A MULTIFACETED PERSPECTIVE ON SKIN CANCER PREVENTION

Inauguraldissertation

zur
Erlangung der Würde eines Doktors der Philosophie
vorgelegt der
Philosophisch-Naturwissenschaftlichen Fakultät
der Universität Basel

von
Daphne Cornelia Reinau
aus Basel (BS)

Basel, 2015

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät

auf Antrag von

Prof. Dr. Christoph Meier

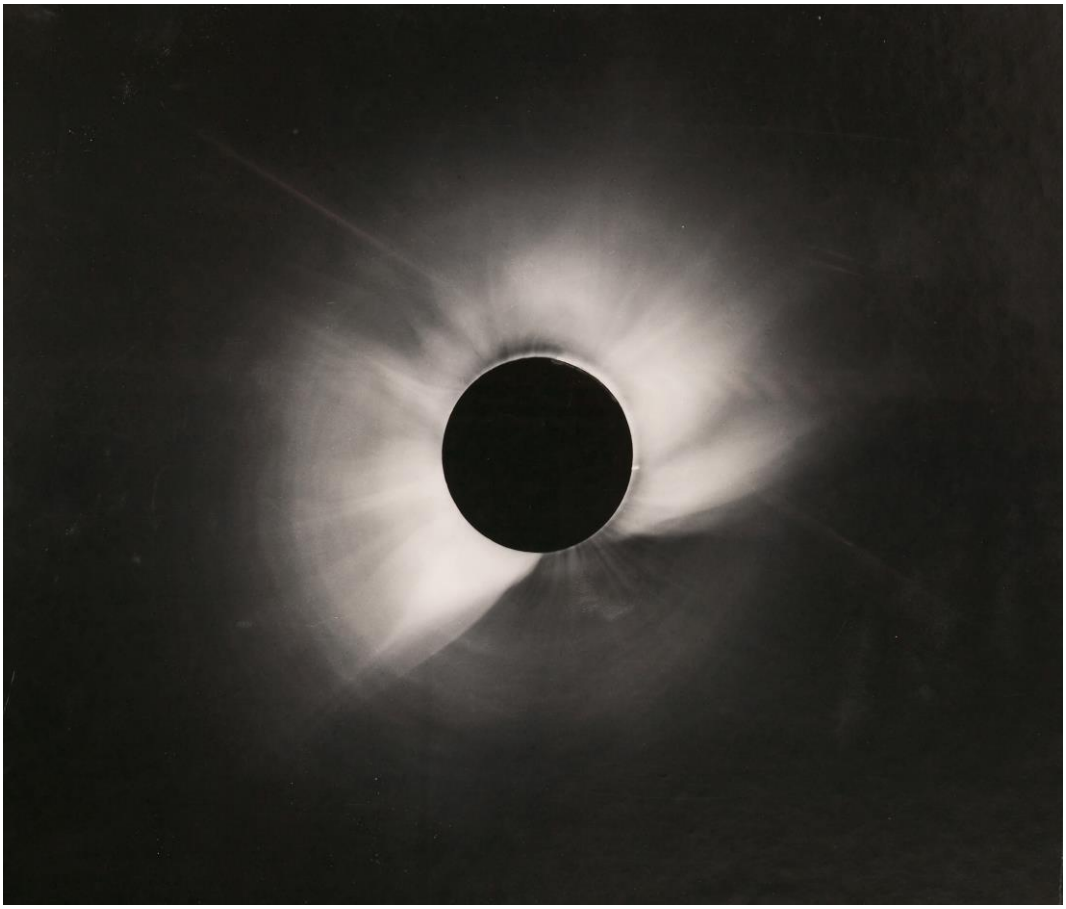
Prof. Dr. Christian Surber

Prof. Dr. Peter Itin

Basel, den 9. Dezember 2014

Prof. Dr. Jörg Schibler

Dekan



Solar eclipse (unknown photographer, silver gelatin print 1920/30)

Photograph courtesy of Collection Ruth and Peter Herzog, Basel

Namensnennung-Keine kommerzielle Nutzung-Keine Bearbeitung 3.0 Schweiz
(CC BY-NC-ND 3.0 CH)

Sie dürfen: **Teilen** — den Inhalt kopieren, verbreiten und zugänglich machen

Unter den folgenden Bedingungen:

Namensnennung — Sie müssen den Namen des Autors/Rechteinhabers in der von ihm festgelegten Weise nennen.

Keine kommerzielle Nutzung — Sie dürfen diesen Inhalt nicht für kommerzielle Zwecke nutzen.

Keine Bearbeitung erlaubt — Sie dürfen diesen Inhalt nicht bearbeiten, abwandeln oder in anderer Weise verändern.

Wobei gilt:

- **Verzichtserklärung —** Jede der vorgenannten Bedingungen kann **aufgehoben** werden, sofern Sie die ausdrückliche Einwilligung des Rechteinhabers dazu erhalten.
- **Public Domain (gemeinfreie oder nicht-schützbare Inhalte) —** Soweit das Werk, der Inhalt oder irgendein Teil davon zur Public Domain der jeweiligen Rechtsordnung gehört, wird dieser Status von der Lizenz in keiner Weise berührt.
- **Sonstige Rechte —** Die Lizenz hat keinerlei Einfluss auf die folgenden Rechte:
    - Die Rechte, die jedermann wegen der Schranken des Urheberrechts oder aufgrund gesetzlicher Erlaubnisse zustehen (in einigen Ländern als grundsätzliche Doktrin des **fair use** bekannt);
    - Die **Persönlichkeitsrechte** des Urhebers;
    - Rechte anderer Personen, entweder am Lizenzgegenstand selber oder bezüglich seiner Verwendung, zum Beispiel für **Werbung** oder Privatsphärenschutz.
- **Hinweis —** Bei jeder Nutzung oder Verbreitung müssen Sie anderen alle Lizenzbedingungen mitteilen, die für diesen Inhalt gelten. Am einfachsten ist es, an entsprechender Stelle einen Link auf diese Seite einzubinden.

Quelle: http://creativecommons.org/licenses/by-nc-nd/3.0/ch/ Datum: 12.11.2013

ACKNOWLEDGEMENTS

The present thesis was accomplished between January 2012 and November 2014 at the Division of Clinical Pharmacy and Epidemiology at the Department of Pharmaceutical Sciences of the University of Basel. I would like to thank everyone who contributed to the realisation of my projects.

My first and heartfelt thanks go to my main supervisor, Prof. Dr. Christian Surber, Department of Dermatology, University Hospital Basel and Zurich, for having given me the opportunity to work on the exciting and interdisciplinary topic of skin cancer prevention. Thank you, Christian, for your constant support and trust! I have very much appreciated your enthusiastic mentorship, your constructive advice, and the challenging discussions.

I am also sincerely thankful to Prof. Dr. Christoph Meier, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, for supervising the two projects based on data from the Clinical Practice Research Datalink (Projects V and VI) and for presenting this thesis to the faculty. Thank you, Christoph, for having offered me such a warm welcome in your research group and for having enabled me to gain insight into the fascinating field of epidemiology!

Further, I would like to express my gratitude to Prof. Dr. med. Peter Itin, Department of Dermatology, University Hospital Basel, for acting as a co-referee of my thesis, and to Prof. Dr. Kurt Hersberger, Division of Pharmaceutical Care, Department of Pharmaceutical Sciences, University of Basel, for taking the chair at the doctoral examination.

I am much obliged to Spirig Pharma Ltd., Egerkingen, and to Galderma S.A., Lausanne, for financial support.

My thanks go as well to those co-authors of the individual manuscripts presented within this thesis who have not yet been mentioned, Nathalie Gerber, Swiss Cancer League, Bern (Project I), Prof. Dr. med. Thomas Diepgen and Melanie Weiss, Department of Social Medicine, Occupational and Environmental Dermatology, University Clinic of Heidelberg (Project II), Prof. Dr. med. Christoph Hatz, Swiss Tropical and Public Health Institute, Basel and Institute of Social and Preventive Medicine, University of Zurich, Carole Achermann and Noah Arnet, Department of Pharmaceutical Sciences, University of Basel (Project III), Ralf Blumenthal, Professional Association of German Dermatologists (BVDD), Berlin (Project IV), and Susan Jick, Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA (Projects V and VI), for their valuable contributions.

For the English proofreading of this thesis, I wish to extend my cordial thanks to Maria Tranter.

I gratefully acknowledge the Zurich Cancer League and the teachers of the schools involved in the evaluation of a sun safety education programme (Project I) as well as the team around Mr. Werner Parini, Head of Passenger Terminal Department Basel-Mulhouse Airport, and the staff of the Swiss Tropical and Public Health Institute Basel involved in the investigation of sun protective behaviour of vacationers (Project III) for their active support and the pleasant cooperation. A special thank-you goes to the voluntary study participants of these two projects which could not have been realised without their availability and kind patience.

Many thanks are due to Carmen Brunner, Spirig Pharma Ltd., Egerkingen (Project I), and Pascal Egger, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel (Projects V and VI), for their invaluable technical assistance.

Moreover, I would like to thank my colleagues from the Division of Clinical Pharmacy and Epidemiology, namely Dr. Claudia Becker, Fabienne Biétry, Marlene Blöchliger, Delia Bornand, Dr. Saskia Bruderer, Pascal Egger, Noel Frey, Dr. Patrick Imfeld, Dr. Cornelia Schneider, Dr. Julia Spöndlin, Nadja Stohler, and Dr. J. Claire Wilson, for their great cooperativeness and the friendly work atmosphere. Thank you all for the unforgettable time we spent together!

Last but not least, my warmest thanks go to my family and friends for their continuous encouragements and the everlasting support throughout the years.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS XIII

SUMMARY XVII

1 INTRODUCTION 21

1.1 Effects of ultraviolet radiation on human health 3

1.2 Epidemiology of skin cancer 5

1.3 Population groups at increased risk of photocarcinogenesis 7

1.4 Skin cancer primary prevention 9

1.5 Skin cancer secondary prevention 12

1.6 Skin cancer prevention campaigns 13

2 AIMS OF THE THESIS 15

3 EVALUATION OF A SUN SAFETY EDUCATION PROGRAMME FOR PRIMARY SCHOOL STUDENTS IN SWITZERLAND (PROJECT I) 19

3.1 Abstract 21

3.2 Introduction 22

3.3 Methods 22

3.4 Results 24

3.5 Discussion 31

4 OUTDOOR WORKERS' SUN-RELATED KNOWLEDGE, ATTITUDES, AND PROTECTIVE BEHAVIOURS: A SYSTEMATIC REVIEW OF CROSS-SECTIONAL AND INTERVENTIONAL STUDIES (PROJECT II) 35

4.1 Abstract 37

4.2 Introduction 38

4.3 Methods 39

4.4 Results 40

4.5 Discussion 52

5 SUN PROTECTIVE BEHAVIOUR OF VACATIONERS SPENDING HOLIDAYS IN THE TROPICS AND SUBTROPICS (PROJECT III) 55

5.1 Abstract 57

5.2 Introduction 58

5.3 Methods 59

5.4 Results 60
5.5 Discussion 66
6 SKIN CANCER PREVENTION, TANNING, AND VITAMIN D: A CONTENT ANALYSIS OF PRINT MEDIA IN GERMANY AND SWITZERLAND (PROJECT IV) 69
6.1 Abstract 71
6.2 Introduction 72
6.3 Methods 72
6.4 Results 74
6.5 Discussion 82
7 EPIDEMIOLOGY OF BASAL CELL CARCINOMA IN THE UK: INCIDENCE, LIFESTYLE FACTORS, AND COMORBIDITIES (PROJECT V) 85
7.1 Abstract 87
7.2 Introduction 87
7.3 Methods 88
7.4 Results 89
7.5 Discussion 93
8 NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND THE RISK OF NONMELANOMA SKIN CANCER (PROJECT VI) 95
8.1 Abstract 97
8.2 Introduction 98
8.3 Methods 99
8.4 Results 102
8.5 Discussion 109
9 FINAL DISCUSSION AND OUTLOOK 111
10 SYNOPSIS 119
APPENDIX 123
Project I: Self-administered questionnaire 125
Project III: Questionnaires for standardised face-to-face interviews 127
Project V: Unpublished supplementary material 137
REFERENCES 139

LIST OF ABBREVIATIONS

ASR	Age-standardised incidence rate
BCC	Basal cell carcinoma
BMI	Body mass index
CI	Confidence interval
CMM	Cutaneous malignant melanoma
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase
CPRD	Clinical Practice Research Datalink
DFMO	Difluoromethylornithine
DNA	Deoxyribonucleic acid
GP	General practitioner
HPV	Human papilloma virus
IBD	Inflammatory bowel disease
ICNIRP	International Commission on Non-Ionising Radiation Protection
IR	Incidence rate
MHRA	Medicines and Healthcare Products Regulatory Agency
NMSC	Nonmelanoma skin cancer
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds ratio
OR_{adj}	Adjusted odds ratio
OTR	Organ transplant recipient
py	Person-years
RA	Rheumatoid arthritis
RCT	Randomised controlled trial

Rx	Medical prescription
SCC	Squamous cell carcinoma
SD	Standard deviation
SPF	Sun Protection Factor
SSR	Standardised rate ratio
UK	United Kingdom
UPF	Ultraviolet Protection Factor
USA	United States of America
UV	Ultraviolet
UVA	Ultraviolet A radiation
UVB	Ultraviolet B radiation
UVC	Ultraviolet C radiation
UVI	Ultraviolet Index
UVR	Ultraviolet radiation

SUMMARY

Solar ultraviolet radiation has been acknowledged as the main culprit for the three major types of skin cancer which are among the most numerous (basal cell carcinoma [BCC], squamous cell carcinoma [SCC]) and most dangerous (cutaneous malignant melanoma) malignancies in Caucasian populations.

