the DerSimonian and Laird method) was adopted [72]; otherwise, the fixed-effects model (the Mantel–Haenszel method) was used [73]. Funnel plots and Egger's linear regression method were used to evaluate potential publication bias [74]. Sensitivity analysis was conducted to identify studies that significantly contributed to the between-study heterogeneity, and the pooled results were re-estimated after excluding these studies [75]. All statistical analysis was performed through R software (R Foundation for Statistical Computing, Vienna, Austria).

2.2.2 Results

2.2.2.1 Study Selection

Figure 2.1 shows the results from the literature search and study-selection procedure. A total of 748 studies were evaluated based on the search criteria. Six original cohort studies that investigated the skin cancer incidence rate for patients receiving NB-UVB treatment were identified according to the inclusion criteria defined. articles were included in the meta-analysis. Of note, 3 relevant articles were excluded: Man *et al.* [56] was excluded due to newer article (Hearn et al. [58]) published using the same patient group; Black *et al.* [57] was excluded due to extensive missing data; and Osmencevic *et al.* [60] was excluded due to cross-sectional design, with incomparable results with the 6 selected cohort studies. Among included research, three reported SIR [58, 59, 62], which can be included in sub-analysis.

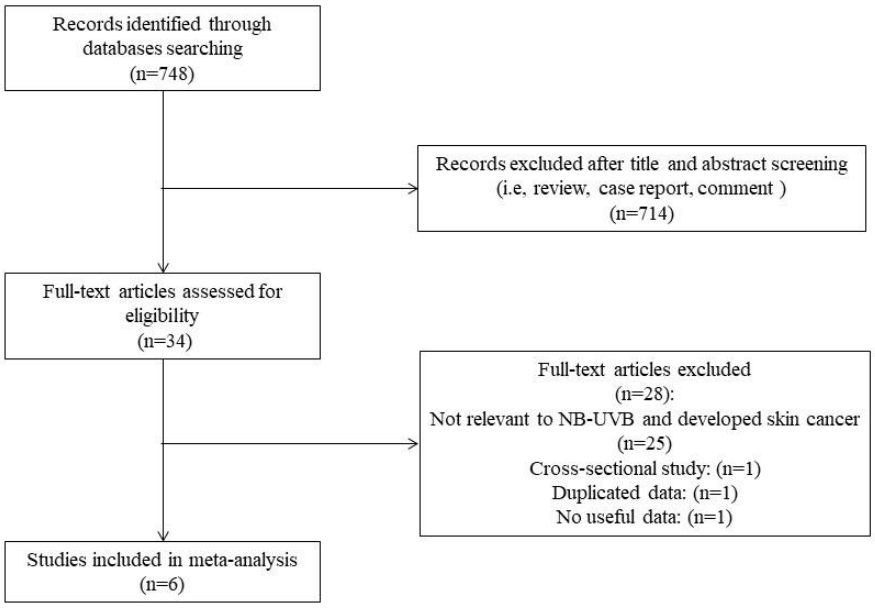

Figure 2.1 Flowchart of Search Strategy and Study Selection

2.2.2.2 Study Characteristics

Detailed characteristics of selected studies are presented in Table 2.2, and results of data extraction are shown in Tables 2.3 and Table 2.4. The overall working sample consisted of 5,337 participants with follow-up time ranging from 398 to 24753 person-years (minimum 1 month, maximum 21 years). Two studies were carried out in Italy [61, 63] and the rest were in Germany [55], Scotland [58], Korea [59] and Spain [62] with one study in each country. Two studies reported SIR for KC [59, 62], and two articles provided SIR of BCC and SCC separately [58, 62]. Weischer et al. mentioned that skin type may be potential risk factor, however, there was lack of skin type information in their study [55]. Three articles reported skin type information for their participants,

but they did not report incidence rate based on skin type [58, 59, 61]. Ortiz-Salvador *et al.* found no difference in skin cancer incidence based on skin type [62]. Raone *et al.* did not report skin type information in their research [63]. All included studies' quality score was above 6.

Table 2.2 Characteristic of Included NB-UVB Studies

Study [Ref.]	Year	Country	Sample Size (n)	Mean Age	Follow-up Time	Reported Estimate	Cumulative Dosage (J/cm^2)	Total Treatment Sessions	Findings	Quality Score
Weischer *et al.*[55]	2004	Germany	126	45.5	Mean: 5.6 yrs Range: 3-9 yrs p-y:726	IR	Mean:35.75 Range: 0.81-886	Mean: 44.2 Range:1-441	No increased skin cancer risk for patients with NB-UVB	6
Hearn *et al.*[58]	2008	Scotland	3,867	34*	Median: 5.5 yrs Range: NR p-y: 24753	IR; SIR	NR	Median: 29 IQR: 19-53	No increased skin cancer risk for patients with NB-UVB	8
Jo *et al.*[59]	2011	Korean	445	43.9	Mean: 2.8 yrs Range: 0.25-11 yrs p-y:1274	IR; SIR	Mean: 45.2 Range: 0.1-354.6	Mean: 33.6 Range: 1-232	No increased skin cancer risk for patients with NB-UVB	7
Maiorino *et al.*[61]	2016	Italy	50	56	Mean: 7.9 yrs Range:1-21 yrs p-y: 398	IR	Mean: 140 (total session ≤ 200); 2007 (total session >200)	Range: 31-3,246	High positive case number of skin cancer for patients with high-	6

									dose NB-UVB treatment	
Ortiz-Salvador *et al.*[62]	2018	Spain	474	47.5	Mean: 5.8 yrs Range: 1.1-14.5 yrs p-y: 2750	IR; SIR	NR	NR	No increased skin cancer risk for patients with NB-UVB	8
Raone *et al.*[63]	2018	Italy	375	46.7	Mean: 6.9 Range: NR p-y: 2580	IR	NR	Mean: 85 Range: 30-502	NB-UVB may increase skin cancer risk especially for KC	6

Ref: reference; IR: incidence rate; SIR: age-standardized incidence rate ratio; yrs: years; p-y: person-years; IQR: interquartile range

* Reported as median.

.

Table 2.3 Incidence Rate of Developed Skin Cancer with NB-UVB Phototherapy in Selected Studies

Study [Ref]	All Cancer		Melanoma		KC		BCC		SCC	
	Case.n	IR (95%CI)	Case.n	IR (95%CI)	Case.n	IR (95%CI)	Case.n	IR (95%CI)	Case.n	IR (95%CI)
Weischer *et al.*[55]	0	68.87 (0-259.8)	0	68.87 (0-259.8)	0	68.87 (0-259.8)	0	68.87 (0-259.8)	0	68.87 (0-259.8)
Hearn *et al.*[58]	17	68.68 (36.1-101.3)	1	4.04 (0-12.0)	16	64.64 (33.0-96.3)	14	56.56 (26.9-86.2)	2	8.08 (0-19.3)
Jo *et al.*[59]	1	78.49 (0-232.3)	0	39.25 (0-148.0)	1	78.49 (0-232.3)	-	-	-	-
Maiorino *et al.*[61]	14	3517.59 (1675.0-5360.2)	2	502.51 (0-1198.1)	12	3015.08 (1309.2-4721.0)	4	1005.03 (20.1-1989.9)	8	2010.05 (617.2-3402.9)
Ortiz-Salvador *et al.*[62]	10	363.64 (138.3-589.0)	0	18.18 (0-68.6)	10	363.64 (138.3-589.0)	6	218.18 (43.6-392.8)	4	145.45 (2.9-288.0)
Raone *et al.*[63]	19	736.43 (405.3-1067.6)	0	19.38 (0-73.1)	19	736.43 (405.3-1067.6)	16	620.16 (316.3-924.0)	3	116.28 (0-247.9)

Ref: reference; IR: incidence rate, case/100000 person-year; KC: keratinocyte carcinoma BCC: basal cell carcinoma; SCC: squamous cell carcinoma

Table 2.4 Age-Standardized Incidence Rate Ratio of Keratinocyte Carcinoma, Basal Cell Carcinoma and Squamous Cell Carcinoma

Study [Ref]	Keratinocyte carcinoma		Basal cell carcinoma		Squamous cell carcinoma	
	SIR (95%CI)	Standard Error	SIR (95%CI)	Standard Error	SIR (95%CI)	Standard Error
Hearn *et al.*[58]	-	-	1.63 (0.89-2.73)	0.47	1.94 (0.53-4.97)	1.13
Jo *et al.*[59]	17.00 (0.40-94.80)	24.08	-	-	-	-
Ortiz-Salvador *et al.*[62]	1.90 (0.64-5.94)	1.35	1.90 (0.40-6.40)	1.53	2.20 (0.50-20.70)	5.15

Ref: reference; SIR: age-standardized incidence rate ratio

2.2.2.3 Meta-analysis Results

In this meta-analysis, skin cancer outcomes data were computed by random-effects model due to the heterogeneity ($I^2 > 50$ and $p < 0.01$) between included studies (Figure 2.2). Incidence rates were log transformed due to non-normal distribution. A continuity correction of 0.5 was employed in all studies. Funnel plots and Egger linear regression test showed there was no publication bias in all models (Appendix 2.1).

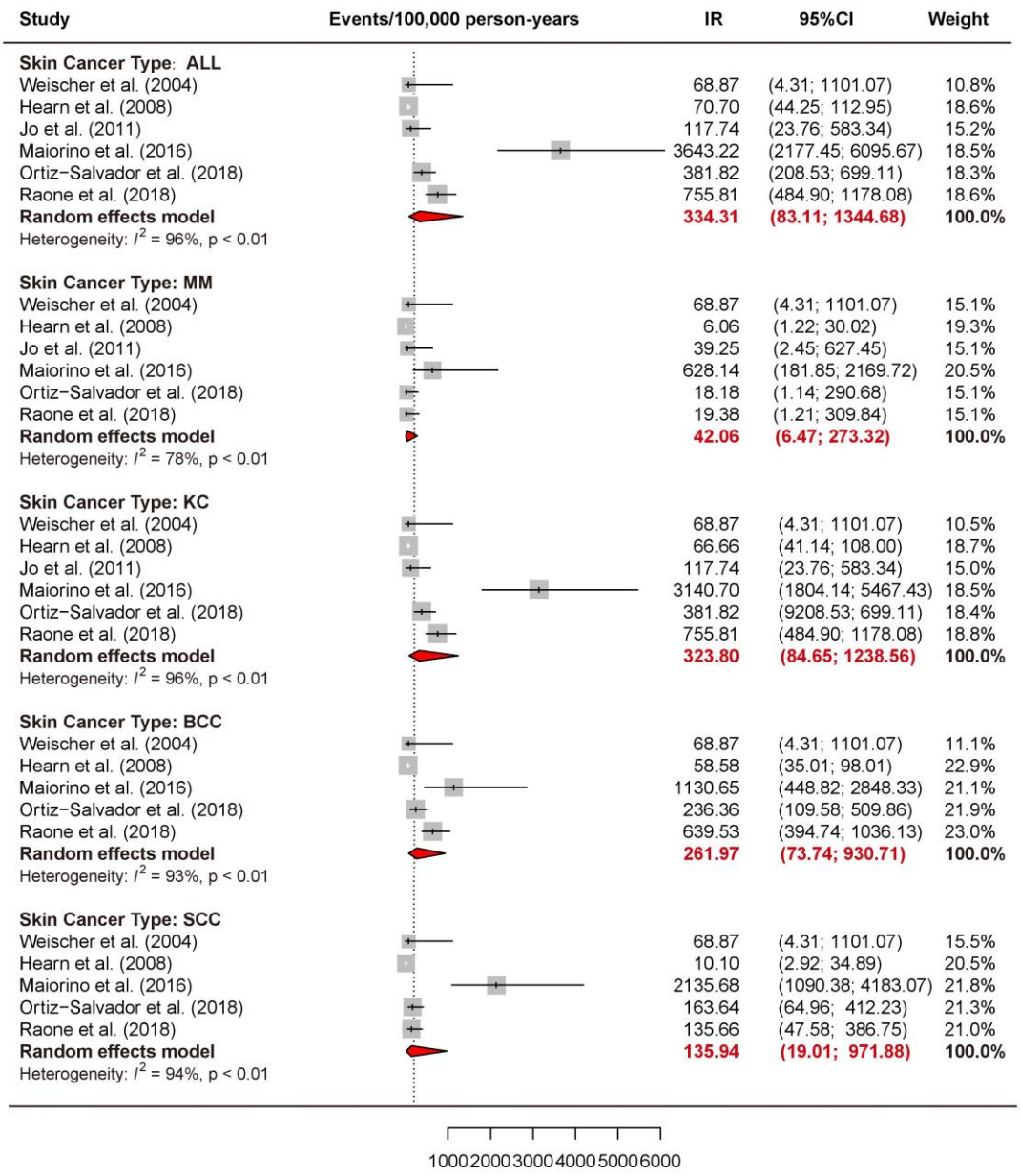

Figure 2.2 Incidence Rate of Skin Cancer with NB-UVB Phototherapy

2.2.2.4 Overall Skin Cancer Incidence Rate

The overall skin cancer incidence averaged 334.31 (95% CI 83.11- 1344.68) cases/100 000 person-years (Figure 2.2). Hearn et al. [58] included the largest follow-up period of 24753 person years, but resulted in fewer events (70.70/100,000 person-years) compared to the majority of studies. Maiorino et al. [61] was an outlier with 3643.22 events per 100,000 person-years. Statistically significant heterogeneity was noted amongst studies with I^2 of 96%. A sensitivity analysis was performed by exclusion of Maiorino et al. [61] resulting in 203.02 (95% CI 60.30- 683.67) events per 100,000 person-years.

2.2.2.5 Incidence Rate of Keratinocyte Carcinoma

Random effects model of the outcomes reported 323.80 events of KC (95% CI 84.65-1238.56) (Figure 2.2). Exclusion of Maiorino et al. [61] resulted in 199.67 events (95% CI 58.1-685.40). Heterogeneity of I^2= 96% was calculated between the outcomes. A separate forest plot (Figure 2.3) analyzing SIRs by fixed-effect model of NMSC in two studies showed an increase risk compared to the general population with SIR ratio of 1.95 (95% CI -0.70-4.59), although this was not statistically significant.

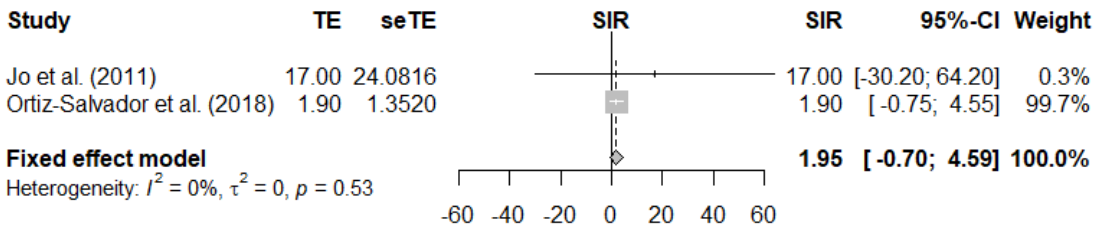

Figure 2.3 Forest Plot of Age-Standardized Incidence Rate Ratio for KC

2.2.2.6 Incidence Rate of Squamous Cell Carcinoma

The pooled number of events for SCC shown on the forest plot was calculated to be 135.95 (95% CI 19.01-971.88) per 100,000 person-years (Figure 2.2). Hearn *et al.* reported number of SCCs as 10.10 (95% CI 2.92-34.89) per 100,000 person-years, which were significantly lower than the other studies. In contrast, Maiorino et al. [61] reported number of SCCs as 2135.68 (95% CI 1090.38-4183.07) per 100,000 person-years. Exclusion of Hearn et al. [58] and Maiorino et al. [61] resulted in events of 280.13 and 64.53 per 100,000 person-years, respectively. SIRs for two studies were plotted on a forest plot (Figure 2.4) and showed a combined SIR via fixed-effect model of SIR ratio of 1.95 (95% CI -0.22-4.12).

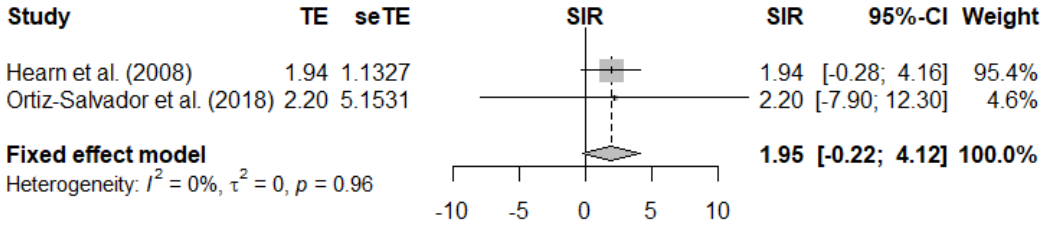

Figure 2.4 Forest Plot of Age-Standardized Incidence Rate Ratio for SCC

2.2.2.7 Incidence Rate of Basal Cell Carcinoma

The number of BCC events (Figure 2.2) among the six studies averaged 261.97 (95% CI 73.74-930.71) per 100,000 person-years. Exclusion of Maiorino et al. [61] decreased events to 177.30 (95% 43.00-731.00) per 100,000 person-years. Further analysis of SIR ratio of two articles via fixed-effect model (Figure 2.5) showed 1.65 (95% CI 0.77-2.53).

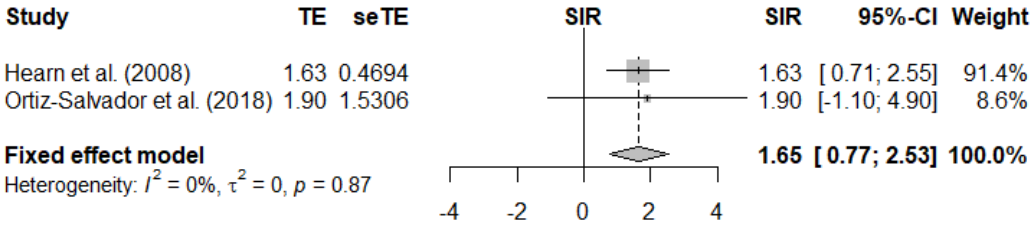

Figure 2.5 Forest Plot of Age-Standardized Incidence Rate Ratio for BCC

2.2.2.8 Incidence Rate of Melanoma

The forest plot of melanoma events (Figure 2.2) showed an average of 42.06 per 100,000 person years (95% CI 6.47-273.32). Overall, the majority of studies did not report any melanoma events except for Hearn et al. [58] with 1 case, and Maiorino et al. [61] with 2 cases. Exclusion of Maiorino et al. [61] decreased event rate to 15.47 (95% CI 5.43-44.10) per 100,000 person-years.

2.2.3 Discussion

To the best of our knowledge, this is the first meta-analysis to assess skin cancer incidence rate for patients who received NB-UVB phototherapy. We found that for patients with NB-UVB treatment, the overall skin cancer incidence rate was 334.31/100,000 person-years (95% CI 83.11- 1344.68). For melanoma, the incidence rate was 42.06/100,000 person-years (95% CI 6.47-273.32), and for KC, the incidence rate was 323.80/100,000 person-years (95% CI 84.65-1238.56). The pooled number of events for BCC (261.97/100,000 person-years, 95% CI 73.74-930.71) was higher than for SCC (135.95/100,000 person-years, 95% CI 19.01-971.88). From SIR sub-analysis, there was a trend for increased risk tendency for KC, SCC and BCC compared to the general population with SIR of 1.95 (95% CI: -0.70-4.59), 1.95 (95% CI: -0.22-4.12) and 1.65 (95% CI: 0.77-2.53) separately, although this was not statistically significant. Our results agreed with NB-UVB is a safer treatment option than PUVA treatment. In 1980s, studies found PUVA results in significant, dose-dependent increased risk of skin cancer, especially for SCC. For example, a study of 4799 patients with average 7 years follow-up duration suggested 6.3 times and 5.7 times higher SCC risk for male and female patients with PUVA treatment respectively ($p<0.05$) [2]. In this meta-analysis, there was no statistically significant correlation between NB-UVB phototherapy and KCs.

The potential reasons for the outlier study (Maiorino *et al.*) [61] having such high incidence rate was 1) selection bias may existed and 2) an outlier patient with multiple skin cancers was included. Participants selection method was not clearly stated in this study. All NB-UVB patients were divided into two groups based on total number of treatment sessions (≤200 *vs* >200). There were 17 patients in group total session ≤200 while 33 patients in group total session >200. The unbalanced group size suggested that patients with potentially higher skin cancer risk (higher treatment session and longer follow-up time) were may chose subjectively. In addition, skin cancer incidence was calculated based on skin cancer cases. Nineteen (19) skin tumors in 6 patients were detected. However, there was a patient diagnosed with 12 KCs. If removing this outlier, only 7 skin cancers identified in 5 patients, and skin cancer incidence should not be too high.

The methodological quality of the included studies was largely heterogeneous. The heterogeneity stemmed from differences in study population characteristics (skin type, countries, and age), follow-up time period, comparator population, sessions and dosage given to patients.

Participants' selection method was not stated clearly in included studies. Skin cancer development varies considerably across populations of different ethnicity and geographical location, and even within populations across age and gender [76]. Jo *et al.* [59], a study performed in Korea with 445 patients, consisted primarily of those with skin types III-V. Skin type III-VI displays relative protection from skin cancers [77], which may contribute to a smaller skin cancer incidence rate in the Jo *et al.* study. Hearn *et al.* [58] recruited mainly skin type I-III patients and other studies reported limited information of skin type. Hearn *et al.* 's study consisted of relatively younger patients with a median age of 34 compared to other studies [58]. As skin cancers are more common

in older patients [78], the skin cancer incidence may be low in the selected population. In addition, since most included studies did not provide age-standardized incidence rate, it was difficult to compare incidence rate of skin cancer among included studies consistently. Potential participant selection bias, differences in skin type and participants' age may contribute to high heterogeneity.

Besides Jo *et al.* [59] who studied a Korean population, all other included studies were conducted in Europe (two in Italy, one in Germany, one in Scotland and one in Spain). However, incidence rate of skin cancers in the general population in Europe shows significant variation in different countries [79, 80]. The estimated age-standardized incidence rate (standardized to European general population) for melanoma in Italy, Germany, UK and Spain was 18.1, 26.9, 7.4 and 21.2 per 100,000 person-year for male, and 13.7, 29.9, 9.4 and 20.1 per 100,000 person-year for female, respectively [79]. For KC, most studies reported incidence of skin cancer in white populations in Europe, America and Australia. Incidence rate of KC also varies widely from <1/100,000 person-year (for BCC in Africa) to >1000/100,000 person-year (for BCC in Australia) [80]. Geographical differences may be another reason for large heterogeneity in studies in the meta-analysis. Although performing subgroup analysis can find out probable causes for the significant heterogeneity, we were not able to conduct sub-analysis of these potential factors due to the lack of data.

Due to lack of incidence rate for general population in most included studies, it was difficult to assess whether NB-UVB treatment increased skin cancer risk compared to the general population. Since our meta-analysis was performed on crude incidence rate and most included studies were conducted in Europe, we chose skin cancer crude incidence rate for the general population in Germany and UK as comparison. Our findings suggested higher BCC incidence rate

(261.97/100,000 person-years) compared to the crude incidence rate in Germany (111.7/100,000 person-years for male and 118.3/100,000 person-years for female) [81]. Our pooled incidence rate of BCC (261.97/100,000 person-years) was also higher than crude incidence rate in UK (range from 128.7-196.4 per 100,000 person-years in different countries) [82]. The incidence rate for SCC (135.95/100,000 person-years) and MM (42.06/100,000 person-years) in our meta-analysis were higher than those in Germany (SCC: 32.1/100,000 person-years for male and 27.6/100,000 person-years for female; MM: 19.9/100,000 person-years for male and 22.4/100,000 person-years for female). Besides, the incidence rate for NMSC (323.80/100,000 person-years), SCC (135.95/100,000 person-years) and BCC (261.97/100,000 person-years) in this meta-analysis were all higher than the highest direct standardized incidence rate in UK (154.31/100,000 person-years, 33.02/100,000 person-years, 121.29/100,000 person-years, respectively) [80]. For melanoma, the crude incidence rate by worldwide region and country ranges from 0.2/100,000 person-years in India to 55.4/100,000 person-years in New Zealand [76]. The pooled incidence rate for melanoma for patients with NB-UVB treatment was higher than most incidence rates for general populations around the world. However, only two studies reported development of melanoma in this meta-analysis.

Although our meta-analysis results indicated a relatively high incidence rate of skin cancer for patients with NB-UVB phototherapy, we should be cautious to interpret these findings. Due to lack of adequate comparison groups, we cannot extrapolate if there is increasing risk of skin cancer in patients with NB-UVB phototherapy. As Hearn *et al.* suggested if increased risk of skin cancer in patients receiving NB-UVB phototherapy existed, it might be associated with cumulative dosage and numbers of exposure [58]. However, our included studies had limited information on

cumulative dosage and total number of treatment sessions. In addition, determination of safe maximum lifetime limits including total cumulative dosage and number of sessions should be studied.

Another limitation was insufficient total sample size and follow-up years. Hearn *et al.* [58] contained largest sample size in included studies (3,867), and accounted for more than half of the overall meta-analysis sample (5,337). In addition, except for Hearn *et al.* [58] who reported follow-up time as a median value (5.5 years), other studies reported follow-up years as a mean value (range 2.8-7.9 years), which may skew follow-up time. Therefore, the limited sample size and follow-up time may not be sufficiently powered to detect an increased risk of cancer if one existed.

2.2.4 Conclusion

From our meta-analysis results, overall skin cancer incidence rate was 334.31 (95% CI 83.11-1344.68) cases/100 000 person-years in patients with NB-UVB therapy. It was difficult to draw a conclusion on whether NB-UVB phototherapy increases skin cancer risk due to the lack of adequate comparison groups. It was difficult to provide consistent comparison for incidence studies with different methodologies. Therefore, the methodologies should be clearly stated. Large range of confidence interval suggested that more rigorous-designed studies with large sample size, long follow-up time, comparison groups and treatment details (cumulative dosage and total sessions) are required.

Chapter 3: Electronic Database Creation of Patients in Psoriasis and Phototherapy Clinic-Skin Care Center, BC, Canada

3.1 Data Source

Psoriasis and Phototherapy Clinic - The Vancouver General Hospital Skin Care Centre is one of the largest and busiest clinics in Vancouver. It opened in February 1976 at the former Shaughnessy Hospital in Vancouver and was relocated to the Vancouver General Hospital in 1995. Each year over 35,000 patient treatments are performed. It offers programs to treat and educate patients with common skin diseases such as psoriasis, eczema, and skin lymphoma. The clinic is equipped with whole body stand-up units for BB-UVB, NB-UVB, and UVA therapy.

Data was collected on patients' clinical records stored at Psoriasis and Phototherapy Clinic - The Vancouver General Hospital Skin Care Centre, Vancouver, Canada. Paper records of patients ending whole body UV treatment before January 2011 were stored at another place. Therefore, our phototherapy treated patients include those receiving treatment after January 2011. Some of these patients may have received initial treatment session as early as February 1976. Vitiligo patients receive phototherapy in the Vitiligo Clinic Unit; therefore, no vitiligo patients were included in this database.

Pathological reports of BCC, SCC, and melanoma, its subtypes, and its anatomic site were confirmed from Sunset Database, which is the pathology intranet database with results from 1980 to present in the Provincial Health Services Authority, Vancouver Coastal Health, Fraser Health, and Providence Health Care, until June 2019. Provincial Health Services Authority, Vancouver

Coastal Health, Fraser Health, and Providence Health are publicly funded healthcare regions within the Canadian province of British Columbia, which oversee hospitals and treatment centers where biopsies and tissue specimens are obtained. Our patient cohort had pathology reports confirmed until June 2019.

3.2 Electronic Database Structure

Data extraction forms are attached in appendixes (Appendix 3.1). The medical records were directly accessed on site at Psoriasis and Phototherapy Clinic using hardcopy patient charts. Patients were identified through personal health number (PHN). A unique study ID was given to each patient. The created electronic database of patients in Psoriasis and Phototherapy Clinic-Skin Care Center, BC, Canada was named as Psoriasis and Phototherapy Clinic Database (PPCD) hereafter.

3.2.1 Characteristic Information

Characteristics information, including study ID, gender (male/female), birth year, Fitzpatrick skin type (I-VI), diagnosis (psoriasis, eczema, lichen planus, etc.), history of skin cancer and minimal erythemal dose for NB-UVB treatment, of all patients was collected in one Excel sheet.

3.2.2 Phototherapy Treatment Information

Treatment details including study ID, treatment type, individual sessions date and individual dosage were collected. Each patient had treatment Excel sheets by treatment type. Cumulative dosage and total treatment session were calculated for all patients based by treatment type.

3.2.3 Pathological Confirmation of Skin Cancers

Pathological confirmation from Sunset Database checking was summarized in one Excel including study ID, presence of skin cancer, type of skin cancer, date and anatomical site of skin cancer. The end of follow-up date of this study was June 14, 2019.