The present thesis comprises six individual projects providing a multifaceted perspective on the prevention of these tumours.

Project I evaluated a school-based sun safety education programme developed by the Swiss Cancer Leagues. Primary school students in the Canton of Zurich (North-Eastern Switzerland) were asked to answer a questionnaire regarding their sun-related knowledge, behaviour, and sunburn experience shortly before and one year after the intervention (repeated cross-sectional assessment). Based on the data from more than 3000 students, the sun safety education programme was effective in sustainably improving children's sun-related knowledge and possibly to some extent in decreasing sunburn rates, but had no obvious impact on the examined sun protective behaviours (use of sunscreen, seeking shade).

Project II represents a systematic review of cross-sectional and interventional studies on sun-related knowledge, attitudes, and protective behaviours of outdoor workers. The 52 relevant publications identified through an electronic search of medical literature databases (PubMed, Embase, PsycINFO) and an extensive hand search suggested that outdoor workers' sun protective behaviours are largely inadequate and sunburn rates are high (50-80% per season). However, there is evidence that sun safety education in outdoor occupational settings is effective in increasing workers' protective behaviours and presumably also in reducing sunburn incidence.

Project III investigated sun protective behaviour and sunburn experience of vacationers spending holidays in the tropics or subtropics. The 1165 standardised face-to-face interviews conducted among air passengers waiting in the departure or baggage claim area at the Airport Basel-Mulhouse (Switzerland/France) and among vacationers waiting for pre-travel health advice at the Travel Clinic of the Swiss Tropical and Public Health Institute Basel (Switzerland) revealed that almost all respondents used sunscreen at the holiday destination. Nevertheless, wearing a sunhat and protective clothing as well as seeking shade were clearly less common sun protection methods. The assessed sunburn rate among the

324 interviewed returning air passengers was alarmingly high, with 44% having suffered from sunburn during their holiday stay.

Project IV comprehensively analysed the content and quality of 2103 print media articles pertaining to skin cancer prevention and related topics (solaria, vitamin D) published in Germany and Switzerland over a one-year period (2012-2013). Whereas skin cancer secondary prevention received little press attention, primary prevention was a frequently covered media topic. However, the delivered information was generally rather superficial. By far the most common and often sole sun protection recommendation made was the use of sunscreen. In total, 27% of all analysed articles contained misleading or erroneous statements which were mostly related to the use of sunscreen and vitamin D issues.

Projects V and VI are based on data derived from the Clinical Practice Research Datalink, a large, well-validated primary care database established in the United Kingdom (UK).

Project V estimated BCC incidence in the UK and characterised affected patients regarding lifestyle factors and comorbidities. The calculated age-standardised BCC incidence in adults rose from 119 to 165 per 100 000 person-years between the years 2000 and 2011. According to the matched case-control analysis including 57 121 BCC cases and 57 121 BCC-free controls, BCC risk was slightly increased in alcohol drinkers, but reduced in smokers and in individuals with a body mass index outside the normal range. BCC was associated with various comorbidities related to iatrogenic or non-iatrogenic immunosuppression.

Project VI explored whether patients regularly exposed to systemic nonsteroidal anti-inflammatory drugs (NSAIDs) are at a reduced risk of nonmelanoma skin cancer (NMSC). The matched case-control analysis comprised 65 398 BCC cases, 65 398 BCC-free controls, 7864 SCC cases, and 31 456 SCC-free controls. Overall, NSAID use was not negatively associated with BCC, but when looking exclusively at users of single NSAID substances there was a suggestion of a reduced BCC risk in regular users of aspirin and ibuprofen. SCC risk was slightly decreased in regular users of any NSAIDs, with the strongest risk reduction observed in current users of coxibs. These findings provide evidence that patients predisposed to NMSC may benefit from chemoprevention with NSAIDs.

Chapter 1

INTRODUCTION

1.1 Effects of ultraviolet radiation on human health

Sunlight is the main source of human exposure to ultraviolet radiation (UVR), albeit exposure through indoor tanning devices (subsequently referred to as solaria) is gaining increasing importance. In photobiology, UVR is commonly defined as the part of the electromagnetic spectrum spanning the wavelengths from 200nm to 400nm. It can be subdivided into UVA (UVAI: 400-340nm; UVAII: 340-320nm), UVB (320-290nm), and UVC (290-200 nm). The biological effects of solar UVR to skin and eyes are attributed to UVA and UVB, since UVC is virtually completely blocked by the terrestrial atmosphere.[1]

The erythema solare ('sunburn') represents the best-recognised, acute cutaneous response to UVR and is characterised by the classical signs of inflammation, such as redness, warmth, tenderness, and oedema. The energy-rich UVB photons are about 1000-fold more effective than UVA photons in inducing erythema. However, UVA contributes more than previously thought, given its predominance in the UVR component that reaches the Earth's surface.[2]

In addition, acute UVR exposure can provoke various photodermatoses. With a prevalence of up to 20%, the immunologically mediated polymorphous light eruption (colloquially termed 'sun allergy') is the commonest form. It particularly affects young women in temperate climates and is mostly triggered by UVA.[3,4]

Chronic effects of UVR on the skin comprise photocarcinogenesis, photoimmuno-suppression, and photoageing.[5]

Based on a large body of epidemiological and biological evidence, UVR has been acknowledged as the main culprit for the three major types of skin cancer, namely basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and cutaneous malignant melanoma (CMM).[6] First, the incidence of these tumours increases with decreasing latitude, i.e. with increasing ambient solar radiation. They most often affect fair-skinned sun sensitive individuals and are found in greatest density on sun-exposed body parts.[7] Secondly, UVR causes specific DNA lesions, either directly through photochemical reactions following absorption by DNA bases (primarily UVB) or indirectly through oxidative damage following absorption by other endogenous chromophores that generate reactive oxygen species (primarily UVA). If not repaired before replication, these DNA lesions may lead to mutations in the cellular genome and eventually to carcinogenesis. People with a genetic DNA repair defect (e.g. xeroderma pigmentosum patients) are hypersensitive to UVR and at a several-

fold increased risk of skin cancer.[8,9] Finally, the capacity of UVR to induce cutaneous malignancies has been experimentally demonstrated in animal models.[10-12]

The down regulation of the immune surveillance system upon UVR facilitates the growth of cancerous cells as well as the expression of latent herpes simplex and human papilloma viruses (HPVs).[13] The latter have been associated with cutaneous SCC, but it is still unclear whether they are causally involved in the development of the tumour.[14]

UVR is the most important extrinsic factor in skin ageing. As a consequence of damage to keratinocytes, melanocytes, fibroblasts, and endothelial cells, the clinical features of photoageing include epidermal atrophy, mottled pigmentation, lentigines (pigmented macules), wrinkling, elastosis (accumulation of fragmented, abnormally thickened elastin fibres), and telangiectasias (permanently dilated small blood vessels). Both UVA and UVB are involved in photoageing, but the longer wavelength UVA is considered the major contributor because it penetrates deeper into the dermis where the most striking histological changes are observed.[15-17]

Analogous to the sunburn of the skin, acute UVB exposure can damage the corneal epithelium and lead to a transient painful inflammation of the eyes known as photokeratitis or 'snow blindness'.[18]

Ocular disorders linked to chronic UVR exposure encompass some types of cataract, noncancerous conjunctival growths (pterygium, pinguecula), and SCC of the cornea and conjunctiva. Furthermore, there is some but not conclusive evidence for a role of UVR in the aetiology of ocular melanoma and age-related macular degeneration.[19,20]

The only recognised beneficial effect of UVR on human health is cutaneous vitamin D photosynthesis.[18] Its action spectrum is very similar to the one of sunburn, lying in the UVB portion of sunlight and peaking at around 300 nm. However, maximum vitamin D concentrations are already reached after exposure of a relatively small skin surface to UVR doses well below the minimal erythema dose. Thus, incidental protected sun exposure usually results in vitamin D levels considered sufficient to maintain musculoskeletal health and potentially to prevent extra-skeletal disorders associated with vitamin D deficiency such as certain internal cancers and autoimmune diseases.[21,22] Interestingly, vitamin D has been shown to have a protective effect against UVB-induced photodamage *in vitro* and *in vivo*. It is therefore speculated that vitamin D photosynthesis may represent an evolutionary

conserved feedback mechanism to protect the skin from the deleterious consequences of UV irradiation.[23]

This thesis will focus on the prevention of skin cancer, which is from a public health point of view the most momentous adverse effect of UVR exposure.

The aims of the presented research projects are described in detail in Chapter 2 and include

- an evaluation of a school-based sun safety education programme,
- an overview of skin cancer prevention in outdoor occupational settings,
- an investigation of sun protective behaviour and sunburn experience of vacationers,
- a content analysis of print media related to skin cancer prevention,
- an investigation into the epidemiology of BCC,
- and an analysis of the impact of nonsteroidal anti-inflammatory drugs (NSAIDs) on the risk of BCC and SCC.

1.2 Epidemiology of skin cancer

BCC and SCC, which originate from keratinocytes and are collectively referred to as nonmelanoma skin cancer (NMSC), represent the most common malignancies in Caucasian populations. It is estimated that between two and three million cases of NMSC occur globally each year,[24] with roughly 80% of these being BCCs.[25] Incidence rates (IRs) increase substantially around the fifth decade and reach their maximum during the seventh and eighth decades of life.[26] By far the highest age-standardised incidence rates (ASRs) have been reported from Australia (> 1000/100 000 person-years [py] for BCC), where the risk of being treated for NMSC before the age of 70 years is more than 60%, followed by the USA (>170/100 000 py for BCC).[27,28] In Europe, the highest ASRs have been found in Switzerland, Italy, and the UK (> 70/100 000 py for BCC).[28] However, most of the available incidence data are derived from single local surveys, which are limited by sampling and underreporting. The true extent of the disease is difficult to determine, as cancer registries do not routinely record NMSC due to the large numbers of clinical diagnoses without histological confirmation, high cure rates, and lack of hospitalisations.[26,29] Moreover, the reported IRs and ASRs usually refer to an individual's first NMSC episode and do not take into account multiple primary lesions in the same patient. Yet figures based on first-time diagnoses are likely to underestimate the full burden of NMSC, given that the 3-year cumulative risks of

developing a subsequent BCC after the first BCC and a subsequent SCC after the first SCC are as high as 44% and 18%, respectively.[30]

Metastasis from NMSC, especially from BCC, is rare and mortality is low. Nevertheless, the tumours cause significant morbidity (local tissue destruction, high recurrence rates)[26,31] and costs to the health care system.[32,33]

With around 230 000 newly affected patients globally each year, the incidence of CMM, which derives from melanocytes, is much lower than the incidence of NMSC. In developed regions, CMM is currently the eighth most frequently diagnosed cancer (excluding NMSC). Among adults under 40 years of age, it ranks at the second position, as – unlike NMSC – a considerable proportion of CMMs occur relatively early in life. The highest world ASRs have been registered in New Zealand and Australia (35.8 and 34.9/100 000 py), followed by Switzerland (20.3/100 000 py), the Netherlands (19.4/100 000 py), and Scandinavia (up to 19.2/100 000 py). High ASRs have also been reported from the UK (14.6/100 000 py) and the USA (14.3/100 000 py).[34] As is NMSC, CMM is much less common in people of colour than in people of Caucasian ancestry.[35]

CMM has a high malignant potency, meaning that metastatic spread may already arise from very small tumour masses.[36] Once the tumour has metastasised to distant sites, it is almost always incurable and the median survival time is only between 6 and 9 months.[37] Mortality rates recorded for New Zealand, Australia, Switzerland, the Netherlands, and Norway come to 4.7, 4.0, 2.4, 2.8, and 3.6 per 100 000 py, respectively.[34]

Along with people's sun seeking behaviour and the popularity of indoor tanning, the worldwide incidences of both NMSC and CMM have dramatically increased over the past decades. However, this trend has partly also been explained by improved registration procedures and growing awareness of skin cancer among health professionals and the public resulting in a rising number of tumour diagnoses at a very early stage. Accordingly, in many countries, mortality rates have increased less prominently, remained stable, or even decreased in recent years.[28,38-40]

1.3 Population groups at increased risk of photocarcinogenesis

Aside from individual risk factors (genetics, phenotypic characteristics such as fair skin and hair colour, freckles, and a high number of naevi),[41-43] certain population groups are particularly prone to photodamage and therefore present essential target audiences for skin cancer prevention campaigns.