3.2.4 Summary Sheet

Cumulative dosage, total treatment session, first and last date of treatment and pathological confirmation details were linked to patients' characteristics information through study ID in a summary Excel sheet. All Excel documents are stored on a secure computer within VGHRI server.

Baseline age was calculated by treatment start year minus birth year, censor age was calculated by end of follow-up year minus birth year. Multiple skin cancer sites were generated as separate records.

Chapter 4: Incidence and Profile of Skin Cancer in Patients Undergoing Ultraviolet-B Therapy

All patients receiving UVB phototherapy were selected from the PPCD database. Data collected included demographic information (baseline age, censored age, gender, skin type, diagnosis and history of skin cancer), treatment information (treatment start date, treatment type, date of treatments and treatment fluence), and pathological confirmation of skin cancers (skin cancer type, anatomic site, and diagnosis date). Since PUVA has been proved increases skin cancer risk [83], patients receiving any PUVA will be excluded.

4.1 Data Analysis

All skin cancers that occurred among patients after receiving phototherapy were included. If multiple skin cancers occurred in an individual patient, these were generated as separate records. Recurrent skin cancers diagnosed at the sites of earlier lesions were excluded. Person-years was counted from date of starting treatment to end date of follow-up. Cumulative dosage and total number of treatment sessions were calculated for all patients. Baseline age was calculated by treatment start year minus birth year, and censored age was calculated by end of follow-up year minus birth year.

4.1.1 Descriptive Analysis

The distribution of demographic characteristics, including gender, skin type, diagnosis, history of skin cancer and treatment type, was reported with frequency and proportion. Baseline age, censored age, follow-up time, cumulative dosage, and total treatment sessions were reported with

mean, median and standard deviation (SD). The incidence of skin cancer after receiving UVB phototherapy was summarized by gender, skin type and treatment type. Lifetime skin cancer incidence was estimated on the number of patients with skin cancer and follow-up time. Average lifetime was considered as 75 years. Lifetime skin cancer incidence risk was calculated as per 100 persons with following formula:

$$Lifetime\ risk = \frac{75\ years}{Average\ follow\text{-}up\ time} \times \frac{100\ persons}{Sample\ size} \times Number\ of\ skin\ cancer\ patients$$

4.1.2 Definition of Skin Cancer Incidence

Skin cancer incidence was calculated as patient-based incidence rate, case-based incidence rate and registration-based incidence rate. Patient-based incidence rate was assessed as the number of patients with first occurrence of skin cancer after phototherapy divided by total follow-up years. Case-based incidence rate was calculated with the total number of new skin cancers. Registration-based incidence was used the same code method of skin cancer as BC cancer registry, which only considering multiple melanoma as separate record.

4.1.3 Crude Incidence Rate (CIR) and Age-standardized Incidence Rate (ASIR)

All incidence rates were expressed per 100,000 person-years with 95% confidence interval (CI). Overall crude incidence rate was reported for individual-, case- and registration-based incidence separately. Age at the follow-up time was categorized into ≤40, 41-60 and >60, and age-specific incidence rates were reported. Calculations were carried out separately for persons with single and multiple skin cancers. The age-standardized incidence rate (ASIR) with 95% CI of skin cancers was calculated by standardizing age to the 1991 Canadian population (in order to compare with

ASIR reported in the McLean *et al.* study, which standardized age to 1991 Canadian population [26]), which were reported on Statistics Canada website [84].

4.1.4 Site-specific Incidence Rate

For site-specific incidence rates, the numbers of pathological confirmed tumors on each body site were divided by the total number of person-year and standardize to 1991 Canadian general population.

4.1.5 Correlation of Fitzpatrick Skin Type with NB-UVB Minimal Erythemal Dose and Incidence of Skin Cancer

The Spearman correlation was performed to explore the relationship between skin type and MED for NB-UVB phototherapy. Coefficient and P value were reported.

Skin cancer incidence in UVB phototherapy patients was reported by skin type. ASIR with 95% CI was standardized to 1991 Canadian general population. Incidence and risk analysis were also performed separately in patients receiving BB-UVB and NB-UVB phototherapy. The overall total number of treatment session for UVB phototherapy was total sum of number of treatment sessions for BB-UVB and NB-UVB therapy. The lower endpoint of 95% CI was reported as 0 if when it was below 0. Z test was used for examining difference of skin cancer incidence rate in two different groups. Statistical analysis was performed with R (R Foundation for Statistical Computing, Vienna, Austria, version 3.6.1, 2019).

4.2 Results

4.2.1 Study Population

We reviewed 3,554 medical charts of patients receiving whole-body phototherapy at Psoriasis and Phototherapy Clinic - The Vancouver General Hospital Skin Care Centre, BC, Canada. Fourteen (14) patients did not receive any UVB treatment and 34 patients received SPUVA. Therefore, these 48 patients were excluded and a total of 3,506 participants were included in analysis.

4.2.2 Descriptive Characteristics

Demographic characteristics are presented in Table 4.1. In our sample, 57.0% of patients were male. Patients' skin types were mainly skin type II to IV (82.1%). Most patients were diagnosed with psoriasis (60.9%) and eczema (26.4%). 83 (2.3%) patients had a history of skin malignancy before commencing phototherapy.

Table 4.1 Demographic Characteristics of Study Population (N=3,506)

Characteristics	**N (3,506)**	**%**
Gender		
Male	1,999	57.0
Female	1,507	43.0
Skin Type		
I	83	2.4
II	566	16.1

III	1,395	39.8
IV	917	26.2
V	475	13.5
VI	44	1.3
Unknown	26	0.7
Diagnosis		
Psoriasis	2,136	60.9
Eczema	925	26.4
Pruritus	211	6.0
Lichen Planus	52	1.5
Mycosis Fungoides	45	1.3
Polymorphous Light Eruption	40	1.1
Granuloma Annulare	24	0.7
Others*	73	2.1
Previous Skin Cancer (Before Treatment)		
Yes	82	2.3
No	3,424	97.7
Treatment Type		
BB-UVB Only	1,025	29.2
NB-UVB Only	1,555	44.4
BB-UVB + NB-UVB	742	21.2

UVB combined UVA	184	5.2

*Others: polymorphous light eruption; granuloma annulare; progressive macular hypomelanosis; folliculitis; eosinophilic folliculitis; pityriasis rosea; parapsoriasis; solar urticaria; lymphomatoid papulosis; morphea; mastocytosis; delusion of parasitosis; lichen sclerosis; grover's disease; acne; follicular mucinosis; erythroderma; cutaneous plasmacytoma; lichen amyloidosis; pigmented purpuric dermatosis.

The mean (SD) censored age of cohort was 51.8 (0.3) and median censored age was 50. The mean (SD) follow-up years for whole cohort, BB-UVB phototherapy patients and NB-UVB phototherapy patients was 7.1 (0.1) years, 9.6 (0.1) years and 6.9 (0.1) years (median: 5.9 years, 7.9 years and 5.3 years, respectively).

4.2.3 Incidence of Skin Cancer

Details of individual-based and case-based skin cancer incidence after receiving UVB phototherapy was shown by gender and treatment type in Table 4.2. In total, 79 patients developed skin cancer (53 males and 26 females) with a total of 170 skin cancers. Among these patients, 27 (34.2%) patients developed multiple skin cancers (range 2-29 sites).

Table 4.2 Individual-based, Case-based and Registration-based Skin Cancer Incidence by Gender

Skin Cancer Type	**Individual-based Skin Cancer Incidence**			**Case-based Skin Cancer Incidence**			**Registration-based Skin Cancer Incidence**		
	All (n=3,506)	Male (n=1,999)	Female (n=1,507)	All (n=3,597)	Male (n=2,075)	Female (n=1,522)	All (n=3,515)	Male (n=2,005)	Female (n=1,510)

MM	8	5	3	17	11	6	17	11	6
BCC	51	34	17	120	92	28	51	34	17
SCC	20	14	6	33	26	7	20	14	6
All	79	53	26	170	129	41	88	59	29

MM: melanoma; BCC: basal cell carcinoma; SCC: squamous cell carcinoma

Estimated lifetime risk of melanoma, BCC and SCC in patients with UVB phototherapy was 3%, 16%, and 7% respectively

4.2.4 Individual-based, Case-based and Registration-based Crude Incidence Rate

Crude incidence rate (CIR) for individual-based, case-based and registration-based was reported in Table 4.3. Overall CIR of all types developed skin cancer was 317.6 (95% CI: 253.1-393.7) and 651.0 (95%CI: 558.5-754.5)/100,000 person-years for individual-based and case-based, respectively. Registration-based incidence rate was slightly larger than individual-based incidence rate.

Table 4.3 Individual-based, Case-based and Registration-based Crude Incidence Rates by Gender (event/100,000 person-year, 95% CI)

Incidence Type	All patients	Male	Female
Individual-based	317.6 (253.1-393.7)	363.3 (274.9-471.6)	252.9 (168.7-365.3)
Case-based	651.0 (558.5-754.5)	839.5 (703.7-994.1)	381.5 (277.4-512.6)
Registration-based	351.6 (283.7-431.1)	403.1 (309.6-516.3)	279.1 (190.4-395.6)

CIR increased with age and was low before age 40 years. In patients developing skin cancer, 34.2% had multiple skin cancer cases. CIR for patients with single skin cancer site was 36.0 (95% CI: 6.0-118.9)/100,000 person-years in participants under 40 years, rising to 383.6 (95% CI: 274.0-523.1)/100,000 person-years after age 60 years (Table 4.4). CIR for patients with multiple skin cancer sites was 18.0 (95% CI: 0.9-88.7)/100,000 person-years in participants under 40 years, rising to 217.7 (95% CI: 138.4-327.1)/100,000 person-years after age 60 years (Table 4.4).

Table 4.4 Skin Cancer Individual-based Crude Incidence Rate in UVB Phototherapy Patients

		All persons with skin cancer		**Persons with single skin cancer**		**Persons with multiple skin cancer**	
Censored age (years)	Person years	Number of persons	CIR (95%CI)	Number of persons	CIR (95%CI)	Number of persons	CIR (95%CI)
≤40 (n=1,038)	5,557.8	3	54.0 (13.7-146.9)	2	36.0 (6.0-118.9)	1	18.0 (0.9-88.7)
41-60 (n=1,281)	9,672.9	18	186.1 (113.8-288.4)	13	134.4 (74.8-224.0)	5	51.7 (18.9-114.6)
>60 (n=1,187)	9,646.6	58	601.2 (460.8-771.8)	37	383.6 (274.0-523.1)	21	217.7 (138.4-327.1)
Overall	24,877.5	79	317.6 (253.1-393.7)	52	209.0 (157.7-272.0)	27	108.5 (73.0-155.7)

CIR: crude incidence rate; CI: confidence interval

4.2.5 Individual-based and Case-based Age-standardized Incidence Rate

ASIR was calculated for individual-based (first skin cancer) and case-based (all skin cancer) independently. ASIRs was reported by skin cancer type, gender and treatment type in UVB phototherapy patients (Table 4.5). Overall individual-based ASIR was 149.1 (95% CI: 111.5-187.2)/100,000 person-year, while overall case-based ASIR was 264.1 (95% CI: 219.4-308.8)/100,000 person-year.

Individual-based ASIRs for melanoma, BCC and SCC were 23.1/100,000 person-year, 92.4/100,000 person-year and 33.9/100,000 person-year, respectively. Case-based ASIRs for melanoma, BCC and SCC were 34.7/100,000 person-year, 181.6/100,000 person-year and 47.8/100,000 person-year, respectively.

Patients with BB-UVB phototherapy had significantly higher ASIR than patients with NB-UVB phototherapy for all types of skin cancer (e.g., overall individual ASIR for BB-UVB *vs* NB-UVB: 158.9/100,000 person-year *vs* 93.8/100,000 person-year, Z-score: 2.12, $p<0.05$; overall case-based ASIR for BB-UVB *vs* NB-UVB: 287.9/100,000 person-year *vs* 167.5/100,000 person-year, Z-score: 3.32, $p<0.05$).

There was no statistically difference of ASIRs between males and females (e.g., overall individual ASIR for male *vs* female: 123.0/100,000 person-year *vs* 148.5/100,000 person-year, Z-score: -0.70, $p>0.05$; overall case-based ASIR for male *vs* female: 261.9/100,000 person-year *vs* 211.1/100,000 person-year, Z-score: 1.17, $p>0.05$).

Table 4.5 Skin Cancer Individual-based and Case-based Age-standardized Incidence Rate in UVB Phototherapy Patients by Treatment Type and Gender*

Cancer type	UVB (n=3,506) ASIR/100,000 people (95% CI)			BB-UVB (n=1,945) ASIR/100,000 people (95% CI)			NB-UVB (n=2,340) ASIR/100,000 people (95% CI)		
	All (n=3,506)	Male (n=1,999)	Female (n=1,507)	All (n=1,945)	Male (n=1,090)	Female (n=855)	All (n=2,340)	Male (n=1,380)	Female (n=960)
Individual-based									
All skin cancers	149.4 (111.5-187.2)	123.0 (87.9-158.1)	148.5 (86.1-210.9)	158.9 (106.2-211.6)	113.7 (75.4-152.1)	166.4 (81.9-250.8)	93.8 (64.8-122.9)	99.3 (61.4-137.3)	101.1 (46.1-156.1)
Melanoma	23.1 (1.1-45.2)	12.5 (1.5-23.5)	27.2 (0.0-63.4)	32.6 (0.2-65.0)	9.4 (0.5-18.3)	41.9 (0.0-100.3)	7.3 (1.9-12.7)	7.7 (0.7-14.7)	6.8 (0.0-15.4)
KC	126.2 (95.5-157.0)	110.5 (77.1-143.8)	121.2 (70.3-172.1)	126.3 (90.6-161.9)	104.3 (67.5-141.1)	124.5 (63.5-185.5)	86.5 (58.7-114.4)	91.6 (55.2-128.1)	94.4 (41.0-147.7)
BCC	92.4 (65.8-183.6)	75.0 (48.5-101.5)	93.9 (48.0-139.9)	94.0 (62.8-125.2)	75.8 (45.5-106.1)	100.8 (44.4-157.2)	55.2 (33.3-77.1)	50.1 (24.3-75.8)	73.1 (25.6-120.7)
SCC	33.9 (18.4-49.3)	35.5 (15.3-55.8)	27.3 (5.4-49.2)	32.3 (15.0-49.6)	28.5 (7.6-49.4)	23.7 (0.4-46.9)	31.4 (14.2-48.5)	41.6 (15.8-67.4)	21.2 (0.0-45.5)