1.3.1 Children

Although skin cancer itself is rare in children, extensive UVR exposure during childhood has been associated with an increased risk of cutaneous carcinogenesis later in life.[44] Studies comparing the occurrence of CMM in populations who have migrated between areas with different levels of ambient UVR (so-called migration studies) revealed that individuals who were exposed to intense sunlight early in life had a disproportionally high risk of developing CMM, even if the period of exposure was relatively brief.[45] In accordance, several case-control studies have suggested a positive relationship between childhood sun exposure, BCC,[46,47] and SCC.[48-50] Biological plausibility supports these findings. Due to different anatomic structures, epidermal and dermal stem cells may be more exposed to UVR in children's skin compared to adult skin. In children, the epidermodermal junction is still reduced, possibly leading to increased UVR exposure of some areas of the basal layer including melanocytes and interfollicular epidermal stem cells.[51] Moreover, epithelial and melanocytic stem cells located in the bulge region of the hair follicle may be less UV-protected in vellus hair, which is the predominant hair type in children, compared to terminal hair.[52] In addition, UVR might have the greatest biological effectiveness in initiating CMM during peak melanocytic activity which occurs early in life.[53]

1.3.2 Outdoor workers

People who regularly work outdoors by virtue of their employment (e.g. construction workers, farmers, gardeners, and mountain guides) receive about two to three times the annual UVR exposure doses of people who principally work indoors.[54] As a consequence, outdoor workers are at significantly increased risk of BCC[55] and to a greater extent of SCC,[56] which has been particularly associated with chronic-cumulative sun exposure.[7] A potential relationship between outdoor occupation and the occurrence of CMM, whose pathogenesis has been linked to intense intermittent (i.e. recreational) sun exposure rather than chronic sun exposure, is still under discussion.[7] However, there is growing evidence that CMM on

habitually sun-exposed body sites such as the face, head, and neck ('chronic sun damage melanoma') is more common among outdoor workers, whereas CMM on habitually covered body sites ('non-chronic sun damage melanoma') is more common among office workers.[57]

In certain countries and under defined circumstances, skin cancer caused by solar UVR is recognised as an occupational disease for which compensation claims can be made.[58,59]

1.3.3 Travellers to sunny destinations

While during the 19th and early 20th century, people of higher social classes carefully avoided excessive sunlight to prevent sunburn and damage to complexion, recreational sunbathing gained rising popularity and a suntan became a symbol of well-being and fashion in the late 1920s.[60,61] Social changes after World War II and the increasingly easy accessibility to air travel have enabled a wide public to spend year-round holidays at tropical or subtropical destinations with intense UV irradiation.[62] Non-photoadapted skin is thereby typically exposed to substantial amounts of UVR,[63] either accidentally or intentionally in order to acquire a tan, which is for many people still an express purpose of vacations.[64,65] Accordingly, sunburn rates among travellers were found to be as high as 100% already after a short holiday in the sun.[66] A history of sunburns has been clearly linked to the development of skin cancer (in particular CMM and BCC),[7] but it is at present not known whether sunburns are simply a marker for intense intermittent sun exposure or an additional independent risk factor.[38]

1.3.4 Organ transplant recipients

Compared to the general population, organ transplant recipients (OTRs) have an approximately 100-fold, 10-fold, and 2-fold increased risk of developing SCC, BCC, and CMM, respectively. Furthermore, the tumours tend to be larger and more aggressive in OTRs than in immunocompetent patients.[67,68] These observable facts are largely explained by the chronic iatrogenic immunosuppression to prevent organ rejection, which eases unrestricted proliferation of cancer-initiated cells. In addition, certain immunosuppressive drugs exert specific photosensitising and oncogenic effects beyond immunosuppression.[69-71] Even so, UVR remains the main aetiological factor for posttransplant cutaneous malignancies.[69] In the pathogenesis of SCC, HPV infections are also thought to play a crucial role, since in OTRs HPV DNA can be detected in up to 90% of the lesions (in non-immunosuppressed SCC patients the prevalence of HPV infections is lower, although it still exceeds 50%).[70]

1.4 Skin cancer primary prevention

1.4.1 Sun protection

As exposure to solar UVR is the major modifiable risk factor for skin cancer, sun protection represents the most important primary prevention strategy. In decreasing order of effectiveness, recommended sun protection measures comprise seeking shade, wearing protective clothing including a sunhat, and applying sunscreen.[72,73]

The best method to reduce UVR exposure is to avoid the sun during the 4-hour period around solar noon when 50-60% of the total daily UVR dose reaches the earth's surface.[1] The time of solar noon depends on the geographical position. In Switzerland, for example, the sun reaches its zenith at about 13.30 pm, whereas at the Spanish Atlantic coast, noon is not until 14.40 pm (Central European Summer Time).[74]

Typical shade structures such as canopies, beach umbrellas, and dense foliage generally reflect or absorb direct UVR, but the scattered component still reaches into the shade. Hence shade from direct sunlight alone does not offer sufficient UV protection.[75,76]

Clothes covering large areas of the skin are a suitable means of photoprotection. However, the amount of UVR filtered out by textiles is influenced by various factors: (1.) weave density (thick, tightly woven fabrics transmit less UVR than thin, loosely woven fabrics), (2.) material (wool and synthetic materials provide more UV protection than cotton), (3.) colour (dark fabrics absorb more UVR than light fabrics), (4.) tension (loose-fitting clothes protect better than tight-fitting, stretched clothes), and (5.) condition (wet, worn, and faded textiles offer reduced UV protection). Excellent protection is provided by clothes pre-treated with UV absorbers.[72,77]

Sunhats should ideally have a 360° brim of at least 7.5 cm width in order to shade the face, ears, and neck.[78]

Complementary to the aforementioned sun protection measures, or in situations where they are not applicable, the use of sunscreen is advised. In a community-based randomised controlled trial (RCT), regular application of these topical photoprotectants has proven effective in preventing NMSC and CMM as well as premature skin ageing.[79-81]

The active agents of sunscreens are broadly divided into two categories: inorganic (formerly physical) and organic (formerly chemical) UV filters. Inorganic UV filters include the metal

oxides titanium dioxide and zinc oxide which attenuate UVR by absorption, scattering, and reflection. Organic UV filters such as salicylates, cinnamates, camphor derivatives, benzophenones, and dibenzoylmethanes are aromatic compounds with multiple conjugated double bonds which act by absorbing UVR. Through delocalization of electrons upon absorption of UV photons, the molecules are transferred into an excited, energy-rich state. By dissipating energy in form of heat or fluorescent radiation, they return to their stable, low-energy ground state and can be activated again.[82]

Depending on their absorption spectrum, UV filters are further classified as UVA, UVB, and UVA+UVB (broad-spectrum) absorbers. Modern sunscreens usually contain a combination of different UV filters in order to protect against the entire UV spectrum as do more natural forms of sun protection (shade, clothing).[83]

The level of protection provided by a specific sunscreen product is indicated by the Sun Protection Factor (SPF). The SPF is calculated as the ratio of the UVR dose that induces the first perceptible erythema on sunscreen-protected skin to the UVR dose that induces the same erythema on unprotected skin and is therefore principally a measure of UVB protection.[84] In the European Commission Recommendation on the efficacy of sunscreen products and the claims made relating thereto, four protection categories for sunscreens have been defined: low protection (SPF 6, 10), medium protection (SPF 15, 20, 25), high protection (SPF 30, 50), and very high protection (SPF 50+). The degree of UVA protection is related to the SPF value. In order to offer minimum recommended UVA protection as expressed by the UVA logo, the UVA protection factor (determined *in vitro* or *in vivo* using the Persistent Pigment Darkening method) must be equal or greater than 1/3 SPF.[85,86]

Yet the actual protection offered by sunscreens is greatly determined by the mode of application. Sunscreen ought to be applied liberally and evenly to all sun-exposed skin areas before going out into the sun. Furthermore, it should be regularly reapplied to compensate for initial underapplication and to replace product that may have been removed by sweat, water, towelling, or friction with clothing or sand.[72,87]

1.4.2 Systemic chemoprevention

As poor compliance limits the effectiveness of topical sun protection, there has been growing interest in exploring orally administered natural and synthetic agents for skin cancer prevention.

In animal and *in vitro* studies, a number of secondary plant compounds such as carotenoids and polyphenols have been shown to exert antioxidant, anti-inflammatory, immunomodulatory, and anticarcinogenic properties (DNA repair activities, inhibition of proliferation and angiogenesis, induction of apoptosis).[88,89] In humans, oral supplementation with beta-carotene or green tea catechins over several weeks proved effective in modestly increasing the skin's erythema threshold.[90,91] However, large RCTs evaluating photocarcinogenesis as an outcome failed to demonstrate protective effects (carotenoids)[92] or are lacking at present (polyphenols).[93,94]

Among synthetic pharmaceuticals considered as chemopreventive agents, retinoids are the most studied. Through interaction with nuclear retinoid receptors, they alter gene transcription and modulate cell proliferation, differentiation, and apoptosis. The evidence for a role in CMM prevention is still preliminary, but numerous RCTs showed that retinoids significantly reduce the risk of NMSC. Yet substantial adverse side effects limit their use to selected high risk patients (e.g. OTRs, xeroderma pigmentosum patients) when the benefits appear greater than the risks.[94-96]

Further potential candidates for skin cancer chemoprevention include antilipidemics (statins and fibrates), NSAIDs, and difluoromethylornithine (DFMO). Antilipidemics (principally investigated in the chemoprevention of CMM) exhibit anti-inflammatory, immunomodulatory, anti-proliferative, angiostatic, and pro-apoptotic activities through various molecular mechanisms, e.g. through the inhibition of post-translational isoprenylation required by Ras and other signalling proteins. NSAIDs and DFMO inhibit cyclooxygenase (COX) and ornithine decarboxylase, respectively, both enzymes which are induced by UVR and correlated with tumour formation. Although these substances yielded promising results in preclinical studies, clinical efficacy and safety is yet to be determined.[93-97]

1.4.3 Avoidance of solaria

Similar to solar UVR, artificial UVR emitted from solaria has been classified as carcinogenic to humans.[6] According to several comprehensive meta-analyses, people with a history of indoor tanning are at significantly increased risk of contracting both NMSC and CMM.[98-100] This does not seem surprising considering that tanning beds often have higher UVR emissions than mid-latitude summer sunlight.[101,102] It has been estimated that more than 450 000 new NMSC cases and 10 000 CMM cases are attributable to indoor tanning each year in the USA, Europe, and Australia and could thus be prevented by strict avoidance of solaria.[103]

1.5 Skin cancer secondary prevention

Secondary prevention (i.e. early detection) of skin cancer aims at averting advanced tumour stages and thereby at reducing morbidity and mortality.

Skin cancer fulfils several criteria making it amenable to population-based screening programmes: the disease is a common health problem, there is a safe and inexpensive screening method (suspected skin lesions are readily detectable by visual inspection of the entire body surface), and the disease is highly curable at low costs when diagnosed early. Nonetheless, many health organisations do not recommend routine skin cancer screening for the general population, since to date no scientific evidence exists from RCTs proving its effectiveness. The worldwide first nation-wide skin cancer screening programme was implemented in 2008 in Germany, where residents with statutory health insurance aged 35 years or older have been entitled to a biennial skin cancer screening by a trained general practitioner (GP) or dermatologist. Evaluation of this programme is currently under way, but preliminary findings from the preceding pilot study in Schleswig-Holstein, the northernmost federal state of Germany, already indicate that population-based screening has led to favourable changes in tumour stage distribution and a marked reduction in CMM mortality.[104-106]

Beside skin examinations by health professionals, regular skin self-examinations represent the second pillar of skin cancer secondary prevention. However, the few studies on this topic suggest that the lay public is often not able to distinguish benign from potentially malignant skin lesions that warrant a consultation with a physician for further evaluation.[107]

1.6 Skin cancer prevention campaigns

The message that sun exposure is associated with the development of skin cancer started to be directed to the public in the 1930s, when UVR became widely recognised as a carcinogen. By the 1950s, articles in the popular press pertaining to suntanning and sunburn fairly commonly mentioned the risks of photoageing and skin cancer from excessive UVR exposure.[108] In 1980, the first large social marketing campaign to raise awareness of skin cancer prevention was launched in Australia. In the USA and several European countries, population-wide skin cancer prevention programmes were initiated in the mid- and late 1980s. Using mass media and specific interventions tailored to various high-risk settings, these campaigns have aimed to increase people's knowledge about skin cancer, to decrease the desirability of a suntan, to promote sun protective behaviour, and to foster early detection of malignant skin lesions. In addition, particularly in Australia, the campaigns placed emphasis on providing shade in public areas and on encouraging organisations such as local governments, schools, and outdoor workplaces to adopt sun protection policies.[109,110] The Australian campaigns have been thoroughly evaluated and have proven effective in improving people's sun protective behaviour and in reducing sunburn incidences.[111] Moreover, there are indications of declining skin cancer incidences among younger generations who have been exposed for the greatest portion of their life to prevention messages.[38,112,113] In a number of other countries where sun-safety interventions have not been similarly coordinated and sustained, the achieved increase in sun-related knowledge has not yet transferred into meaningful behavioural changes and reduced sunburn as well as skin cancer rates.[109,114-116]

Yet in several parts of the world, the growing awareness of skin cancer has resulted in progress in early detection and consequently, despite an increase in incidences, in stable or even declining skin cancer mortality.[28,38-40]

Chapter 2

AIMS OF THE THESIS

The six individual projects presented within this thesis provide a multifaceted perspective on the prevention of UV-induced cancers of the skin.