Case-based									
All skin cancers	264.1	262.9	211.1	287.9	273.3	245.8	167.5	185.2	158.6
	(219.4-308.8)	(213.6-310.2)	(140.6-281.5)	(227.2-348.6)	(217.0-329.5)	(151.6-339.9)	(130.2-204.7)	(135.8-234.6)	(92.5-224.7)
Melanoma	34.7	21.7	38.5	46.4	22.9	55.6	10.9	10.0	11.4
	(11.7-57.7)	(8.5-34.9)	(0.2-76.7)	(13.0-79.8)	(10.0-35.8)	(0.0-116.0)	(4.6-17.2)	(2.5-17.4)	(1.1-21.8)
KC	229.4	240.2	172.6	241.5	250.4	190.2	156.6	175.2	147.2
	(191.0-267.7)	(193.7-286.6.)	(113.5-231.8)	(195.8-287.2)	(196.2-304.5)	(118.0-262.4)	(120.6-192.6)	(127.1-223.3)	(83.0-211.3)
BCC	181.6	185.1	139.9	194.5	194.3	158.2	109.4	113.4	114.5
	(147.3-215.8)	(145.0-225.2)	(86.4-193.5)	(153.3-235.7)	(147.7-240.9)	(92.3-224.0)	(79.7-139.0)	(75.6-151.2)	(60.0-169.10)
SCC	47.8	55.1	32.7	47.0	56.1	32.0	47.2	61.8	32.6
	(30.6-65.0)	(31.5-78.6)	(7.6-57.8)	(27.2-66.8)	(28.6-83.6)	(2.4-61.5)	(26.7-67.7)	(32.1-91.5)	(0.0-66.5)

*Age standardized to 1991 Canadian general population; KC: keratinocyte carcinoma; BCC: basal cell carcinoma; SCC: squamous cell carcinoma

Overall individual-based and case-based ASIR were also calculated for psoriasis and eczema population (Table 4.6). Individual-based ASIR for psoriasis and eczema population were 153.3 (95 % CI: 105.1-202.20)/100,000 person-year and 136.5 (95 % CI: 58.3-214.7)/100,000 person-year (Z-score: 0.37, p>0.05). Case-based ASIR for psoriasis and eczema population were 225.5 (95 % CI: 171.3-279.6)/100,000 person-year and 255.2 (95 % CI: 156.8-353.6)/100,000 person-year (Z-score: -0.52, p>0.05). It suggested skin cancer incidence was not significant difference between psoriasis and eczema patients.

Table 4.6 Skin Cancer Incidence for Psoriasis and Eczema Patients*

	Individual-based Incidence		**Case-based Incidence**	
Diagnosis	Number of Individuals	ASIR/100,000 people (95% CI)	Number of Skin Cancers	ASIR/100,000 people (95% CI)
Psoriasis (n=2136)	57	153.5 (105.1-202.20)	93	225.5 (171.3-279.6)
Eczema (n=925)	14	136.5 (58.3-214.7)	34	255.2 (156.8-353.6)

*Age-standardized to 1991 Canadian general population

4.2.6 Site-specific Age-standardized Incidence Rate

One BCC case was excluded due to unknown anatomical location. Head and neck sites had the highest overall incidence of skin cancer (130.6/100,000 person-year). The peak rates were observed on forehead/temple (35.8/100,000 person-year), followed by cheek (25.2/100,000 person-year), nose (19.2/100,000 person-year) and neck (17.3/100,000

person-year) (Table 4.7). Trunk sites had highest incidence of melanoma (24.5/100,000 person-year), facial sites had highest incidence of BCC (103.8/100,000 person-year) and SCC (26.7/100,000 person-year) (Table 4.7).

Table 4.7 Site-specific incidence rate*

Anatomical Site	All skin cancers		Melanoma		Basal Cell Carcinoma		Squamous Cell Carcinoma	
	Tumor No.	**ASIR /100,000 p-y (95% CI)**	**Tumor No.**	**ASIR /100,000 p-y (95% CI)**	**Tumor No.**	**ASIR /100,000 p-y (95% CI)**	**Tumor No.**	**ASIR /100,000 p-y (95% CI)**
Head and Neck								
Overall	**86**	**130.6 (101.7-159.5)**	**3**	**4.3 (0.9-9.2)**	**67**	**100.1 (74.8-125.4)**	**16**	**26.2 (13.0-39.3)**
Scalp	4	4.7 (0.0-9.6)	-	-	4	4.7 (0.0-9.6)	-	-
Forehead/Temple	26	35.8 (21.1-50.4)	-	-	21	29.0 (15.8-42.2)	5	6.8 (0.5-13.0)
Nose	12	19.2 (8.3-30.1)	-	-	12	19.2 (8.3-30.1)	-	-
Cheek	16	25.2 (12.4-38.0)	-	-	11	17.0 (6.5-27.6)	5	8.2 (0.9-15.5)
Lip	8	15.4 (3.9-26.9)	-	-	6	11.8 (1.4-22.1)	2	3.7 (0.0-8.8)
Chin/Jaw	3	4.9 (0.0-10.6)	1	1.7 (0.0-5.0)	2	3.2 (0.0-7.8)	-	-
Ear	6	8.0 (1.5-14.4)	2	2.6 (0.0-6.1)	3	3.8 (0.0-8.0)	1	1.6 (0.0-4.9)
Neck	11	17.3 (6.8-27.8)	-	-	8	11.4 (3.3-19.5)	3	5.9 (0.0-12.6)
Trunk								
Overall	**43**	**75.1 (46.4-103.8)**	**8**	**21.0 (0.0-42.1)**	**31**	**49.4 (30.7-68.1)**	**4**	**4.5 (0.0-9.4)**
Chest	17	29.5 (13.7-45.3)	1	2.4 (0.0-7.2)	12	22.6 (8.4-36.8)	4	4.5 (0.0-9.4)

Abdomen	6	8.4 (1.6-15.2)	1	1.4 (0.0-4.1)	5	6.8 (0.8-12.8)	-	-
Back	20	37.1 (14.1-60.1)	6	17.1 (0.0-37.6)	14	20.0 (9.5-30.6)	-	-
Limbs								
Overall	**40**	**57.0 (38.8-75.2)**	**6**	**9.2 (1.7-16.7)**	**21**	**30.6 (17.3-44.0)**	**13**	**17.2 (7.2-27.1)**
Upper Limb								
Overall	**22**	**29.8 (16.8-42.7)**	**4**	**5.9 (0.0-11.8)**	**13**	**18.5 (8.2-28.8)**	**5**	**5.3 (0.2-10.4)**
Shoulder	13	17.9 (7.7-28.0)	1	1.9 (0.0-5.5)	10	14.3 (5.2-23.4)	2	1.7 (0.0-4.3)
Arm	6	8.3 (1.5-15.0)	3	4.1 (0.0-8.7)	3	4.2 (0.0-9.0)	-	-
Forearm	1	0.5 (0.0-1.6)	-	-	-		1	0.5 (0.0-1.6)
Hand	2	3.0 (0.0-7.3)	-	-	-	-	2	3.0 (0.0-7.3)
Lower Limb								
Overall	**18**	**27.2 (14.4-40.1)**	**2**	**3.3 (0.0-7.9)**	**8**	**12.1 (3.6-20.6)**	**8**	**11.8 (3.3-20.4)**
Buttocks/Flank/Hip	4	5.8 (0.1-11.4)	-	-	4	5.8 (0.1-11.4)	-	
Groin/Genital Region	1	1.7 (0.0-5.0)	-	-	-	-	1	1.7 (0.0-5.0)
Thighs	2	3.3 (0.0-8.0)	1	1.7 (0.0-5.0)	1	1.6 (0.0-4.9)	-	
Legs	10	14.6 (5.2-23.9)	1	1.6 (0.0-4.8)	3	4.7 (0.0-10.1)	6	8.3 (1.3-15.2)
Ankle	1	1.9 (0.0-5.5)	-	-	-		1	1.9 (0.0-5.5)

*Age standardized to 1991 Canadian general population; p-y: person-year

4.2.7 Skin Cancer Incidence Comparison with 2003 BC General Population

Mclean *et al*. reported skin cancer ASIR of 2003 BC general population by skin cancer type, gender and anatomical sites [26]. In their study, ASIR was calculated based on BC cancer registry code, which only multiple melanoma cases were considered as separate records. Therefore, registration based ASIRs in this study were compared to 2003 ASIR for BC general population.

As shown in Figure 4.1, ASIRs were compared by skin cancer type, gender and UVB treatment type. Due to limited melanoma cases in this study, Z test was performed for comparing ASIR of BCC and SCC between patients and general population (Table 4.8). Overall, ASIRs of SCC were not statistically different between patients with overall UVB phototherapy or NB-UVB phototherapy and the general population for both genders (all $p > 0.05$). For male patients with any types of UVB phototherapy, ASIRs of BCC were significantly lower than ASIR for the general population ($Z\text{-score} < 0$, $p < 0.05$).

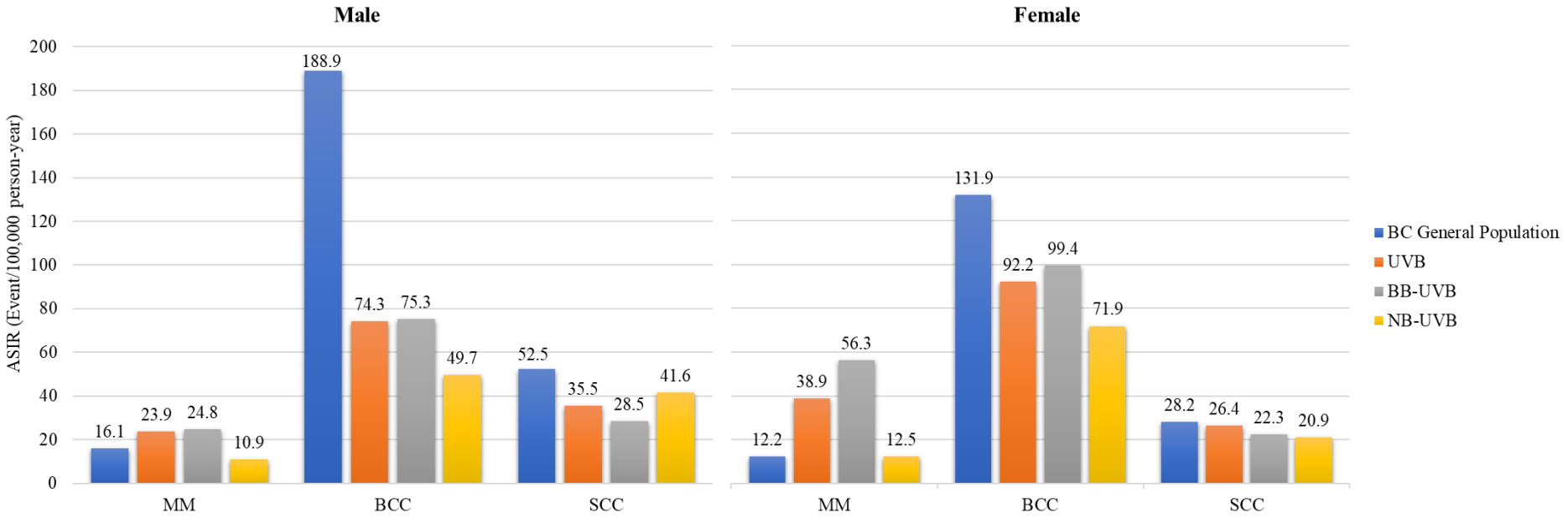

Figure 4.1 Age-standardized Incidence Rate Comparison for Patients with UVB Phototherapy and General Population (MM: malignant melanoma; BCC: basal cell carcinoma; SCC: squamous cell carcinoma)

Table 4.8 Z-test for Age-standardized Incidence Rate of Keratinocyte Carcinoma for UVB Phototherapy Patients and BC General Population

Gender / Treatment Type	Basal Cell Carcinoma				Squamous Cell Carcinoma			
	Male		Female		Male		Female	
	Z score	P value	Z score	P value	Z score	P value	Z score	P value
UVB	-8.29	<0.05*	-1.70	>0.05	-1.60	>0.05	-0.16	>0.05
BB-UVB	-7.22	<0.05*	-1.13	>0.05	-2.20	<0.05*	-0.52	>0.05
NB-UVB	-10.37	<0.05*	-2.48	<0.05*	-0.80	>0.05	-0.59	>0.05

*statistically significant

Registration-based site-specific age-standardized incidence rates for KCs were also compared between patients with UVB phototherapy and general population (Figure 4.2). Due to limited SCC case in each anatomical group, Z test was only performed for BCC (Table 4.9). Male patients had significantly lower BCC incidence at all anatomical sites (Z score<0, $p<0.05$). Although Z test was not conducted for SCC, incidence rates were lower at head and neck, trunk and upper limb sites, but higher at lower limb compared to general population for both genders.

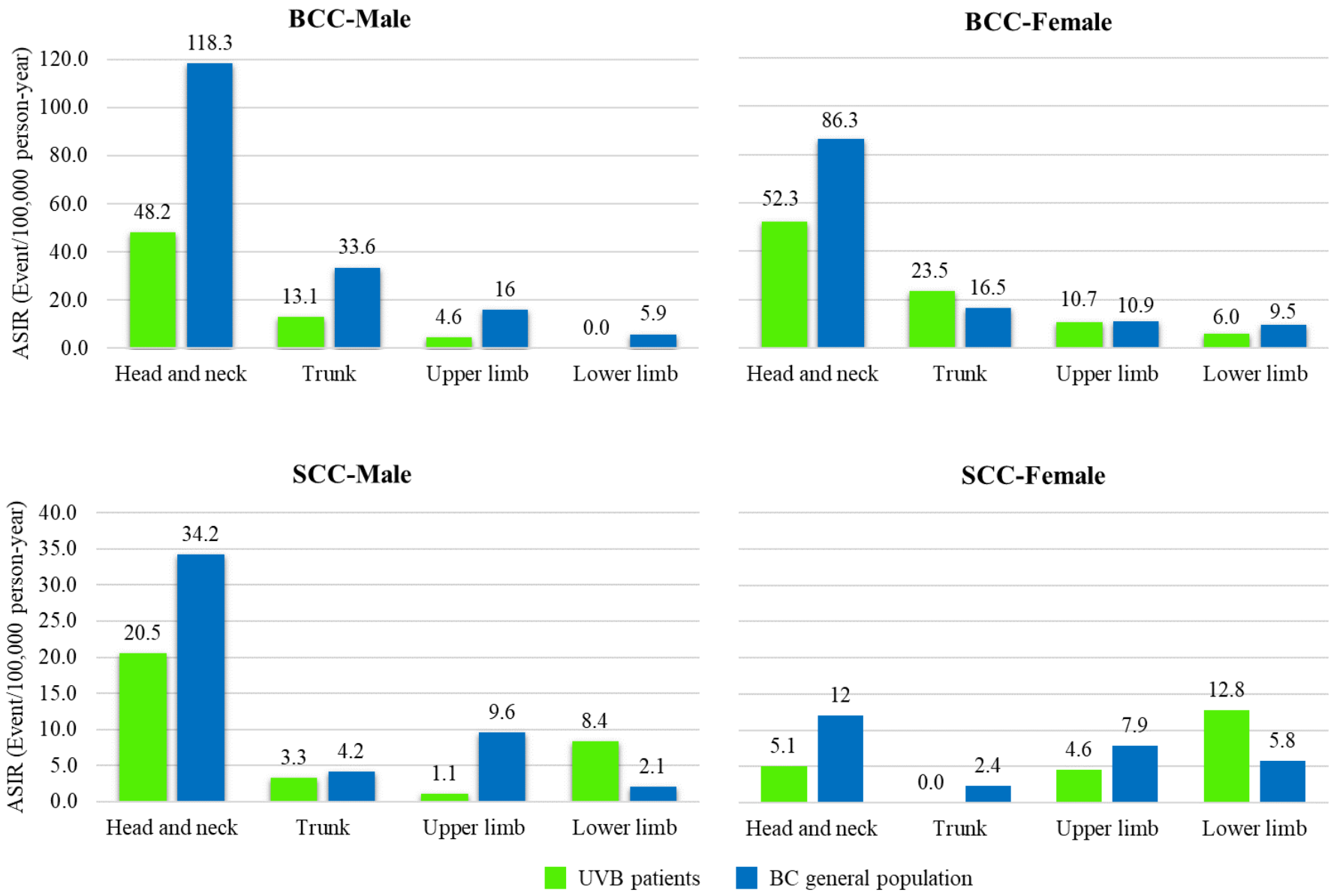

Figure 4.2 Site-specific age-standardized incidence rate comparison for KCs (BCC: basal cell carcinoma; SCC: squamous cell carcinoma)

Table 4.9 Z-test for Registration-based Site-specific Age-standardized Incidence Rate of Basal Cell Carcinoma with UVB Phototherapy and General Population

Gender / Anatomical Site	Basal Cell Carcinoma			
	Male		Female	
	Z score	P value	Z score	P value
Head and neck	-6.19	<0.05*	-1.95	>0.05
Trunk	-3.67	<0.05*	0.58	>0.05
Upper limb	-3.34	<0.05*	-0.02	>0.05
Lower limb	-10.34	<0.05*	-0.57	>0.05

*statistically significant

4.2.8 Correlation of Skin Type with Minimal Erythemal Dose and Skin Cancer Incidence

There were 685 patients with NB-UVB phototherapy who had phototesting performed to determine minimal erythema dose (MED) before treatment. The coefficient of Spearman correlation test was 0.33 with $p<0.001$*. A tendency of increasing MED with skin type was observed (Figure 4.4).

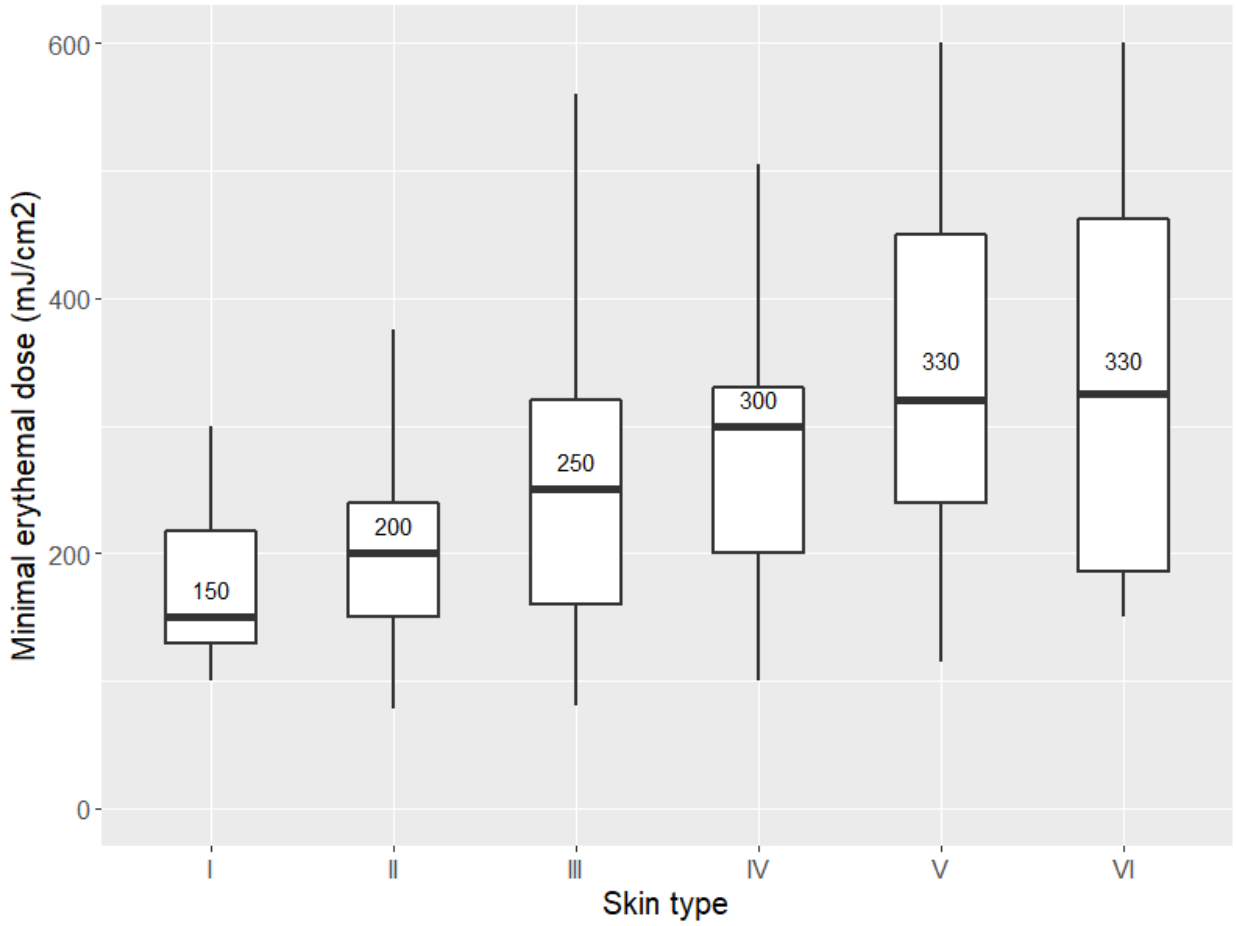

Figure 4.3 Correlation between Skin Type and NB-UVB Minimal Erythemal Dose (n=685) (top, middle and bottom line of box represents for upper quantile, median and lower quantile; the showed value was median value; the longitudinal line of box is the range of distribution)

Individual-based skin cancer ASIRs for patients UVB phototherapy was shown in Table 4.10. Overall individual-based skin cancer ASIRs decreased with higher skin phototypes (ASIR: 272.7, 226.8, 150.5, 76.6, 35.6/100,000 person-years for skin type I to skin type V, respectively).

Table 4.10 Individual-based Age-standardized Incidence Rate in Patients with UVB Phototherapy by Skin Type

Skin Type (n)	Number of patients with skin cancer	ASIR/100,000 p-y (95% CI)
I (83)	4	272.7 (0.0-545.8)
II (566)	24	226.8 (135.0-318.6)
III (1,395)	34	150.5 (85.1-215.8)
IV (917)	10	76.6 (25.8-127.5)
V (475)	2	35.6 (0.0-86.1)
VI (44)	0	-

ASIR: age-standardized incidence rate; p-y: person-year

Chapter 5: Sub-analysis for Correlation between Total Treatment Session, Cumulative Dosage and Risk of Skin Cancer Development

5.1 Data Analysis

Number of total UVB treatment sessions and cumulative dosage should be considered when exploring the risk of developing skin cancer in patients with phototherapy. The accessible charts contained all patients starting treatment from 2011 no matter how many treatment sessions they received. Therefore, risk analysis for correlation between total treatment sessions, cumulative dosage and skin cancer development were performed in patients starting treatment from 2011.

To avoid error resulting from analyzing correlated repeated events, the time to first developing skin cancer was used for patients with multiple skin cancer sites. Total treatment session and cumulative dosage was categorized into 3 groups by tercile. Multivariate logistic regression and Cox-regression analysis was used to assess associations between total number of treatments, cumulative dosage and skin cancer risk, reporting as odds ratio (OR) and hazard ratio (HR), retrospectively. Kaplan-Meier analysis showed the probability of patients of developing skin cancer during the follow-up time interval was not associated with total number of treatments or cumulative dosage.

5.2 Results

5.2.1 Categories of Total Treatment Session and Cumulative Dosage

In total, 2,650 patients followed up for an average of 5.0 years (median: 5.1 years, SD: 2.1 years) from January 2011 to November 2018 were included in the survival analysis. The total treatment

session and cumulative dosage categories by tercile are shown in Table 5.1. The range of total treatment session for BB-UVB and NB-UVB was 1-423 and 1-570, respectively. The range of cumulative dosage for BB-UVB and NB-UVB was 0.01-142.96 J/cm2 and 0.03-962.41 J/cm2.

29 patients developed skin cancer (2 melanoma, 20 BCCs, and 7 SCCs) among the patients included in the sub-analysis.

Table 5.1 Summary of Total Treatment Session and Cumulative Dosage Tercile Groups

	UVB (n=2,650)		BB-UVB (n=1,157)		NB-UVB (n=1,748)	
Groups	Session	Dosage (J/cm^2)	Session	Dosage (J/cm^2)	Session	Dosage (J/cm^2)
Lower tercile	≤ 16	-	≤ 12	≤ 0.78	≤ 18	≤ 5.12
Middle tercile	17-50	-	13 - 34	0.78 – 3.52	19 - 57	5.12 – 29.62
Upper tercile	> 50	-	> 34	> 3.52	> 57	>29.62

5.2.2 Risk Analysis Results

Total number of treatments and cumulative dosage were taken as continuous variables and tercile categorical variables in risk analysis separately. Overall, risk analysis suggested there was no statistically significant correlation between total number of treatments, or cumulative dosage and skin cancer risk (all $p>0.05$ for both multivariate logistic regression and Cox-regression models) (Table 5.2). Also, there was no statistically significant difference of skin cancer risk in patients with higher total number of treatments or cumulative dosage compared to patients receiving lower total number of treatment or cumulative dosage risk (all $p>0.05$ for both multivariate logistic regression and Cox-regression models) (Table 5.3 and Table 5.4).

Table 5.2 Skin Cancer Risk Analysis for Total Number of Treatment and Cumulative Dosage*

Factors	Odds ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
UVB total session	1.004 (0.997-1.011)	0.260	0.996 (0.990-1.002)	0.153
BB-UVB total session	1.000 (0.988-1.012)	0.998	0.999 (0.987-1.013)	0.939
NB-UVB total session	1.006 (0.997-1.015)	0.204	0.992 (0.984-1.001)	0.076
BB-UVB cumulative dosage	0.997 (0.940-1.058)	0.932	0.997 (0.943-1.053)	0.900
NB-UVB cumulative dosage	1.012 (0.996-1.029)	0.148	0.987 (0.973-1.002)	0.084

*Adjusted to censored age, gender and skin type for all models

Table 5.3 Correlation between Skin Cancer Risk and Total Session Tercile Groups*

Total Session	OR (95% CI)	P value	HR (95% CI)	P value
UVB phototherapy				
Lower tercile	Reference	-	Reference	-
Middle tercile	1.51 (0.55-4.19)	0.43	1.55 (0.57-4.23)	0.39
Upper tercile	1.23 (0.44-3.34)	0.69	1.19 (0.43-3.30)	0.73
BB-UVB phototherapy				
Lower tercile	Reference	-	Reference	-
Middle tercile	1.23 (0.28-5.40)	0.79	1.26 (0.30-5.32)	0.76
Upper tercile	1.10 (0.25-4.87)	0.90	1.00 (0.24-4.23)	1.00
NB-UVB phototherapy				
Lower tercile	Reference	-	Reference	-
Middle tercile	1.31 (0.35-4.87)	0.68	1.24 (0.35-4.41)	0.75

Upper tercile	1.36 (0.38-4.89)	0.63	1.09 (0.32-3.78)	0.89

*Adjusted to censored age, gender and skin type for all models; OR: odds ratio; HR: hazard ratio

Table 5.4 Correlation between Skin Cancer Risk and Cumulative Dosage Tercile Groups*

Cumulative Dosage	OR (95% CI)	P value	HR (95% CI)	P value
BB-UVB phototherapy				
Lower tercile	Reference	-	Reference	-
Middle tercile	1.56 (0.37-6.59)	0.54	1.65 (0.40-6.82)	0.49
Upper tercile	0.82 (0.17-3.88)	0.80	0.86 (0.19-3.87)	0.84
NB-UVB phototherapy				
Lower tercile	Reference	-	Reference	-
Middle tercile	2.81 (0.83-9.46)	0.10	2.70 (0.84-8.70)	0.10
Upper tercile	0.64 (0.14-2.97)	0.57	0.53 (0.12-2.41)	0.41

*Adjusted to censored age, gender and skin type for all models; OR: odds ratio; HR: hazard ratio

5.2.3 Kaplan-Meier Survival Curves

Kaplan-Meier survival curves were plotted to show the probability of patients developing skin cancer after getting UVB phototherapy among tercile groups of total number of treatment sessions and cumulative dosage. As shown in Figure 5.1 to Figure 5.5, Kaplan-Meier curves represented similar tendency and suggested there was no significant risk difference among tercile groups, neither for total number of treatment sessions nor for cumulative dosage category (all $p > 0.05$ by using lower tercile group as reference).