Project I aimed at evaluating the impact of a school-based sun safety education programme developed by the Swiss Cancer Leagues on primary school students' sun-related knowledge, protective behaviours, and sunburn rates using a pretest-posttest study design.

The objectives of **Project II** were first to present an overview of outdoor workers' sun-related knowledge, attitudes, and protective behaviours, and second to assess the effectiveness of sun safety education programmes in outdoor occupational settings by conducting a systematic review of the available scientific literature.

Project III sought to investigate sun protective behaviours and sunburn experience of vacationers spending holidays at sunny destinations by means of cross-sectional surveys.

To gain insight into the way skin cancer prevention messages issued by health organisations reach the public, **Project IV** comprehensively analysed the content and quality of print media articles pertaining to skin cancer prevention, solaria, and vitamin D published in Germany and Switzerland over a one-year period between 2012 and 2013.

Based on data derived from the Clinical Practice Research Datalink (CPRD), a large, well-validated primary care database established in the UK, **Project V** aimed at estimating the burden of BCC on the health care system by providing age-standardised UK BCC incidence rates for the time period between 2000 and 2011. Furthermore, in a case-control analysis, the identified BCC patients were characterised regarding lifestyle factors and comorbidities.

In **Project VI**, CPRD data was used to conduct a population-based case-control study investigating whether regular exposure to systemically administered NSAIDs may reduce the risk of NMSC (BCC and SCC).

Chapter 3

PROJECT I

Evaluation of a sun safety education programme for primary school students in Switzerland

Daphne Reinau, Christoph R. Meier, Nathalie Gerber, Christian Surber

European Journal of Cancer Prevention 2014; 23: 303-9

3.1 Abstract

Background The incidence of skin cancer has increased worldwide, with rates being especially high in Switzerland compared to other European countries. Extensive sun exposure during childhood is considered a key factor for skin carcinogenesis.

Objectives To evaluate the impact of a school-based sun safety education programme developed by the Swiss Cancer Leagues on primary school students' sun-related knowledge, protective behaviours, and sunburn rates.

Methods In summer 2011, one-hour sun safety education sessions were held at 33 primary schools throughout the Canton of Zurich (North-Eastern Switzerland). Children in the participating school classes (1st, 2nd, and 3rd graders) answered a questionnaire regarding their sun-related knowledge, behaviours, and sunburn experience shortly before and one year after the intervention.

Results 3110 completed pre-test, and 1738 post-test questionnaires were eligible for analysis. The evaluation of pre-test data revealed considerable room for improvement regarding sun-related knowledge, considering that merely a good half of the children were conscious that the sun may present a hazard to health. Overall, more than 95% of students benefited from the protection of sunscreen (application by parents: 73%; application by child: 66%), but only 36% stated to generally seek shade on sunny days. After the intervention, knowledge increased strongly and significantly ($p<0.0001$), but there was no change in sun protective behaviours (use of sunscreen, seeking shade). However, we observed a non-significant trend towards decreased sunburn rates.

Conclusions The brief one-time sun safety education sessions were effective in sustainably improving children's sun-related knowledge and possibly to some extent in decreasing their sunburn rates.

3.2 Introduction

Extensive exposure to solar ultraviolet radiation (UVR) has been associated with the development of cataract and ocular neoplasms and is the main cause for all major types of skin cancer.[6,117] Along with peoples' sun-seeking behaviour, the incidence of both melanoma and non-melanoma skin cancer in Caucasian populations has dramatically increased over the last decades, with rates being especially high in Switzerland compared to other European countries.[28,38]

Based on epidemiological studies, intense sun exposure during childhood is considered to play a key role in skin carcinogenesis later in life.[45,46,48] Postulated biological mechanisms are an enhanced sensitivity of melanocytes and an increased exposure of epidermal and dermal stem cells (e.g. due to a reduced epidermodermal junction) in children's skin to UVR. [51,118]

Against this background and in view of the fact that preventative habits established during childhood are more likely to be sustainable throughout an individual's lifetime than those acquired during adolescence and adulthood, promoting sun protection in children is an integral part of successful skin cancer prevention.[119]

The Swiss Cancer Leagues have developed a sun safety education programme aimed at primary school students which has been conducted annually during early summer for more than ten years in public schools in several Cantons of Switzerland.

The objective of the present study was to evaluate the impact of the 2011 campaign on children's sun-related knowledge, protective behaviours, and sunburn rates in the Canton of Zurich (North-Eastern Switzerland).

3.3 Methods

3.3.1 Participants and setting

Between May and July 2011, sun safety education sessions targeted at 1st, 2nd, and 3rd graders were held at 33 primary schools throughout the Canton of Zurich. To evaluate the effectiveness of the interventional programme, children in the participating school classes were asked to answer a questionnaire before and after the education session (repeated cross-sectional assessment). Pre-test questionnaires were sent to the class teachers in February 2011 and had to be returned by the day of the education session (one telephone

reminder in April). Post-test questionnaires were completed one year later (April to May 2012). The children filled in both questionnaires at school under supervision of the teacher. Participation was on a voluntary basis.

3.3.2 Interventional programme

The education programme developed by the Swiss Cancer Leagues included several interactive games (described in detail in Fig. 3-1) which aimed essentially at conveying the following sun protection messages: (1.) seeking shade during peak UVR periods (11:00 a.m. - 3:00 p.m.), (2.) wearing a hat with neck flap, protective clothing, and sunglasses, and (3.) applying sunscreen with a sun protection factor of at least 30 on uncovered body parts.

All children received a free sunscreen sample and a sunhat with neck flap.

The education sessions were conducted by four trained staff members of the Zurich Cancer League during a single school lesson (45-50 min) in the presence of a teacher. A maximum of 30 children participated in each session.

Teachers were encouraged to implement sun protection measures during school activities.

3.3.3 Questionnaires

Both questionnaires (pre-test and post-test) were largely identical and consisted of 15 multiple choice items adapted from a previous survey.[120] Questions served primarily to assess children's sun-related knowledge, sun protective behaviours (use of sunscreen, seeking shade), and history of sunburn.

Whereas the pre-test questionnaire prompted children to report if they had *ever* suffered from sunburn, the post-test questionnaire asked specifically for sunburns during the year preceding the survey.

Because all students present in class were encouraged to complete the questionnaires, we added an additional item to the post-test (in place of a knowledge question that did not prove informative in the pre-test) in order to clarify whether or not the child attended the sun safety education lesson the year before.

From the number of correctly answered knowledge items, we calculated a knowledge score (max. 14 points) and classified sun-related knowledge accordingly as 'high' (13-14 points), 'medium' (11-12 points) or 'low' (0-10 points).

3.3.4 Statistical analysis and outcome variables

First we examined the pre-test data separately using descriptive statistics (relative frequencies) and logistic regression analyses. We calculated crude and adjusted odds ratios (OR) as well as the corresponding 95% confidence intervals (CI) to evaluate the associations between several predictor variables (e.g. demographic data) and the following outcomes: low sun-related knowledge, unfavourable sun protective behaviours (not using sunscreen, not seeking shade), and positive history of sunburn. For each outcome, a separate regression model was built. ORs were adjusted for all variables in the model.

We thereafter compared the pre-test data with the post-test data to investigate the impact of the interventional programme on the aforementioned outcomes. Because the questionnaires did not include personal data, we were unable to link individual students' answers from both surveys and thus combined the two samples (pre-test and post-test) in one logistic regression model (separately for each outcome), defining the predictor variable as intervention status: pre-test, post-test without intervention (children who did not attend the interventional programme, internal control group), and post-test with intervention (children who attended the interventional programme, intervention group). ORs were adjusted for sex, age, hair colour, and area of residence.

Area of residence was classified as urban, if the place of school had more than 15 000 inhabitants, and as rural, if the place of school had less than 15 000 inhabitants.[121]

We performed all analyses using SAS 9.3 software (SAS Institute, Cary, NC) and defined statistical significance at the alpha-level of 0.05.

3.4 Results

3.4.1 Study population

We received a total of 3110 completed pre-test questionnaires from all 33 primary schools which subsequently joined the sun safety education programme (assuming a number of 100 eligible students per school, this corresponds to a participation rate of more than 90%).

One year later, 2006 post-test questionnaires were returned (participation rate > 60%). Of the 2006 children who completed the post-test, 1518 (75.7%) had attended the sun safety education session the year before, and 220 (11.0%) had not. The intervention status of the

remaining 268 children (13.4%) was unknown and they were therefore excluded from further analyses.

Table 3-1 presents the demographic characteristics of the study population.

3.4.2 Analysis of pre-test data

Sun-related knowledge

Knowledge about adverse health effects of extensive sun exposure and about sun protection was high, medium, and low in 39.7%, 35.4%, and 24.9% of all students, respectively.

In the multivariate logistic regression analysis (cases: low knowledge, n=774; controls: high knowledge, n=1235; predictor variables studied: sex, age, hair colour, area of residence), low knowledge was significantly associated with lower age ($OR_{6\text{-}7\text{-year olds}}$: 1.45; 95% CI: 1.03-2.06; reference group: 10-11-year olds) and dark hair colour (OR: 1.81; 95% CI: 1.49-2.21; reference group: fair hair colour).

More than half (57.8%) of the respondents agreed with the statement 'the sun can be hazardous to me', 17.8% disagreed, and 24.4% ticked the box 'I don't know'.

Most children considered sunshade (91.7%), sunscreen (89.2%), sunhat (76.7%), and sunglasses (73.7%) as useful sun protective items, but less than half (43.4%) knew that also T-shirts provide good sun protection.

Sun protective behaviours

Of all respondents, 71.3% said that they had been informed by their parents how to protect from the sun. About the same percentage (72.8%) stated that the parents applied sunscreen to them, 65.7% applied sunscreen themselves. Less than 5% did not benefit from the protection of sunscreen (application neither by parents nor by child).

According to the multivariate logistic regression analysis, not using sunscreen (application by child) was significantly associated with younger age, male sex, not seeking shade, and living in a family where sun protection is not a topic of conversation (see Table 3-2).

Though younger children used sunscreen less often themselves than older children, they were more often protected with sunscreen by their parents.

The sex difference was only evident from the age of 8 years on and became more pronounced with further increasing age.

Merely 36.2% of the students stated to generally seek shade on sunny days, 58.4% and 3.0% reported to do so only sometimes or never, respectively (no data available for the remaining 2.4%).

The multivariate logistic regression analysis for not seeking shade (cases: students who seek shade only sometimes or never, n=1908; controls: students who generally seek shade, n=1126; predictor variables studied: sex, age, hair colour, area of residence, sun-related knowledge, sun protection as a topic of conversation in parental home) revealed no sex differences. However, there was a significant relationship between not seeking shade, increasing age ($OR_{10\text{-}11\text{-year olds}}$: 1.54; 95% CI: 1.16-2.06; reference group: 6-7-year olds), and living in a family where sun protection is not a topic of conversation (OR: 1.54; 95% CI: 1.23-1.91).

Area of residence, sun-related knowledge, and hair colour had neither an impact on the use of sunscreen (application by children or parents) nor on seeking shade.

Sunburns

Overall, 42.5% of children reported a positive history of sunburn (at least one sunburn during lifetime), and 47.7% stated to have never experienced sunburn (the remaining 10.8% did not know).

In the multivariate logistic regression analysis, we identified male sex, higher age, fair hair colour, rural area of residence, and not seeking shade as predictors for a positive sunburn history. The use of sunscreen had no influence (see Table 3-3).

3.4.3 Impact of the interventional programme

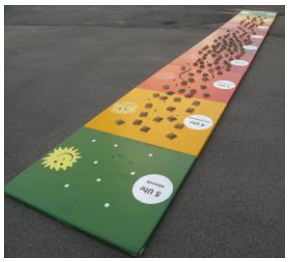
Table 3-4 summarises the effects of the sun safety education programme.

While sun-related knowledge increased strongly and significantly after the intervention, we observed no change in sun protective behaviours (use of sunscreen, seeking shade).

Due to different recall periods (ever vs. one year preceding the survey), a comparison of sunburn rates between pre-test and post-test was not reasonable. However, we compared sunburn rates reported in the post-test between children who had attended the education session the year before and those who had not. We found some evidence for a reduction in sunburn rates in the intervention group, albeit statistical significance was narrowly missed.

Memory game

- Material: pictures relating to sun protection attached in plastic cones
- Procedure: after each correctly matched pair, the respective picture was discussed with regard to sun protection means



Sun path

- Material: wooden board (450 x 80 cm) covered with pointed pieces of wood in different sizes, representing the intensity of the sun during the course of the day
- Procedure: while walking barefoot over the sun path, children could experience with their senses how strongly the sun 'stings' at different times of the day

Sun labyrinth

- Material: wooden labyrinth covered with reflective mirror foil; small metal balls; polarized sunglasses
- Procedure: children had to wear sunglasses in order to direct the metal balls through the labyrinth (game only conducted under sunny weather conditions)

Sun slingshot

- Material: wooden sun with painted face and a mouth opening attached to a stand (height: 160 cm); tennis ball; sunscreen sample
- Procedure: each hit with the tennis ball through the sun's mouth opening triggered a mechanism which released a sunscreen sample from the back side

Figure 3-1 Interactive games conducted during the sun safety education sessions (incomplete selection)

Table 3-1 Demographic characteristics of the study population

		Pre-test	Post-test with intervention	Post-test without intervention
Total	n (%)	3110 (100)	1518 (100)	220 (100)
Sex				
Male	n (%)	1536 (49.4)	721 (47.5)	123 (55.9)
Female	n (%)	1574 (50.6)	797 (52.5)	97 (44.1)
Hair colour				
Fair (red, blond)	n (%)	1061 (34.1)	544 (35.8)	59 (26.8)
Dark (brown, black)	n (%)	2049 (65.9)	974 (64.2)	161 (73.2)
Area of residence				
Urban	n (%)	1328 (42.7)	729 (48.1)	118 (53.7)
Rural	n (%)	1717 (55.2)	485 (32.0)	49 (22.3)
Unknown	n (%)	65 (2.1)	304 (20.0)	53 (24.1)
Age	mean (SD, range)	8.17 (1.00, 6-11)	8.96 (0.92, 6-12)	8.56 (1.23, 6-12)

SD, standard deviation

Table 3-2 Multivariate logistic regression analysis for the use of sunscreen (pre-test data)

	Cases: No use of sunscreen (application by child) Controls: Use of sunscreen (application by child)				
	Cases	Controls	OR*	(95% CI)	p-value
Sex					
Male	437	983	1.00	Referent	
Female	380	1061	0.82	(0.69-0.97)	0.02
Age group					
6-7 years	292	548	1.00	Referent	
8 years	273	634	0.82	(0.67-1.00)	0.05
9 years	192	663	0.55	(0.44-0.69)	<0.0001
10-11 years	60	199	0.55	(0.40-0.77)	0.0004
Hair colour					
Dark	532	1370	1.00	Referent	
Fair	285	674	1.09	(0.91-1.30)	0.36
Area of residence					
Rural	433	1148	1.00	Referent	
Urban	367	856	1.16	(0.98-1.37)	0.09
Seeking shade					
Generally	268	799	1.00	Referent	
Sometimes	497	1151	1.33	(1.11-1.58)	0.002
Never	32	52	1.62	(1.00-2.60)	0.05
Sun-related knowledge					
High	322	824	1.00	Referent	
Medium	291	714	0.95	(0.79-1.16)	0.62
Low	204	506	0.91	(0.73-1.13)	0.39
Sun protection is topic of conversation in parental home					
Yes	547	1539	1.00	Referent	
No	148	284	1.33	(1.06-1.68)	0.01

CI, confidence interval; OR, odds ratio
* adjusted for all variables listed in the table

Table 3-3 Multivariate logistic regression analysis for a positive history of sunburn (pre-test data)

	Cases: Positive history of sunburn (at least one sunburn during lifetime) Controls: No history of sunburn				
	Cases	Controls	OR*	(95% CI)	p-value
Sex					
Male	635	770	1.00	Referent	
Female	687	683	0.81	(0.70-0.95)	0.01
Age group					
6-7 years	337	469	1.00	Referent	
8 years	424	461	1.26	(1.04-1.54)	0.02
9 years	426	411	1.45	(1.19-1.77)	0.0003
10-11 years	135	112	1.64	(1.22-2.20)	0.001
Hair colour					
Dark	800	1020	1.00	Referent	
Fair	522	433	1.52	(1.29-1.78)	<0.0001
Area of residence					
Rural	786	750	1.00	Referent	
Urban	502	678	0.72	(0.62-0.84)	<0.0001
Seeking shade					
Generally	448	574	1.00	Referent	
Sometimes	807	803	1.25	(1.06-1.47)	0.01
Never	40	43	1.28	(0.81-2.01)	0.30
Use of sunscreen					
Yes, application by parents and child	593	656	1.00	Referent	
Yes, application only by child	255	268	1.01	(0.82-1.24)	0.93
Yes, application only by parents	308	340	1.00	(0.83-1.22)	0.96
No	23	30	0.86	(0.49-1.52)	0.60

CI, confidence interval; OR, odds ratio
* adjusted for all variables listed in the table

Table 3-4 Multivariate logistic regression analysis for the effects of the sun safety education programme

Cases:	**Low sun-related knowledge**				**No use of sunscreen (application by child)**				**Seeking shade only sometimes or never**				**At least 1 sunburn during the year before post-test**			
Controls:	High sun-related knowledge				Use of sunscreen (application by child)				Seeking shade generally				No sunburn during the year before post-test			
	Cases	Controls	OR* (95% CI)	p-value	Cases	Controls	OR* (95% CI)	p-value	Cases	Controls	OR* (95% CI)	p-value	Cases	Controls	OR* (95% CI)	p-value
Intervention status																
Pre-test	744	1235	1.00 Referent		817	2044	1.00 Referent		1908	1126	1.00 Referent		-	-	-	
Post-test without intervention	52	108	0.73 (0.51-1.05)	0.09	55	151	0.92 (0.66-1.28)	0.63	139	77	1.00 (0.74-1.34)	0.99	60	140	1.00 Referent	
Post-test with intervention	137	965	0.26 (0.21-0.32)	<0.0001	375	1068	1.04 (0.89-1.23)	0.61	965	524	0.96 (0.83-1.11)	0.55	317	1048	0.76 (0.53-1.07)	0.11

CI, confidence interval; OR, odds ratio
* adjusted for sex, age, hair colour, and area of residence

3.5 Discussion

The present investigation is on one of the largest studies evaluating a sun safety education programme for primary school students in Europe and includes data from more than 3000 children.

The results of the pre-test survey were well in line with those obtained in a cross-sectional study investigating sun-related knowledge and sun protective behaviours among school students in the Canton of Basel-Stadt (North-Western Switzerland) in 2010.[120]

We identified substantial room for improvement with regard to sun-related knowledge, considering that merely a good half of the surveyed children were conscious that the sun may present a hazard to health.

Applying sunscreen was a commonly used sun protection means, but only a minority of respondents stated to generally seek shade on sunny days. However, whereas the risk of sunburn slightly decreased in those who sought shade, we observed no such risk reduction in sunscreen users, a phenomenon which was likewise described by other authors [122-124] and can at least partly be attributed to a positive correlation of sunscreen use with extended duration of sun exposure.[125]

The increased odds of sunburn for children living in the country might be a consequence of a larger amount of time spent outdoors, since students from rural and urban areas did not differ regarding their sun protective behaviours.

A large body of evidence suggests that females are in general more likely to use sunscreen than males [126]. Interestingly, in our sample, this sex difference only became evident from the age of 8 years on and was more pronounced with further increasing age, which highlights the importance of social influences on sun protection habits.

Parents serve as particularly important role models for young children, as can be seen by the fact that favourable sun protective behaviours were significantly more common among students living in a family where sun protection was a topic of conversation. Accordingly, O'Riordan et al. found that sun protection practices and sunburn experience of children aged 5 to 12 years and their parents were closely correlated.[127]

Based on a Community Guide systematic review published in 2004[128] and updated in 2012,[129] the US Task Force on Community Preventive Services found strong evidence of the

effectiveness of primary school interventions in increasing students' sun-related knowledge and protective behaviours as well as in decreasing their sunburn rates.

In another review of sun protection programmes aimed at children under age 14, Buller et al. concluded that only multiunit presentation programmes consistently improved sun protective behaviours, while short-duration presentations were primarily able to improve sun-related knowledge.[130] A recent French study came to the same conclusions.[131]

The interventional programme evaluated in this study was highly effective in increasing knowledge and possibly to some extent in decreasing sunburn rates, but had no obvious impact on the examined sun protective behaviours.

It should be noted that in our investigation the follow-up period between intervention and post-test was considerably longer and children were on average younger than in most of the studies included in the Community Guide systematic review.

Taking into account that 73% of respondents reported that their parents applied sunscreen to them, measuring changes in sunscreen application by the children themselves is probably not an adequate way to assess the impact of a sun safety intervention in such a young age group.

Moreover, the questionnaire used did not account for alterations in sun protective behaviours other than using sunscreen and seeking shade (e.g. wearing protective clothing) that could have initiated the observed post-interventional trend towards decreased sunburn rates.

To summarise, the evaluated one-hour sun safety education sessions were effective in sustainably improving children's knowledge about adverse health effects of extensive sun exposure and about sun protection and possibly in decreasing their sunburn rates. However, we did not observe any changes in sun protective behaviours following the intervention, which might be in part a consequence of methodological limitations related to the survey instrument.

Even though high sun-related knowledge does not correlate in every respect with favourable behaviours, it provides an essential basis for successful skin cancer prevention.

An approach to further enhance protective behaviours could be the implementation of school-based multiunit education sessions[130] including environmental changes (e.g. the erection of shade structures in schoolyards) and family involvement. Bearing in mind the

important role of parents regarding sun protection in young children, sun safety should be addressed within the scope of parent-teacher conferences.

Chapter 4

PROJECT II

Outdoor workers' sun-related knowledge, attitudes, and protective behaviours:

a systematic review of cross-sectional and interventional studies

Daphne Reinau, Melanie Weiss, Christoph R. Meier, Thomas L. Diepgen, Christian Surber

British Journal of Dermatology 2013; 168: 928-40

4.1 Abstract

Background Sun protection is a major concern for outdoor workers as they are particularly exposed to solar ultraviolet radiation and therefore at increased risk of developing some forms of skin cancer, cataract, and ocular neoplasm.

Objectives First: to provide an overview of outdoor workers' sun-related knowledge, attitudes, and protective behaviours as reported in the literature. Second: to evaluate the effectiveness of sun safety education programmes in outdoor occupational settings.

Methods We conducted a systematic review of the literature by searching three electronic databases (PubMed, Embase, PsycINFO) from their inception up to 25 April 2012. An extensive hand search complemented the database searches.

Results We identified 34 relevant articles on descriptive studies and 18 articles on interventional studies. Considerable numbers of outdoor workers were found to have sun sensitive skin types; sunburn rates per season ranged from 50% to 80%. Data concerning outdoor workers' sun-related knowledge and attitudes were scarce and controversial. The reported sun protective behaviours were largely inadequate, with many workers stating that they never or only rarely wore a long-sleeved shirt (50-80%), sun protective headgear (30-80%), and sunscreen (30-100%) while working in the sun. However, there is growing evidence that occupational sun safety education is effective in increasing outdoor workers' sun protection habits and presumably in decreasing sunburn rates.

Conclusions Occupational sun safety education programmes offer great potentials for improving outdoor workers' largely insufficient sun protective behaviours. It is hoped that in the future committed support from the healthcare authorities, cancer foundations, employers and dermatologists open the way for rapid and uncomplicated implementation of sun safety education programmes.

4.2 Introduction

Solar ultraviolet radiation (UVR) has been classified as a human carcinogen[6] and plays an essential role in the aetiology of skin cancer.[7] There is also a causal relationship between UVR exposure and the development of some forms of cataract and possibly ocular neoplasm.[117]

Outdoor workers (people who mainly work outdoors) are exposed to the sun to a particularly high extent. Several UV- dosimetry studies have shown that the occupational UVR exposure limits considered safe by the International Commission on Non-Ionising Radiation Protection (ICNIRP)[132] are greatly exceeded in various typical outdoor occupations (e.g. construction and agricultural work).[133-139]

Two recently published meta-analyses provide epidemiological evidence that outdoor workers are at significantly increased risk of developing non-melanocytic skin tumours (basal cell and squamous cell carcinomas) compared with indoor workers.[55,56]

The association between outdoor occupation and the occurrence of cutaneous malignant melanoma (CMM) is less clear. Some studies indicate that CMM on sun-exposed parts of the body such as the head, face, and neck is more frequent in outdoor workers, whereas CMM on other areas such as the trunk and limbs seems to be more common in indoor workers.[140-142] The pathogenesis of CMM has been linked to intermittent intense UVR exposure (characteristic of leisure activities) rather than to chronic-cumulative UVR exposure (characteristic of long-term outdoor work).[7]

Several authors also described positive correlations between UVR-related eye disorders and outdoor occupation.[143-145]

Sun protection to prevent the harmful health effects of UVR is a major concern for outdoor workers. The ICNIRP recommends the erection of shade structures at workplaces, seeking shade at least during work breaks, scheduling breaks at solar noon, wearing suitable clothing (long trousers, shirts with sleeves), a wide-brimmed hat (preferably with neck flaps), and sunglasses, as well as applying sunscreen with a protection factor of no less than 15 - 30 on uncovered body parts.[146]

The aims of our systematic review were (1.) to present an overview of outdoor workers' sun-related knowledge, attitudes, and protective behaviours and (2.) to evaluate the effectiveness of sun safety education programmes in outdoor occupational settings.

4.3 Methods

We conducted a systematic review of the literature by searching three electronic databases (PubMed, Embase, PsycINFO) from their inception up to 25 April 2012. An extensive hand search complemented the database searches.