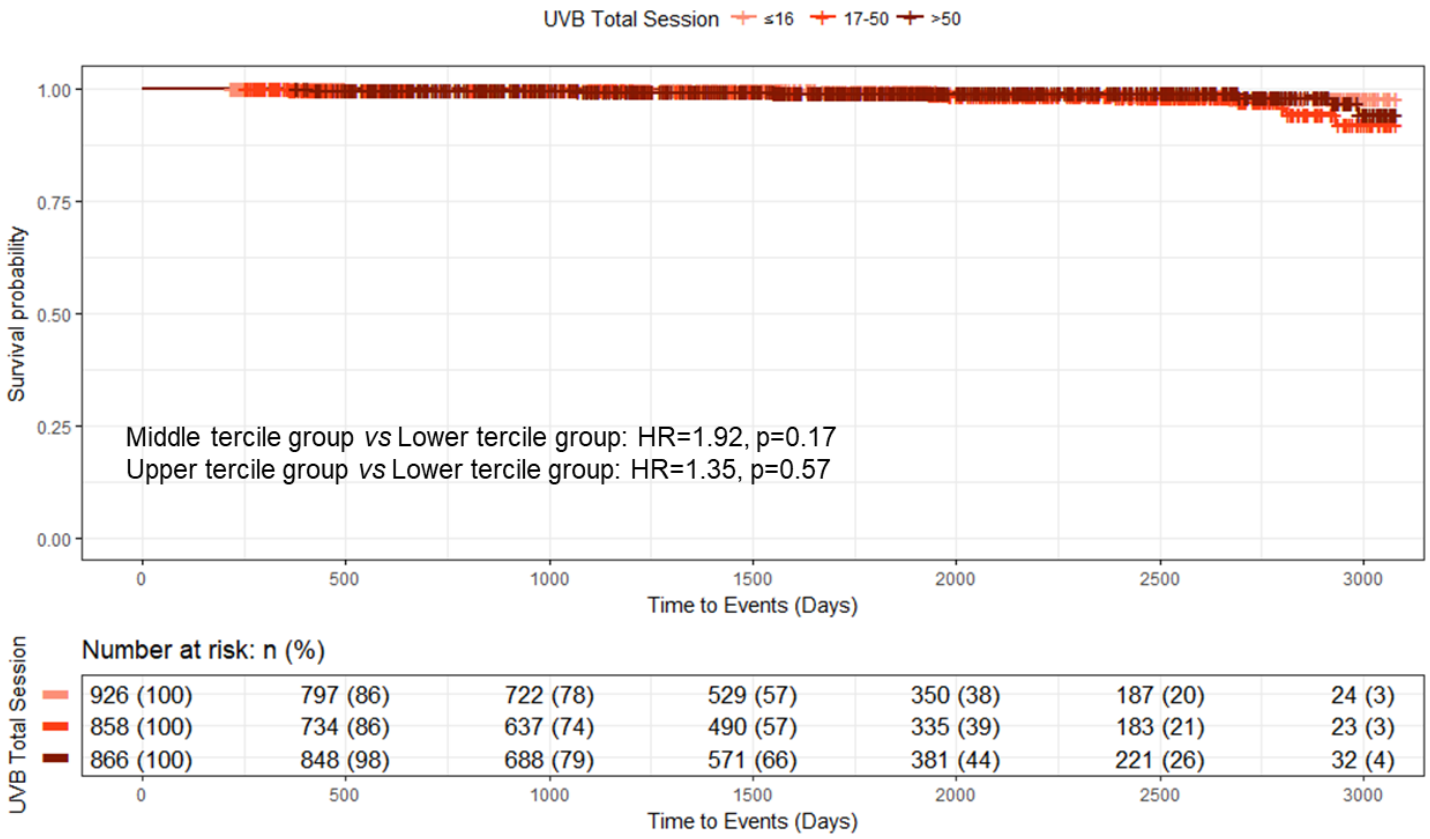

Figure 5.1 Kaplan-Meier Curves for Skin Cancer Development Stratified by UVB Total Number of Treatment Session

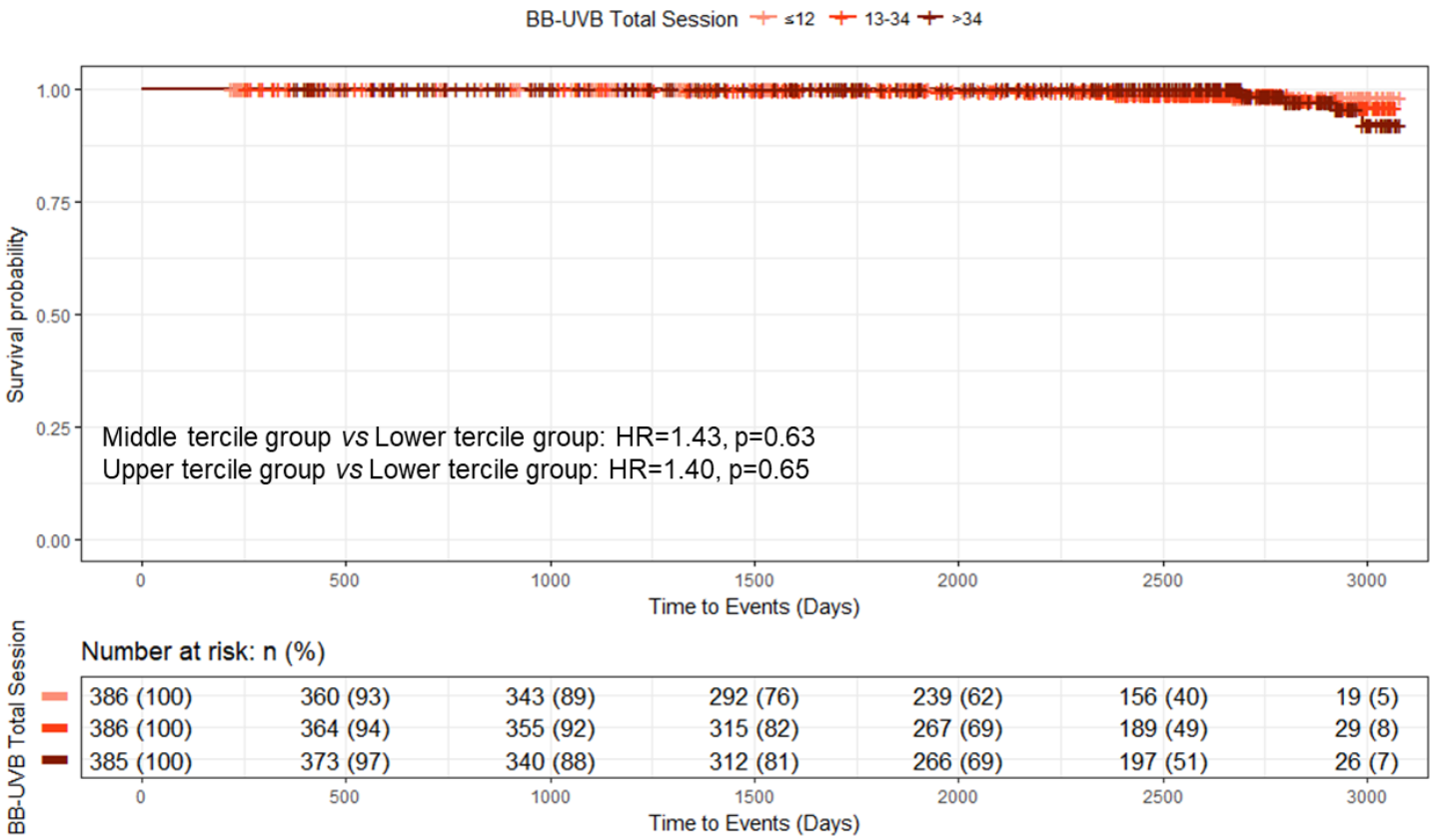

Figure 5.2 Kaplan-Meier Curves for Skin Cancer Development Stratified by BB-UVB Total Number of Treatment Session

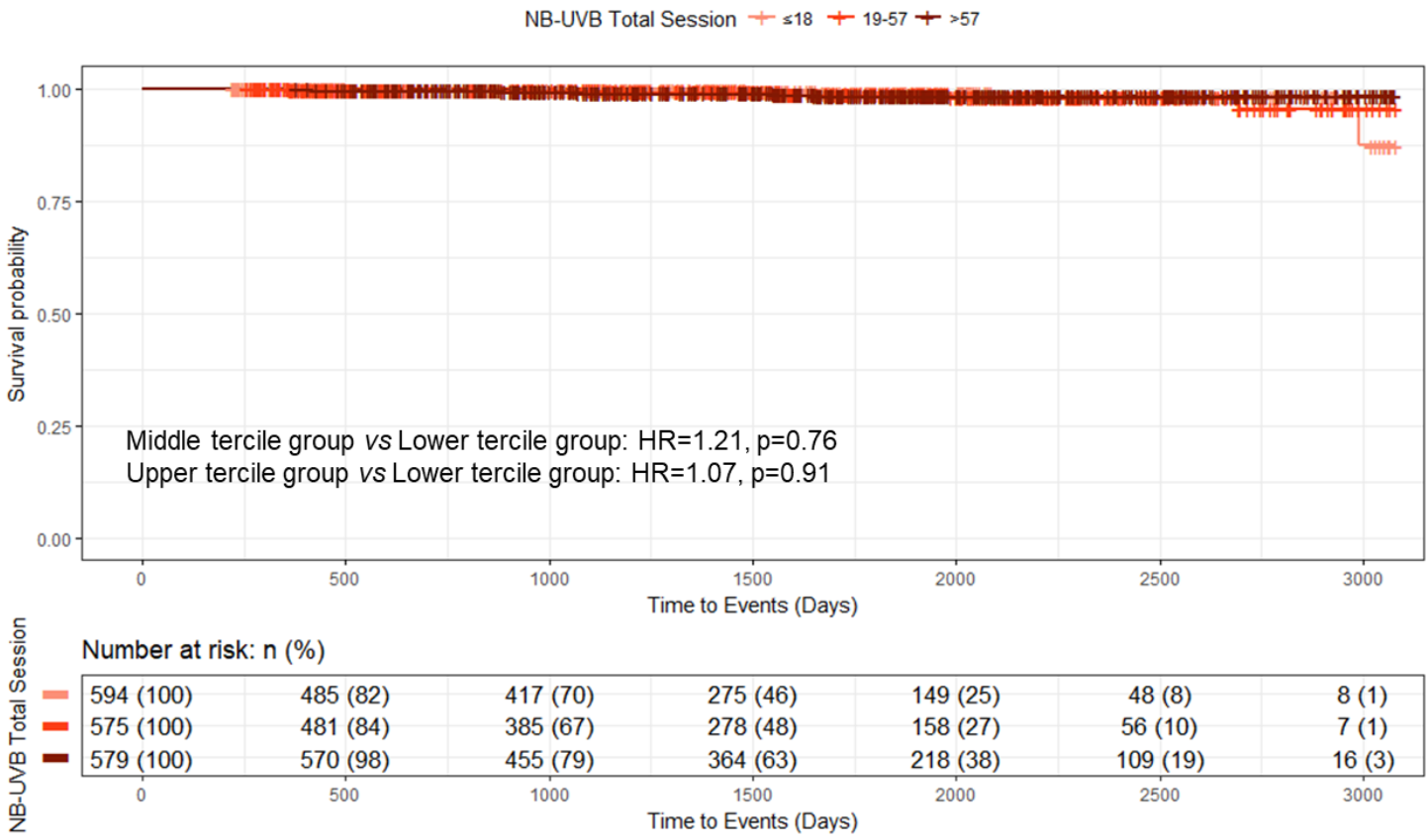

Figure 5.3 Kaplan-Meier Curves for Skin Cancer Development Stratified by NB-UVB Total Number of Treatment Session

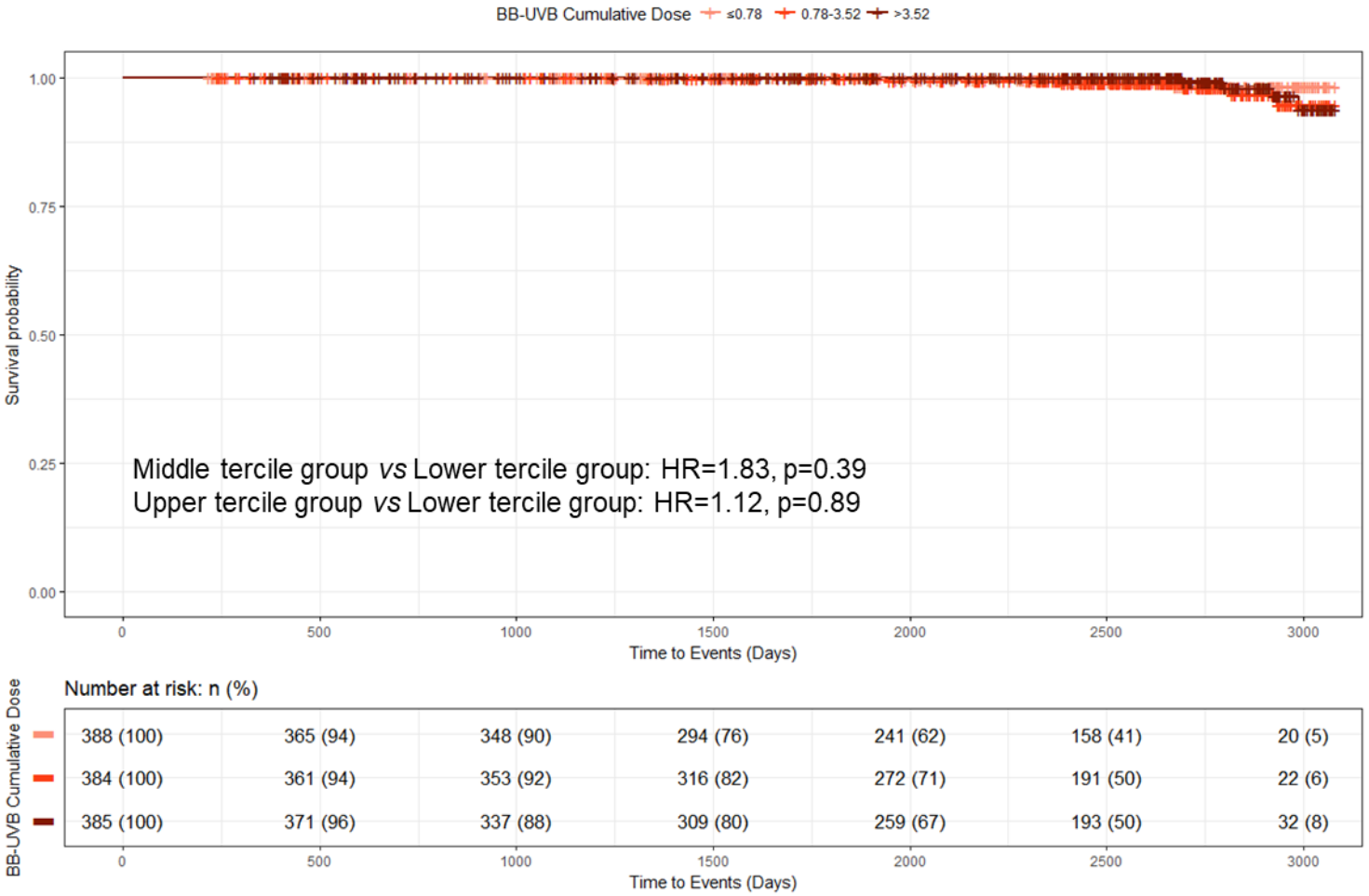

Figure 5.4 Kaplan-Meier Curves for Skin Cancer Development Stratified by BB-UVB Cumulative Dosage