We used the following Medical Subject Headings (MeSH) to browse PubMed and slightly adapted these search terms to browse Embase and PsycINFO:

('Health Knowledge, Attitudes, Practice' OR 'Health Behaviour' OR 'Health Education' OR 'Health Promotion' OR 'Primary Prevention' OR 'Secondary Prevention' OR 'Questionnaires') AND ('Skin Neoplasms/prevention and control' OR 'Sunburn/prevention and control' OR 'Eye/radiation effects' OR 'Ultraviolet Rays/adverse effects' OR 'Sunlight/adverse effects' OR 'Sun screening Agents') AND ('Occupational Health' OR 'Occupational Diseases/prevention and control' OR 'Occupational Exposure/prevention and control' OR 'Occupational Exposure/adverse effects' OR 'Environmental Exposure/prevention and control' OR 'Environmental Exposure/adverse effects' OR 'Workplace')

The literature search was limited to studies in humans and articles with abstracts, without any restrictions on language or study design.

We included all identified cross-sectional studies on outdoor workers' sun-related knowledge, attitudes, and protective behaviours as well as all interventional studies examining the effectiveness of sun safety education programmes in outdoor occupational settings. Articles reporting on protective strategies against UVR emitted from artificial sources (e.g. welding arcs) were excluded.

We extracted information on characteristics of the study population, study design, and outcome variables (sun-related knowledge and attitudes, sun protective behaviours, sunburn rates) by means of predefined data extraction tables.

Two reviewers (DR, MW) independently assessed the quality of the retrieved interventional studies using the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies.[147] There were no discrepancies in the overall ratings of the studies.

4.4 Results

4.4.1 Characteristics of the studies

The electronic search of literature databases resulted in 428 hits (PubMed: 107; Embase: 302; PsycINFO: 19). After removing duplicates and reviewing abstracts and full texts, we identified 36 relevant articles. The hand search yielded 16 additional articles, giving a total of 52 articles included in this systematic review.

Thirty-four publications analysed outdoor workers' sun-related knowledge, attitudes, and protective behaviours solely descriptively (cross-sectional studies).[137-139,143,148-177] Eighteen articles reported on 16 different interventional studies evaluating the effectiveness of sun safety educational programmes in outdoor occupational settings.[178-195]

Most articles were published in North America (27), Europe (11), and Australia/New Zealand (10). The remaining studies came from Israel (2), Brazil (1), and Japan (1).

The occupational groups most often surveyed were agricultural workers/farmers (15), construction/road workers (13), and aquatic personnel (7).

4.4.2 Skin type distribution and frequency of sunburns

Green et al.[151] observed a significant underrepresentation of people with fair or medium complexion and a tendency to sunburn among workers in long-term outdoor occupations in Australia. A French study[156] and three US studies[169,173,190] likewise reported relatively low sun sensitivity among construction workers, letter carriers, and farmworkers (Latinos).

The findings from other investigations in various geographical regions do not support the assumption that outdoor workers generally have skin types that can cope better with solar radiation: several authors stated that at least half of the workers surveyed across different outdoor occupations had sun sensitive skin (skin types I and II according to the Fitzpatrick classification).[137,148,153,175-177] Furthermore, skin type distribution among a sample of German outdoor workers and the general population was found to be roughly equivalent.[174]

Between 50% and 80% of the outdoor workers got sunburnt during the year (or season) before data collection (self-reported data).[148,152,160,174,178,181-183,187]

4.4.3 Sun-related knowledge

Merely a few studies assessed outdoor workers' knowledge about the adverse health effects of excessive sun exposure and sun protection.

Unverricht and Knuschke[174] reported only limited knowledge among German workers in various outdoor occupations.

A small sample of Swiss building workers were aware of some negative effects of UVR, but the risk was primarily perceived in relation to erythema, indicating little knowledge about the long-term effects of UV exposure.[139]

Thirty-five per cent of Californian farmworkers said they had no knowledge about skin cancer[169] and forty-three per cent of Wisconsin dairy farmers did not know that skin cancer could be fatal[161].

Farmers in Georgia (USA)[165] and Austria[160] were generally well informed about skin cancer facts, as were construction workers surveyed in Australia.[149]

While Hammond et al.[153] found that knowledge about skin cancer was not associated with favourable sun protection habits in roadmen, horticulture workers, and construction workers, Parrott et al.[166] reported a direct impact of knowledge on behaviour adaptation in farmers.

4.4.4 Attitudes towards skin cancer, suntan, and sun protection

Remarkable proportions (40-60%) of American farmers and watermen (corresponds to fishermen) were well aware of the risk of developing skin cancer later in life,[148,161,165,168] but most did not expect it to affect their ability to work.[161,165] In watermen, there was a significant positive relationship between the perceived chances of getting skin cancer and sunscreen use.[148]

Across various occupational groups, most outdoor workers questioned expressed a desire for suntanned skin.[148,149,159,161,182]

Although more than 80% of Austrian farmers considered sun protection necessary, only half of them thought it easy to implement the recommended measures while farming.[160] The proportion was somewhat larger among Georgia farmers: 73% felt confident about their ability to wear a wide-brimmed hat at work, 63% did so to use sunscreen, and 48% to wear a long-sleeved shirt.[165]

As barriers to the use of sun protection, outdoor workers frequently mentioned forgetfulness, time-consuming application and the sticky consistency of sunscreens, as well as feeling too hot when wearing hats and long-sleeved shirts.[156,161,172]

Three studies assessed the influence of sun protection product costs. While Georgia farmers did not view costs as a disincentive to using sun protection[165] and Austrian tinsmiths (corresponds to plumbers) were willing to spend up to US $40 for sun protection products,[175] half of French construction workers claimed that they would rather use a sunscreen if it were available free of charge at the building site (although no more than 6% spontaneously mentioned the high price as a reason for not using sunscreen).[156]

4.4.5 Primary prevention strategies

Shade

For outdoor workers it is often not possible to work in the shade, but choosing to take breaks indoors or in a place well sheltered from the sun (especially at midday when the sun is strongest) can substantially reduce the daily UVR exposure.[196,197]

Only a few studies examined whether outdoor workers avoid sun exposure around noon: Among Turkish farmers, 31% admitted to working when the sunlight was perpendicular,[189] and no more than half of Austrian farmers[143] and 35% of British construction workers[159] reported minimising exposure to direct sunlight in the middle of the day. In contrast, 91% of workers on an Australian building site were observed to spend their breaks in the shade.[137]

Sun protective clothing

More than half (50-80%) of farmers and building workers surveyed in North America[161,165,167,171,195], Australia[149], Britain[159], and Japan[154] reported never or only rarely wearing a long-sleeved shirt when working in the sun.

American lifeguards wore T-shirts only 15% of the time (median weekly percentage).[138] However, 60% of Australian lifesavers stated to wear long-sleeved shirts on sunny days often or always.[182]

In a field study among line staff of Telecom Australia, Borland et al. observed 13% wearing long-sleeved shirts. 66% wore short-sleeved shirts, 17% sleeveless shirts or singlets and 4% no shirt at all.[180] Gies et al. monitored workers on an Australian building site, 8% wore no shirt, but 67% of the rest wore a collared shirt of thick, dark, or ultraviolet protection factor

(UPF)-rated material.[137] Observations among US farmers, construction workers, and road workers revealed that 95% did not wear a long-sleeved shirt.[165]

Austrian tinsmiths who were asked to test different sun protective items at the building site preferred short-sleeved to long-sleeved shirts and high-tech synthetic microfiber textiles to cotton as they maintain an agreeable body climate.[175]

Sun protective headgear

Table 4-1 shows self-reported frequencies of outdoor workers' use of a head cover.

Percentages of outdoor workers who stated that they never or rarely wore adequate sun protective headgear at work varied between approximately 30% and 80%. Data from field observations showed similar ranges.[137,165,180]

Wearing a sunhat was found to be more common among men than women.[157,162,171]

Outdoor workers seem to prefer headwear of cotton over headwear of high-tech synthetic microfiber, as cotton better soaks up the sweat. Neck protection was accepted, unless the design was too extreme (such as flaps towards the throat).[175]

Sunscreens

Table 4-2 shows self-reported frequencies of outdoor workers' sunscreen use.

The vast majority of agricultural and construction workers surveyed rarely or never applied sunscreen at work. Workers pursuing a profession by or in the water or in high mountain areas were somewhat more likely to wear sunscreen, but considerable proportions (30-40%) still did not use it most of the time.

Female workers were significantly more likely to use sunscreen than their male counterparts.[157,162,163,168,170,171]

Using sunscreen seems to be less accepted by outdoor workers than by indoor workers.[150,151,176] Austrian tinsmiths preferred sunscreens in form of a spray (especially transparent spray) as it is easy to apply even with dirty hands.[175]

Sunglasses

Wearing sunglasses was repeatedly reported to be the sun protection method most often used by outdoor workers.[138,149,152,173,183] However, it has been suggested that outdoor workers wear sunglasses to protect themselves against glare rather than against UVR.[175]

Over 80% of US lifeguards and aquatic instructors said they wore sunglasses when outside on a sunny day.[152] The weekly fraction of time during which sunglasses were worn by another sample of US lifeguards was 82%.[138]

Around half of Canadian outdoor workers (profession not specified)[162] and 61% of Australian construction workers[149] stated that they often or always wore sunglasses. In a US field study, 74% of farmers, construction workers, and road workers were observed with tinted eye protection.[165]

Nevertheless, more than two thirds of US farmworkers[169] and Turkish farmers[189] as well as British[159] and Japanese[154] construction workers never or only rarely wore sunglasses.

4.4.6 Secondary prevention strategies

Data on outdoor workers' secondary skin cancer prevention strategies (skin examinations to detect early signs of cancer) are scarce.

Just under half of British construction workers stated to check their skin regularly for moles or unusual changes.[159] Forty per cent of Georgia farmers[167] and Maryland watermen[148] reported to do so merely occasionally or never.

Over two thirds of Georgia farmers admitted not knowing exactly how to conduct a skin cancer self-examination.[165,167] Moreover, the majority had never undergone dermatological examination by a medical professional,[165,166] a finding that also applied to Michigan farmers.[168]

At least a third of Australian construction workers stated to have received a skin check during the year preceding the survey.[149]

4.4.7 Effectiveness of sun safety education programmes

Table 4-3 summarises the effects of diverse sun safety education programmes (interventions) in outdoor occupational settings.

Overall, 7 of the 16 interventional studies retrieved assessed the influence of educational programmes on sun-related knowledge; four found a statistically significant improvement after the education session.

Eight studies measured changes in attitudes towards skin cancer, sun protection, and suntan, but only one study documented a significant positive short-term effect of the intervention.

All 16 studies evaluated sun protective behaviours before and after intervention. In 13 studies, significant improvements of at least one of these behaviours were observed (in two additional studies[183,185] there was a similar, but non-significant trend). Six authors reported positive long-term effects of 12 months or more. Most favourable changes were found for the use of sunscreen.

Four studies investigated the influence of sun safety education on the occurrence of sunburn. All of them showed a significant decrease in incidence rates after the intervention.

We rated the quality of three interventional studies as high and of the remaining 13 studies as moderate. The most frequent reasons for deductions in quality ratings were a low or unknown proportion of subjects who agreed to participate and a high proportion of dropouts during follow-up.

Table 4-1 Self-reported frequency of outdoor workers' use of sun protective headgear

Reference	Geographical region	Data collection method	Occupational group	Number of study participants	Sex (% male)	Definition of headgear	Self-reported use of sun protective headgear		
							Rarely or never	Sometimes	Often or always
Cioffi et al., 2003[149]	Australia	Questionnaire	Construction workers	142	98%	Brimmed-hat	35%	11%	54%
						Baseball cap	41%	19%	40%
Dobbinson et al., 1999[182]	Australia	Questionnaire	Lifeguards	134	67%	Wide-brimmed hat	31%	14%	55%
Ing et al., 2002[155]	Canada	Questionnaire	Farmers	207	ND	Wide-brimmed hat			35%
Lichte et al., 2010[158]	Germany, Austria, Switzerland	Standardised interview	Mountain guides	283	100%	None	38%	18%	44%
Madgwick et al., 2011[159]	Britain	Questionnaire	Construction workers	360	100%	Wide-brimmed hat with neck protection	77%		
Malak et al., 2011[178]	Turkey	Questionnaire*	Farmers	157	44%	Headgear (incl. headscarf)		100%	
Marlenga, 1995[161]	USA	Questionnaire*	Farmers	202	100%	Wide-brimmed hat	76%	11%	13%
Marrett et al., 2010[162]	Canada	Standardised telephone interview	Outdoor workers (not specified)	1330	75%	None			58%
Mayer et al., 2007[190]	USA	Questionnaire	Letter carriers	2662	70%	Wide-brimmed hat	57%	11%	32%
Oliveira et al., 2011[164]	Brazil	Questionnaire*	Aquatic instructors	95	57%	Hat	60%		
Parrott et al., 1996[165]	USA	Questionnaire	Farmers	155	ND	Wide-brimmed hat	43%		
Robinson et al., 2004[167]	USA	Standardised telephone interview*	Farmers	686	70%	Wide-brimmed hat with neck protection	46%	16%	39%
Salas et al., 2005[169]	USA	Standardised interview*	Farmworkers	326	100%	Any hat			100%[†]
						Wide-brimmed hat	77%	14%	10%
Scerri et al., 2002[170]	Malta	Standardised interview	Outdoor workers (not specified)	88	58%	Hat	55%	8%	37%
Schenker et al., 2002[171]	USA	Standardised telephone interview	Farmers (farm operators)	1833	90%	Hat with sun brim such as baseball cap		70%	
Schmid-Kubista et al., 2010[143]	Austria	Questionnaire*	Farmers	297	46%	None	16%		
Shoveller et al., 2000[172]	Canada	Standardised interview	Outdoor workers (not specified)	546	80%	None	42%		
Weber et al., 2007[175]	Austria	Questionnaire	Tinsmiths	13	ND	None	60%		

*Question asked for the general frequency of wearing sun protective headgear (not restricted to working time); [†] Most farmworkers wore a baseball cap; ND: No data

Table 4-2 Self-reported frequency of outdoor workers' sunscreen use

Reference	Geographical region	Data collection method	Occupational group	Number of study participants	Sex (% male)	Self-reported sunscreen use		
						Rarely or never	Sometimes	Often or always
Bridges & Ehrlich, 2005[148]	USA	Questionnaire*	Watermen	63	100%	35%		
Cioffi et al., 2003[149]	Australia	Questionnaire	Construction workers	142	98%	25%	40%	34%
Dobbinson et al., 1999[182]	Australia	Questionnaire	Lifeguards	134	67%	6%	9%	85%
Hall et al., 2009[152]	USA	Questionnaire*	Lifeguards and aquatic instructors	987 -1686	Most female	< 40%		
Inaba & Mirbod, 2007[154]	Japan	Questionnaire	Traffic control workers Construction workers	204 115	100% 100%	76% 100%		
Ing et al., 2002[155]	Canada	Questionnaire	Farmers	207	ND			25%
Laporte, 2006[156]	France	Questionnaire	Construction workers	525	100%	92%		
Lichte et al., 2010[158]	Germany, Austria, Switzerland	Standardised interview	Mountain guides	283	100%	36%	20%	45%
Madgwick et al., 2011[159]	Britain	Questionnaire	Construction workers	360	100%	40%		
Malak et al., 2011[178]	Turkey	Questionnaire*	Farmers	157	44%	99%		
Marlenga, 1995[161]	USA	Questionnaire*	Farmers	202	100%	73%	19%	8%
Marrett et al., 2010[162]	Canada	Standardised telephone interview	Outdoor workers (not specified)	1330	75%			29%
Mayer et al., 2007[190]	USA	Questionnaire	Letter carriers	2662	70%	47%	19%	34%
Oliveira et al., 2011[164]	Brazil	Questionnaire*	Aquatic instructors	95	57%	31%		
Parrott et al., 1996[165]	USA	Questionnaire	Farmers	155	ND	49%		
Robinson et al., 2004[167]	USA	Standardised telephone interview*	Farmers	686	70%	65%	14%	21%
Salas et al., 2005[169]	USA	Standardised interview*	Farmworkers	326	100%	97%	1%	2%
Scerri et al., 2002[170]	Malta	Standardised interview	Outdoor workers (not specified)	88	58%	67%	8%	25%
Schenker et al., 2002[171]	USA	Standardised telephone interview	Farmers (farm operators)	1833	90%	69%		
Schmid-Kubista et al., 2010[143]	Austria	Questionnaire*	Farmers	297	46%	16%		
Shoveller et al., 2000[172]	Canada	Standardised interview	Outdoor workers (not specified)	546	80%	77%		
Stock et al., 2009[195]	USA	Questionnaire*	Road workers	148	100%	81%		
Unverricht & Knuschke, 2007[174]	Germany	Questionnaire and diary	Construction workers Agricultural workers PE teachers	31 17 18	ND	57% 93% 69%		
Weber et al., 2007[175]	Austria	Questionnaire	Tinsmiths	13	ND	30%	30%	40%

*Question asked for the general frequency of sunscreen use (not restricted to working time); ND: No data

Table 4-3 Effects of sun safety education programmes in outdoor occupational settings

Reference Geograph. region Study quality	Study population	n (Retention rate)	Study design Data collection method	Follow-up period	Study arms	Intervention										Statistically significant effects of intervention (p < 0.05)			
						Educational lecture	Educational video	Information brochures	Posters	Logos	Skin examinations	Eye examinations	Sun protective gear	UV photo of the face	Interactive tasks	Knowledge	Attitudes towards skin cancer, sun protection, and suntan	Sun protective behaviours	Sunburns
Azizi et al., 2000[179] Israel Moderate	Outdoor workers water supply 100% male Av. age: 42 y	2.Follow-up: 144 (68%)	Non-randomised controlled trial Questionnaire	8 months 20 months	IG 1 IG 2 IG 3	2 intervention pulses: at beginning of the study (upper row) and 12 months later (lower row) ●										NA	NA	2.Follow-up: Use of sunscreen ↑ in IG 1, 2 & 3 *(+105-141%, +77-113%, & +25-61%)* Sun-exposed skin area ↓ in IG 1 *(-25%)* Daily UVR exposure dose ↓ in IG 1 & 2 *(-33% & -18%)* Rate of skin self-examination ↑ in IG 1 & 2 *(+71% & +53%)*	NA
Borland et al., 1991[180] Australia Moderate	Line staff Telecom Australia	Pretest: 599 Obser-vations of 1-4-person teams Follow-up: 627 Obs.	Randomised controlled trial Direct observation	3 months	IG CG		●	●	●							NA	NA	Use of appropriate clothing ↑ Use of sun protective headgear: NS Seeking shade: NS	NA
Buller et al., 2005[181] Andersen et al., 2008[178] USA, Canada Moderate	Ski area employees (68% outdoor workers) 62% male Age: 39% <30 y 78% <50 y	1.Follow-up: 2119 (56%) 2.Follow-up: 1463 (39%)	Randomised controlled trial Pretest: Questionnaire Follow-up: Standardised telephone interview	3-4 months 9-12 months	IG CG			●	●	●					●	NA	NS	Sun protective behaviour in winter (1.follow-up): NS Sun protective behaviour in summer (2.follow-up): Use of sunscreen ↑ (adj.OR=1.43, 95% CI=1.20-1.71) Use of sunglasses ↑ (OR=1.26, 95% CI=1.08-1.48) Use of sun protective headgear: NS Seeking shade: NS	Winter: ↓ (-6%) Summer: ↓ (OR= 0.78, 95% CI= 0.64-0.95)

Table 4-3 continued

Reference Geograph. region Study quality	Study population	n (Retention rate)	Study design Data collection method	Follow-up period	Study arms	Intervention										Statistically significant effects of intervention (p < 0.05)			
						Educational lecture	Educational video	Information brochures	Posters	Logos	Skin examinations	Eye examinations	Sun protective gear	UV photo of the face	Interactive tasks	Knowledge	Attitudes towards skin cancer, sun protection, and suntan	Sun protective behaviours	Sunburns
Dobbinson et al., 1999[182] Australia Moderate	Lifeguards 67% male Age: 45% < 20 y	263	Cross-sectional study: Comparison between state A (IG, 10-year skin cancer prevention programme for lifesavers) and state B (CG, no programme) Questionnaire	No pretest	IG CG	?	?	?	●	●			●		●	NA	NS	Regular use of sunscreen ↑ (+12%) Regular wearing of long-sleeved shirts ↑ (+21%) Regular use of headgear ↑ (+34%) Regular use of shade shelters ↑ (+15%)	↓ (-23%)
Geller et al., 2001[183] USA High	Lifeguards and aquatic instructors 31% male Av. age: 21 y	194 (88%)	Randomised controlled trial Questionnaire	6-8 weeks	IG CG	●		●	●				●		●	NS	NS	NS	↓
Girgis et al., 1994[184] Australia Moderate	Outdoor workers electrical company 99% male Av. age: 41 y	142 (77%)	Randomised controlled trial Questionnaire, diary	1 month	IG CG	●		●			●					↑ (+4%)	NS	Use of a high level of sun protection ↑ (+16%)	NA
Glanz et al., 1998[185] USA Moderate	Outdoor recreation staff 33% male Av. age: 20 y	30 (67%)	Pretest-posttest study Questionnaire	1 month	IG	●		●	●	●			●		●	NS	NS	NS	NA
Glanz et al., 2001[186] USA Moderate	Outdoor recreation staff 39% male Av. age: 21 y	1.Follow-up: 144 (82%) 2.Follow-up: 66 (38%)	Randomised controlled trial Questionnaire	2 months 5 months	IG 1 IG 2 CG	● ● Abbreviated educational programme after the 1.follow-up survey		● ●	● ●	● ●			 ●		● ●	1. & 2. Follow-up: ↑ in both IG (+15%)	NA	1.Follow-up: Use of sun protection ↑ in IG 1 2.Follow-up: NS	NA

Table 4-3 continued

Reference Geograph. region Study quality	Study population	n (Retention rate)	Study design Data collection method	Follow-up period	Study arms	Intervention										Statistically significant effects of intervention (p < 0.05)			
						Educational lecture	Educational video	Information brochures	Posters	Logos	Skin examinations	Eye examinations	Sun protective gear	UV photo of the face	Interactive tasks	Knowledge	Attitudes towards skin cancer, sun protection, and suntan	Sun protective behaviours	Sunburns
Hiemstra et al., 2012[187] USA Moderate	Lifeguards 40% male Av. age: 19 y	3014 (?)	Pretest-posttest study Questionnaire	1 summer season	IG	●							●		●	NA	↓	Use of sun protection ↑	↓ *(-5%)*
Lombard et al., 1991[188] USA Moderate	Lifeguards (no further description)	Not reported (study in 2 swimming pools)	Pretest-posttest study Direct observation	1 month	IG	●		●	●	●			●		●	NA	NA	Use of sun protection ↑ (+47%) In 1 swimming pool the management declared the use of sun protection to be compulsory after the intervention	NA
Malak et al., 2011[189] Turkey Moderate	Farmers 44% male Av. age: 39 y	157 (81%)	Pretest-posttest study Questionnaire	6 months	IG	●			●				●			↑ *(+29%)*	NA	Use of sunscreen ↑ *(+10%)* Working outdoors at noon ↓ *(-15%)* Wearing of protective clothing: NS Use of sunglasses: NS Consulting a physician in case of skin changes ↑ *(+17%)*	NA
Mayer et al., 2007[190] Mayer et al., 2009[191] USA High	Letter carriers 70% male Av. age: 43 y	3.Follow-up: 2190 (82%) 4.Follow-up: 2057 (77%)	Randomised controlled trial Questionnaire	3 months 12 months 24 months 36 months	IG CG	●			●	●			●			NA	NA	3.Follow-up: Use of sunscreen ↑ (*+12%*; adj.OR=2.03, 95% CI=1.60-2.58) Use of a wide-brimmed hat ↑¨ (*+13%*; adj.OR=2.88, 95% CI=2.31-3.61) 4.Follow-up: IG: Effects maintained CG: Use of sunscreen ↑ *(+8%)* and wide-brimmed hats ↑ *(+11%)* After the 3.follow-up only supply of sunscreen After the 3.follow-up abbreviated educational programme and supply of sun protective gear	NA
Mullan et al., 1996[192] USA Moderate	Farmers Approx. 50% male Approx. 80%>50 y	1689 (NA)	Pretest-posttest study (heterogeneous groups) Questionnaire	12 months	IG CG		●	●		●			●			NA	NA	Use of sun protection ↑ (adj.OR=1.28, 95% CI=1.03-1.60)	NA

Table 4-3 continued

Reference Geograph. region Study quality	Study population	n (Retention rate)	Study design Data collection method	Follow-up period	Study arms	Intervention										Statistically significant effects of intervention (p < 0.05)			
						Educational lecture	Educational video	Information brochures	Posters	Logos	Skin examinations	Eye examinations	Sun protective gear	UV photo of the face	Interactive tasks	Knowledge	Attitudes towards skin cancer, sun protection, and suntan	Sun protective behaviours	Sunburns
Reding et al., 1998[193] USA Moderate	Farmers 85% male 69% > 40 y	301	Randomised controlled trial Standardised telephone interview	8-11 months	IG 1 IG 2 CG			●					●			NS	NS	NS	NA
Shani et al., 2000[194] Israel Moderate	Outdoor workers water supply Av. age: 43 y	101	Cross-sectional study: Comparison between workers who received a skin cancer education (IG) and workers who were employed by the same company after the campaign(CG) Questionnaire, camera, spectro-photometre	No pretest Data collection 3 years after the inter-vention	IG CG	●		●			●	●	●			NA	NA	Use of sun protection ↑	NA
						Legal regulations concerning free supply and obligatory use of sun protective gear at the time of data collection													
Stock et al., 2009[195] USA High	Road workers 100% male Av. age: 47 y	1.Follow-up: 148 (91%) 2.Follow-up: 144 (89%)	Randomised controlled trial Questionnaire, spectro-photometre	Immediate 2 months 12 months	IG 1 IG 2 IG 3 IG 4 CG		A B A B							● ●		1.Follow-up: ↑ in all IG (no group differences) 2. & 3. Follow-up: NA	1.Follow-up: ↑ in all IG (no group differences) 2. & 3. Follow-up: NA	1.Follow-up: NA 2. & 3. Follow-up: Use of sun protection ↑ in IG 1, 2 & 3 (no group differences)	NA

Percentages in italics, absolute numbers (comparison of percentages before and after intervention without taking into account changes in the control group); Percentages non-italicised, relative numbers (comparison of percentages before and after the intervention under deduction of changes in the control group).
Av. age, average age; CI, confidence interval; CG, control group; IG, intervention group; NA, not assessed; NS, nonsignificant; OR, odds ratio; UVR, ultraviolet radiation; y, years; ↑, increase; ↓, decrease.