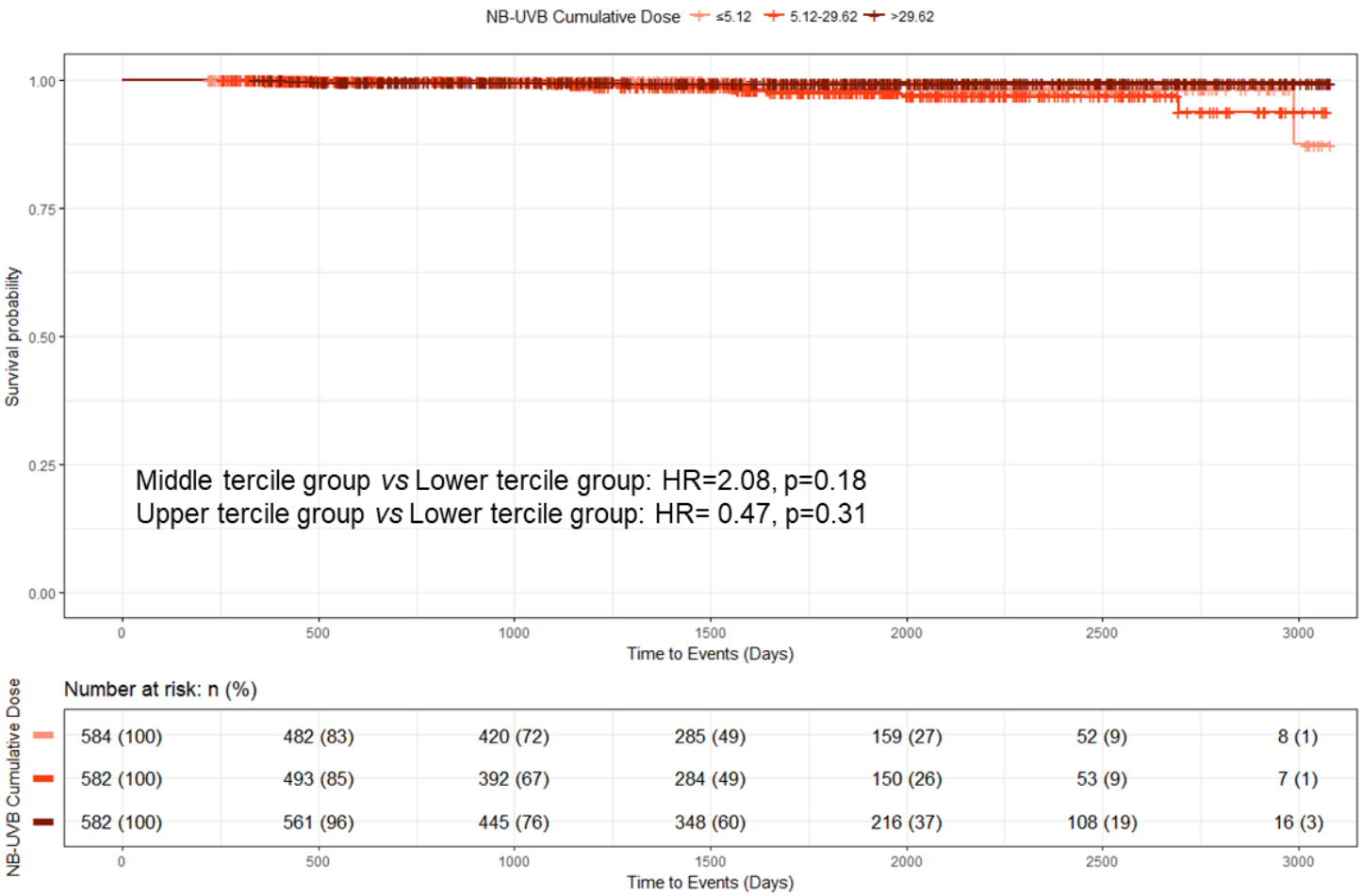

Figure 5.5 Kaplan-Meier Curves for Skin Cancer Development Stratified by NB-UVB Cumulative Dosage

Chapter 6: Discussion

6.1 Summary of Key Findings

We comprehensively analyzed the incidence rates, anatomical distribution and risk of skin cancer in patients with UVB phototherapy in the Psoriasis and Phototherapy Clinic, Skin Care Center, Vancouver. A total of 3,506 patients (1,999 male and 1,507 female) were analyzed for an average of 7.1 years. A total of 170 new skin cancers identified in 79 patients after receiving UVB phototherapy without SPUVA.

6.1.1 Incidence of Skin Cancer in Patients with UVB Phototherapy

In UVB phototherapy patients, individual-based overall ASIR (identified by first developed skin cancer) was 149.1 (95% CI: 111.5-187.2)/100,000 person-year. Case-based overall ASIR (identified by all skin cancers) was 264.1 (95% CI: 219.4-308.8)/100,000 person-year. Registration-based incidence rate was slightly larger than individual-based incidence rate. Although neither BB-UVB nor NB-UVB significantly increased skin cancer incidence comparing to general population, patients with BB-UVB phototherapy had significantly higher ASIR than patients with NB-UVB phototherapy for all types of skin cancer (e.g., overall individual ASIR for BB-UVB *vs* NB-UVB: 158.9/100,000 person-year *vs* 93.8/100,000 person-year, Z-score: 2.12, $p<0.05$; overall case-based ASIR for BB-UVB *vs* NB-UVB: 287.9/100,000 person-year *vs* 167.5/100,000 person-year, Z-score: 3.32, $p<0.05$). .

In patients developing skin cancer, 34.2% were affected by multiple skin cancers. Skin cancer incidence increased with age and was low for patients below 40 years old. Also, individual-based skin cancer ASIRs decreased with higher skin phototypes (ASIR: 272.7, 226.8, 150.5, 76.6, 35.6/100,000 person-years for skin type I to skin type V, respectively). Anatomical distribution

suggested that head and neck sites had highest skin cancer rates. The tendency of skin cancer incidence in age and skin type were similar with tendency in general population.

Registration based ASIR comparison with the BC general population suggested male patients had significant lower BCC incidence compared to general population. Head and neck had lower KCs incidence compared to general population.

6.1.2 Risk Assessment of Total Treatment Sessions, Cumulative Dosage and Skin Cancer Development

Multivariate logistic regression and survival analysis suggested statistically significant correlations were not identified between total number of treatment sessions or cumulative dosage and the risk of skin cancer developing (overall UVB total treatment session: OR=1.004 (p=0.26), HR=0.996 (p=0.15); BB-UVB cumulative dosage: OR=0.997 (p=0.93), HR=0.997 (p=0.90); NB-UVB cumulative dosage: OR=1.012 (p=0.15), HR=0.987 (p=0.08)).

No statistically significant difference of skin cancer risk in patients receiving higher total number of treatment sessions or cumulative dosage compared to lower total number of treatment sessions or cumulative dosage was found (total treatment session >50 vs ≤16： OR=1.23 (p=0.69), HR=1.19 (p=0.73); BB-UVB cumulative dosage >3.52 vs ≤0.78 J/cm^2: OR=0.82 (p=0.80), HR=0.86 (p=0.84);NB-UVB cumulative dosage >29.62 vs 5.12 J/cm^2: OR=0.64 (p=0.57), HR=0.53 (p=0.41)).

6.2 Risk of Skin Cancer in Patients with UVB Phototherapy

Compared to previous studies assessing UVB phototherapy and skin cancer risk, we comprehensively analyzed data with different statistical models and provided multiple perspectives to get a better understanding of skin cancer risks in patients with UVB phototherapy.

To our knowledge, published studies assessing UVB phototherapy in psoriasis and eczema patients are all incidence studies. The major limitations of these studies are inconsistent definitions of skin cancer incidence and inadequate comparable groups. When comparing to previous published skin cancer incidence results, same incidence definition should be used. Individuals with skin cancer had high risk of multiple skin cancers [17, 18]. However, only three studies described how they accounted for skin cancer multiplicity [61-63]. Reasons for lacking information on skin cancer multiplicity may be due to limitations in data collection methods through self-reporting, chart data and cancer registries. Patient self-reporting and patient record charts may miss skin cancer cases and most cancer registries do not track KCs routinely, and even if KCs are recorded, only the first diagnosis is included [23]. Therefore, incidence based on cancer registry coded might also be different with individual-based or case-based incidence rates. It is necessary to clearly state individual-based, case-based and registration-based incidence of skin cancer in incidence studies. In this study, skin cancer was identified through pathology confirmation, which included all skin cancer cases and details of skin cancer types and anatomical distribution. Therefore, individual-based, case-based, registration-based incidence and site-specific incidence were reported independently.

Ideally, the control group in this study should be patients with matched skin diseases treated with other options besides phototherapy. However, it is logistically difficult to collect information for

patients without phototherapy at the same duration. Therefore, most incidence studies use the general population as a comparable group. Historical or national skin cancer incidence is usually chosen as a comparable group. Ortiz-Salvador *et al.* [62] conducted a study of UVB phototherapy patients in Valencia Spain, between 2002-2016, and compared incidence rate to the general population in Girona, Spain for 1994-2017. Since skin cancer incidence is increasing with time and has geographical difference, and it is difficult to adjust differences in geographic, there are limitations in using these comparable groups. In addition, since older people have higher skin cancer risk [85], age-standardized incidence rates were calculated to directly compare skin cancer incidence in different populations by adjusting differences in the age structures of populations being compared. Methodologically, when comparing incidence in two different population, either one population is mathematically adjusted to have the same age structure as the other; or both populations are mathematically adjusted to have the same age structure as the standard population [86]. In this way, the two groups are given the same age distribution structure. However, all previous publications did not state information of standard population, neither for studying population in their research, nor for compared population. For example, Ortiz-Salvador *et al.* [62] standardized incidence rate to the world population but did not mention the year. Jo et al. [59] did not state which population incidence was standardized to. Therefore, the incidence comparison results in previous studies show some limitations. In this study, we have used provincial general population as a comparable group, which controlled geographical difference for the most parts, and standardized to the same population (1991 Canadian general population) for comparing ASIRs.

Comparing to the BC general population, male patients had significantly lower BCC incidence compared to general population, while both genders had similar melanoma and SCC incidence with general population. Skin cancer incidence increased with age and decreased with higher phototypes in patients with UVB phototherapy. Unfortunately, anatomical skin cancer incidence was not provided with detail groups for BC general population, so it is impossible to compare differences of skin cancer in solar radiation protected sites (trunk, shoulder, upper arm and thigh) and solar radiation exposed sites (face, hands, forearm and legs) between UVB phototherapy patients and BC general population. But compared to general population, head and neck had lower KCs incidence in UVB patients and male patients had statistically significantly lower incidence for BCC. One possible explanation is UVB treatment causes photoadaptation. Photoadaptation describes skin's ability to withstand increasing doses of UV radiation with repeated exposure [87], which leads skin to be more tolerant to UV light. Although few studies assess photoadaptation in UVB phototherapy and skin cancer risk, studies of solar exposure suggested that individuals with chronic solar exposure had lower risk of melanoma [88, 89]. In Mclean et al.'s study, ASIRs was also standardized to ethics, however, ethics was not adjusted in this study due to lack of information.

Although compared to the general population, UVB phototherapy was not found to increase skin cancer incidence, neither for BB-UVB phototherapy nor for NB-UVB phototherapy; BB-UVB phototherapy had significantly higher skin cancer incidence compared to NB-UVB phototherapy. BB-UVB and NB-UVB are commonly used in phototherapy. NB-UVB phototherapy at a wavelength of 311nm has been shown to be more effective than BB-UVB for psoriasis and safer than PUVA in skin cancer development [13]. Our results suggest NB-UVB is safer than BB-UVB.

In Canada, the lifetime risk of melanoma, BCC and SCC was 2%, 13% and 5%, respectively [90]. Most participants in this study were psoriasis patients. It has been suggested that psoriasis patients have a higher risk of certain cancers, including skin cancer [91, 92]. Possible reasons for this may be repeated therapy with coal-tar, UVB and PUVA irradiation or exposure to cyclosporine [93]. There is consistent epidemiology evidence that PUVA increases skin cancer risk, especially for KCs [40, 41]. A strongly dose-dependent increase risk in the SCC was observed [41, 94]. Psoriasis patients treated with cyclosporine may have increased risk of SCCs [95]. Moreover, due to benefits of sunlight on psoriatic skin, psoriasis patients may display sun-seeking behavior, which may also increase skin cancer risk [92]. Based on risk ratio of skin cancer for psoriasis patients provided by a recent meta-analysis, estimated lifetime risk of melanoma, BCC and SCC was 3%, 17% and 11%, respectively [96]. Incidence results in this study suggested lifetime risk of melanoma, BCC and SCC in patients with UVB phototherapy was 3%, 16%, and 7% respectively. The lifetime skin cancer incidence for patients with UVB phototherapy was slightly higher than the general population but lower than the psoriasis population. However, detection bias for skin cancers in patients with skin diseases should be considered since patients with skin diseases visit dermatologists more frequently than the general population.

Due to inadequate sample size and follow-up years, survival analysis was not conducted in previous studies. One recent publication conducted risk analysis of total number of NB-UVB treatment sessions and skin cancer development in a Korean vitiligo population [97]. They suggested NB-UVB phototherapy was not associated with skin cancer risk. Vitiligo patients may benefit from enhanced immune surveillance of skin cancer [98]. It was also suggested that genetic variations in vitiligo patients increased resistance to malignant neoplasms [99]. Moreover, since a

Korean population is mostly skin type III and IV, they are likely to have lower skin cancer risk. Although survival analysis results in our study suggested no statistically significant correlation between total number of treatment sessions or cumulative dosage with skin cancer risk, average 5 year follow-up duration and limited sample size of patients having a high number of total treatment sessions may not be enough for testing statistically significant correlation if one exists.

Indoor tanning is very popular in North America. O'Sullivan suggested indoor tanning was associated with increased skin cancer risk in Canada (relative risk was 1.38 (95% CI: 1.22-1.58), 1.39 (95% CI: 1.10-1.76) and 1.49 (95% CI: 1.23-1.80) for melanoma, BCC and SCC, respectively) [3]. Survival analysis for UVB phototherapy in this study suggested that UVB phototherapy is safer than indoor tanning, which was used by 4.5% of Canadians [100].

Indoor tanning is similar to sun exposure for UVB radiation but 10-15 times stronger than sun exposure for UVA radiation [101]. Over-exposure to UVA radiation might be the reason for increasing skin cancer risk by indoor tanning. Therefore, we also tried to compare UVB fluence from UVB phototherapy with solar UVB radiation. However, it is difficult to assess how much UVB fluence general population receiving from solar radiation. Peters *et al.* assessed solar UVR exposure in outdoor workers in Vancouver [102]. They reported daily solar UVR exposure of outdoor workers in Vancouver ranged from 0.01 standard erythema dose to 19.2 standard erythema dose. One standard erythema dose is equivalent to CIE-weighted irradiation of 100 J/m^2 [103]. It was suggested UVB energy could be estimated as 7.55 times of CIE-weighted energy [104]. Therefore, the estimated maximum daily solar UVB exposure for outdoor workers in Vancouver was 1.45 J/cm^2. One of the advantages of our study was that information on treatment dosage was collected. The average daily dosage of BB-UVB in this study was up to 0.17 J/cm^2. The maximum

BB-UVB single treatment dosage was 1.98 J/cm^2 and 99.95% individual treatment dosage was under 1.00 J/cm^2. Although outdoor workers have higher sun exposure fluence, it provided a comparison that average daily UVB phototherapy dosage was much less than daily solar UV radiation for outdoor workers (0.17 vs 1.45 J/cm^2). The energy patients receiving from UVB phototherapy may be similar with solar radiation at same wavelength possibly explaining no increased skin cancer risk in UVB phototherapy patients.

6.3 Strengths and Limitations of Study

Compared to previous studies assessing UVB phototherapy and skin cancer in psoriasis patients, our study consisted of a larger sample size (3,506) with longer follow-up duration. Among 16 published research studies, 13 recruited less than 500 participants [48-51, 53-55, 57, 59-63]. However, Diffey and Farr suggested that to determine carcinogenic risk with NB-UVB phototherapy requires large multicenter studies recruiting thousand new patients per year and follow up for more than 10 years [105]. Therefore, sample size and follow-up duration in this study might still be inadequate to observe statistically correlation between UVB phototherapy and skin cancer risk.

In addition, almost all previous studies identified skin cancer cases through national or provincial cancer registries, which may result in lower estimation of skin cancer incidence since basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and multiplicity of skin cancer may not be registered. In this study, pathology ascertainment of skin cancer provided more accurate incidence of skin cancer and allowed evaluation of individual-based incidence, case-based incidence, registration-based and site-specific incidence independently. Skin cancer incidence was also compared between patients having BB-UVB and NB-UVB phototherapy.

Incidence with same definition (case-based skin cancer incidence) was compared to the BC provincial general population, which represents the closest demographic structure for patients treated in Vancouver, BC. Potential biases which might be caused by study design and data analysis were well controlled, such as differences in geographic and age structure distribution. Skin cancer incidence profile was reported in age, skin type and anatomical distribution. Multiple perspective data analysis including logistic regression and survival analysis allowed comprehensive evaluation of UVB phototherapy and skin cancer.

There were several limitations for this study. Firstly, we didn't include vitiligo patients since they received treatments in the Vitiligo Clinic at Skin Care Center. But recent publications have assessed NB-UVB phototherapy in vitiligo patients [97]. Secondly, confidence interval of skin cancer incidence for skin type I and V was large due to limited number of patients. However, the decreasing incidence tendency with higher phototypes agreed with similar skin cancer incidence profile between UVB phototherapy patients and general population. Thirdly, sample size and follow-up time for survival analysis may not be adequate to observe statistically significant correlation if one exists.

6.4 Conclusion and Future Directions

No statistically significant difference in skin cancer incidence was observed in patients with UVB phototherapy and the general population. Total number of treatment sessions and cumulative dosage was also not statistically correlated with skin cancer risk. However, lifetime skin cancer incidence for patients with UVB phototherapy was comparable to the general population and psoriasis population. Patients with UVB phototherapy had slightly higher lifetime incidence than

the general population but lower lifetime incidence than a psoriasis population, suggesting UVB phototherapy might be a safe option for treating skin diseases in terms of skin cancer development.

Further studies are needed with longer follow-up duration with treatment dosage information to get a better understanding on the true risk of skin cancer development in patients with UVB phototherapy.

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Appendices

Appendix 1.1 Protocol of Phototherapy in Psoriasis and Phototherapy Clinic-Vancouver General Hospital

Determine Initial Dosage

For all patients receiving phototherapy in Psoriasis and phototherapy clinic-VGH, the initial dosage will be determined based on skin type and treatment type by nurses.

Skin type classifications vary somewhat – some persons of Type V or VI may be classified into a lower category if there is a history of sun burning, and different areas of skin such as those rarely exposed to UV light may be classified as lower skin type.

If a patient has phototest for NB-UVB treatment, initial dose should be set as 70% minimal erythemal dose (MED). If a patient is going from BB-UVB to NB-UVB use a factor of 3 (ie: 300 mJ BB × 3 = 900 mJ NB) to a maximum of 600 mJ BB. If the BB dose is > 600 mJ use a factor of 2 (ie: 610 mJ BB × 2 = 1220 mJ NB). When in doubt a phototest should be done to establish current MED.

Dose Adjustments

With each subsequent dose, increase the UVB according to the following schedule:

Reaction to previous exposure	Dose Increment
No erythema or pain	Up to 10% (up to 25% for doses <200 mJ for NB-UVB)
Mild erythema without pain	Up to 5%

Mild erythema with minimal pain or discomfort lasting < 24 hours	0% give same dose as previous treatment
Moderate erythema with moderate pain or discomfort lasting > 24 hours	-10%
Severe erythema with severe symptoms; or tender skin	Hold treatment

If a patient has break during treatment, the dose will be given as follow:

Time missed	Give % of last dose
01-07 days	Increase as per standard protocol
08 days	100%
09-12 days	80-85%
12-14 days	75%
15-20 days	50%
21-27 days	25%
≥28 days	Start over at base dose* *Do not decrease below initial dose

Determine of exposure times

Exposure times will be determined by a) calculation, b) consulting an exposure table or c) entering doses into unit panel, then pushing the calculation button to display time. Dosing is capped at 3,000 Millijoules for a single treatment.

Source used:

- The Joan Shelk Memorial Phototherapy Workshop Handbook (2004 Dermatology Nurses' Association)
- P&PC Guidelines for Narrow Band 311 UVB Exposure (1998 H.Lui/J.Shapiro/P$PC Staff)

Appendix 2.1 Publication Bias Assessment Results

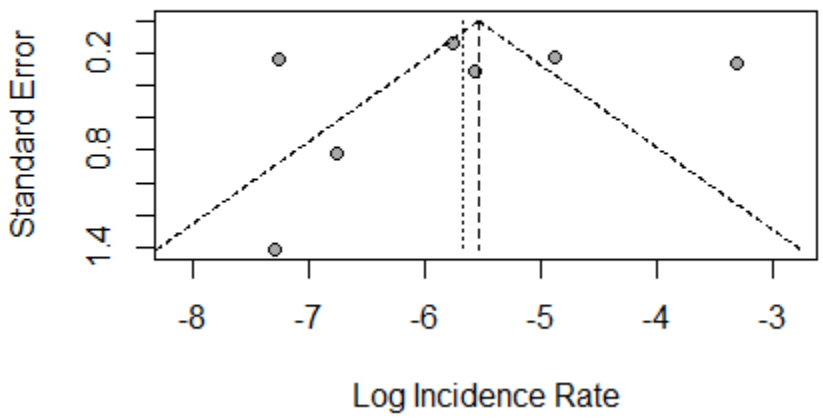

Figure 1. Funnel Plot of Overall Skin Cancer Incidence Rate. Both funnel plot and the Egger test revealed no publication bias (p=0.97 > 0.05).

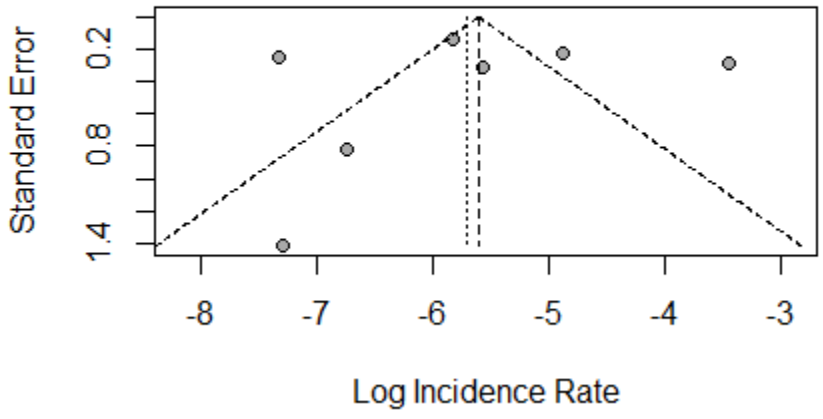

Figure 2. Funnel Plot of Keratinocyte Carcinoma Incidence Rate. Both funnel plot and the Egger test revealed no publication bias (p=0.98> 0.05).

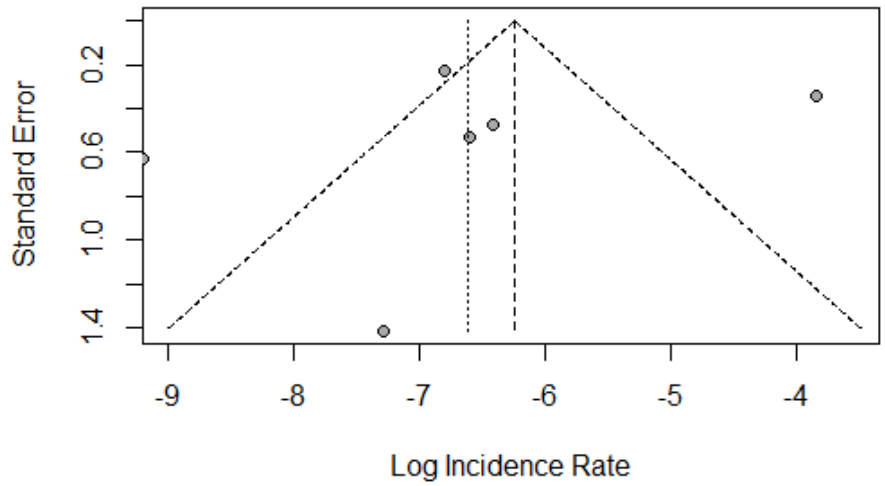

Figure 3. Funnel Plot of Squamous Cell Carcinoma Incidence Rate. Both funnel plot and the Egger test revealed no publication bias (p=0.71 > 0.05).

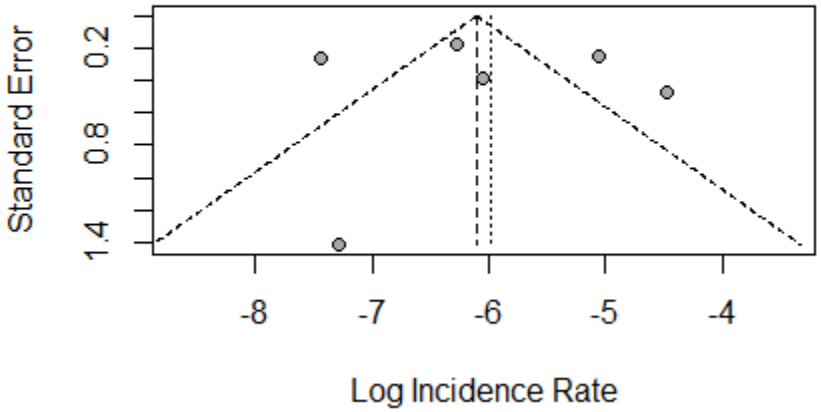

Figure 4. Funnel Plot of Basal Cell Carcinoma Incidence Rate. Both funnel plot and the Egger test revealed no publication bias (p=0.81 > 0.05).

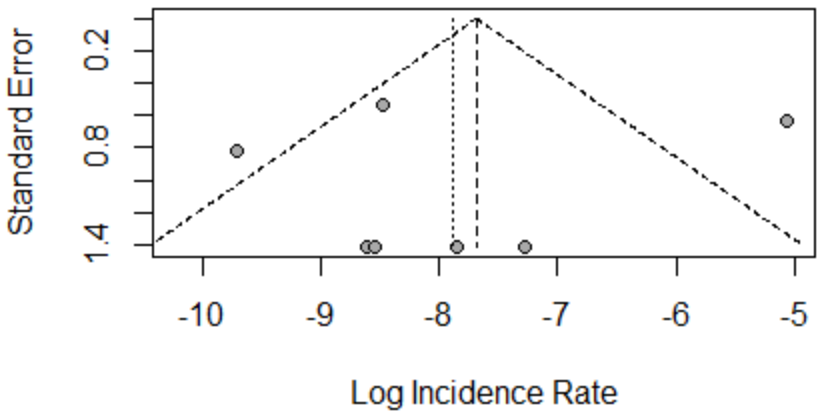

Figure 5. Funnel Plot of Melanoma Incidence Rate. Both funnel plot and the Egger test revealed no publication bias ($p=0.72 > 0.05$).

Appendix 3.1 Data Abstraction Form for Electronic Database Creation

Population Demographics		
PHN (Study ID)		
Gender	☐ Male ☐ Female	
Year of birth		
Area of residence (postal code)		
Previous use of Psoralens+ UVA (PUVA)	☐ Yes ☐ No	
Fitzpatrick skin type	☐ I ☐ II ☐ III ☐ IV ☐ V ☐ VI	
Diagnosis		
History of skin cancer	☐ Yes ☐ No	If Yes, ☐ Basal Cell Carcinoma ☐ Squamous Cell Carcinoma ☐ Melanoma
UV Phototherapy		
Type of phototherapy	☐ BB-UVB ☐ NB-UVB ☐ UVA ☐ Systemic PUVA	
Individual sessions date		

Individual dosage		
Erythema	☐ No erythema ☐ Minimal erythema ☐ Marked red erythema, no edema ☐ Fiery red erythema with edema and tenderness ☐ Fiery red erythema with edema and blistering and tenderness	
Minimal erythema dose for NB-UVB		
Pathological confirmation		
Developed skin cancer	☐ Yes ☐ No	If Yes, ☐ Basal Cell Carcinoma ☐ Squamous Cell Carcinoma ☐ Melanoma ☐ Anatomical of Skin Cancer ☐ Reporting date