4.5 Discussion

Outdoor workers bear a high risk of experiencing adverse health effects caused by solar UVR. Along with their particularly high sun exposure, the results of our systematic review suggest that considerable numbers have sun-sensitive skin types. Accordingly, we found markedly higher sunburn rates among outdoor workers than Buller et al.[114] observed in comparable samples of the general population. Hence, our findings do not support the hypothesis by Green et al.[151] that fair-skinned people with a tendency to sunburn systematically tend to avoid outdoor work.[151]

Despite their increased likelihood of suffering sun damage, most outdoor workers did not engage in adequate sun protective behaviours. Except for the use of sunglasses, they seemed to protect themselves from the sun even less carefully than the general population (reviewed by Kasparian et al.[126] in 2009). This phenomenon can be explained at least partly by the fact that outdoor workers often combine several characteristics generally associated with reluctance to take sun protective measures, such as male sex, low educational background, and adolescent age (refers primarily to lifeguards).[126]

In 2004, the US Task Force on Community Preventive Services found insufficient evidence to determine the effectiveness of skin cancer prevention campaigns in outdoor occupational settings because the limited number of available reports (n=8) showed inconsistent results.[128] Encouragingly, in the last decade further well-designed studies have been published on prevention campaigns, which have proven effective in improving outdoor workers' sun protective behaviours. Based on the findings of the 16 interventional studies included in the present systematic review, we consider there is now sufficient evidence that sun safety programmes in the working environment can foster favourable sun protection habits among outdoor workers.

Additional investigations across different outdoor occupational groups and geographical regions with longer follow-up periods are needed to identify the most promising methods of intervention and to determine the impact of sun safety education on direct health outcomes linked to excessive UVR exposure such as sunburn and skin cancer rates.

In addition to targeting individual workers, it is crucial to encourage employers to develop sun safety policies for their companies, including the erection of shade structures, scheduling work breaks at midday, and ideally the provision of sun protective gear free of

charge at workplaces. The industry is also challenged to bring onto the market affordable sun protection products, which meet outdoor workers' special requirements (e.g. non-sticky sunscreens that are easy to apply and come in large containers, UPF-rated clothes made of light, breathable materials).

To our knowledge, this is the first research paper, which summarizes and compares descriptive data from cross-sectional studies on outdoor workers' sun-related knowledge, attitudes, and protective behaviours. Furthermore, it includes twice as many interventional studies as the latest review published in this field by the US Task Force on Community Preventive Services in 2004.[128]

However, our study has some limitations. Comparison of studies obtained for review resulted in relatively large ranges of reported sunburn rates and sun protective behaviours for a number of reasons: (1.) Data collection methods differed substantially across studies, with questionnaires varying in wording and recall periods, (2.) the risk of getting sunburnt and the sun protection required depend greatly on the geographical location of the workplace, as the intensity of UVR increases with altitude and decreasing latitude,[198] and (3.) outdoor workers represent a heterogeneous study population consisting of diverse occupational groups, each with characteristic distribution patterns of sex, age, and educational background. Due to the small number of studies per geographical region and occupational group, we were largely unable to detect associations between these two variables and the examined outcomes.

Moreover, most studies included were based on workers' self-report and may therefore be subject to social desirability and recall bias, albeit several authors validated self-report against direct observation and found it to be accurate.[173,190,199,200]

With regard to publication bias, the positive effect of sun safety education programmes might have been overestimated.

In conclusion, data from cross-sectional and interventional studies on outdoor workers' sun-related knowledge and attitudes as well as on secondary skin cancer prevention strategies (skin examination to detect early signs of cancer) were scarce and controversial. Self-reported and observed sun protective behaviours were largely inadequate and sunburn rates were high. Nevertheless, there is growing evidence that sun safety education in outdoor occupational settings is effective in increasing workers' sun protective behaviours and presumably also in decreasing their sunburn rates. Based on these findings, sun safety

programmes in the working environment offer great potential for reducing the burden of skin cancer in persons at high risk. It is hoped that in the future committed support from the healthcare authorities, cancer foundations, employers, and dermatologists open the way for rapid and uncomplicated implementation of sun safety education programmes.

Chapter 5

PROJECT III

Sun protective behaviour of vacationers spending holidays in the tropics and subtropics

Daphne Reinau, Carole Achermann, Noah Arnet, Christoph R. Meier,

Christoph Hatz, Christian Surber

British Journal of Dermatology 2014; 171: 868-74

5.1 Abstract

Background The development of malignant melanoma has been associated with intense episodic sun exposure, as it typically occurs during holidays in high UV-index countries.

Objectives To investigate sun protective behaviour and sunburn experience of vacationers spending holidays in the tropics or subtropics.

Methods Using standardised face-to-face interviews, we conducted cross-sectional surveys among air passengers waiting in the departure or the baggage claim area at the Airport Basel-Mulhouse (Switzerland/France), and among vacationers waiting for pre-travel health advice at a travel clinic in Basel (Switzerland).

Results We completed 533, 324, and 308 interviews with departing air passengers, returning air passengers, and vacationers at the travel clinic, respectively. The interviews revealed widespread misconceptions about how to prepare the skin for the sun before holidays (e.g. pre-tanning in the solarium). At the holiday destination, almost all respondents used sunscreen, whereas wearing protective clothing and seeking shade were less practiced. Among the returning air passengers, 44% had got sunburnt during their holiday stay.

Conclusions The sunburn rate among returning vacationers was alarmingly high. Skin cancer prevention campaigns and pre-travel health advice should tackle misconceptions regarding the preparation of the skin for the sun, and emphasize the significance of covering up and seeking shade.

5.2 Introduction

Ultraviolet radiation (UVR) exposure from the sun has been widely acknowledged as the major culprit for melanoma and nonmelanoma skin cancer.[6] Hence, the worldwide rise in skin cancer incidences among fair-skinned populations is primarily attributed to lifestyle changes involving extended sun exposure.[28,38] The easy cost-effective accessibility to air travel and the pursuit of a suntan lead more and more people to journey to sunny resorts in the tropics and subtropics, even for short holidays in the winter months. Yet a 1-week sun holiday already increases the annual UVR dose of indoor workers considerably.[63] Furthermore, this intense episodic, rather than a continuous sun exposure pattern, has been specifically associated with the development of malignant melanoma,[7] which accounts for about three fourths of all skin cancer deaths.[201]

Contrary to popular belief, there are only limited options to prepare your skin for the anticipated sun exposure before holidays. Taking dietary supplements such as carotenoids requires high compliance over several weeks and offers at best a sun protection factor (SPF) of about four.[88,90] Pre-tanning in the solarium leads to an additional UVR load, is therefore harmful to health, and does not afford relevant photoprotection.[202,203]

To prevent skin cancer and other adverse effects of UVR (e.g. premature skin ageing, ocular damage), it is vital for travellers in high UV-index countries to practice adequate sun protective behaviour.[204]

The main objectives of this descriptive study were (1.) to investigate whether and by what means vacationers travelling to holiday destinations in the tropics and subtropics seek to prepare their skin for the planned sun exposure before holidays, (2.) to examine their sun protective behaviour at the holiday destination, and (3.) to assess their sunburn rate at the end of holidays.

5.3 Methods

5.3.1 Study setting and participants

The study comprised three independent cross-sectional surveys in two different settings as displayed in Table 5-1.

Vacationers aged 18 or over with Caucasian skin (Fitzpatrick skin type I-IV) who gave their oral consent and whose holiday destination was in the tropics or subtropics were eligible for study participation.

Table 5-1 Overview of study settings and participants

	Survey 1	**Survey 2**	**Survey 3**
Setting	Airport Basel-Mulhouse (Switzerland/France)	Airport Basel-Mulhouse (Switzerland/France)	Travel Clinic of the Swiss Tropical and Public Health Institute Basel (Switzerland)
Study participants	Departing air passengers waiting in the departure gates	Returning air passengers waiting in the baggage claim area	Vacationers waiting for pre-travel health advice and recommended vaccinations.
Time of data collection	Day of departure	Day of return	1-323 days (median: 37 days) before departure

5.3.2 Data collection

After study approval by the Ethics Committee of Basel, we collected data between February and April 2013 using standardised face-to-face interviews. The interviews lasted 3 to 5 minutes and were conducted in German or French. At the beginning of each interview, the interviewers assessed the respondents' sex, Fitzpatrick skin type (fair: skin type I&II/ medium: skin type III&IV), and density of head hair (dense/ sparse/ bald).

In Survey 1 and Survey 3, questions asked about planned holiday activities, attitudes towards a suntan, preparation of the skin for sun exposure before holidays, and intended sun protective behaviour at the holiday destination (Survey 1: sun protective items in the luggage). Survey 3 additionally contained a question regarding knowledge of adverse effects of UVR. In Survey 2, questions focused on sunburn experience during the preceding holiday stay and sun protective measures undertaken.

5.3.3 Statistical analysis and outcome variables

We analysed the collected data separately by survey and, where appropriate, using a combined dataset. Beside descriptive statistics, we conducted multivariate logistic regression analyses to evaluate associations between several predictor variables (e.g. demographic data) and the following outcomes: (1.) pursuit of a tanned skin (value ≥ 5 on the importance scale depicted in Figure 5-1, controls: scale value < 5), (2.) knowledge of adverse effects of UVR (e.g. skin cancer, ocular damage), (3.) preparation of the skin for the sun before holidays (taking dietary supplements, pre-tanning in the solarium), (4.) favourable sun protective behaviour (virtually always wearing a sunhat/ seeking shade around noon/ wearing sunscreen, controls: subjects following the respective protective measures only sometimes or never; applying sunscreen with SPF ≥30/≥40, controls: sunscreen with SPF <30/<40), and (5.) occurrence of at least one sunburn during the preceding holiday stay. For each outcome, a separate regression model was built which included only respondents with complete data for all examined predictor variables. If not otherwise specified, we calculated adjusted odds ratios (OR_{adj}) with the corresponding 95% confidence intervals (CI) based on the combined dataset, controlling for sex (male/female), age group (18-35 years/> 35 years), Fitzpatrick skin type (fair: skin type I&II/ medium: skin type III&IV), and Survey (Survey 1/Survey 2/Survey 3).

We performed all analyses using SAS 9.3 software (SAS Institute, Cary, NC) and defined statistical significance at the alpha-level of 0.05.

5.4 Results

5.4.1 Characteristics of the study population

We completed 533, 324, and 308 interviews with a participation rate of 91.7%, 86.2%, and 77.3% in Survey 1, Survey 2, and Survey 3, respectively. The characteristics of the study population are summarized in Table 5-2.

Figure 5-1 illustrates the respondents' attitude towards getting a holiday tan (assessed in Survey 1 and Survey 3). In the multivariate model (variables adjusted for sex, age, skin type, intention to sunbathe, Survey), the pursuit of a tanned skin was most pronounced in females (OR_{adj}: 1.72, 95% CI: 1.23-2.40), people aged 18-35 years (OR_{adj}: 2.62, 95% CI: 1.77-3.88), subjects with skin type III&IV (OR_{adj}: 1.48; 95% CI: 1.05-2.07), those who intended to

sunbathe during holidays (OR_{adj}: 5.65, 95% CI: 3.57-8.95), and vacationers interviewed at the airport (OR_{adj}: 7.41, 95% CI: 4.90-11.20). Of those in pursuit of a tanned skin, 11.0% stated they were willing to accept sunburns in order to acquire a tan (12.7% in Survey 1 vs. 2.7% in Survey 3).

5.4.2 Knowledge of the adverse effects of UVR

In reply to the question *"What adverse effects of sunlight on human health are known to you?"* (asked exclusively in Survey 3, no given response options), most respondents mentioned skin cancer (93.5%), followed by sunburn (82.1%), heat-related disorders (e.g. heatstroke, sunstroke, dehydration [55.5%]), premature skin ageing (34.1%), 'sun allergy' (24.4%), and ocular damage (23.1%). Ocular damage was named more often by older people and males, whereas females were more likely to state heat illness. Apart from that, there were no statistically significant differences by sex, age, and skin type.

5.4.3 Preparation of the skin for the sun

Overall, 5.7% of vacationers (7.9% in Survey 1 vs. 2.0% in Survey 3) sought to prepare their skin before holidays for the anticipated sun exposure by taking dietary supplements. Of these, 68.8% chose a product containing carotenoids and 22.9% a vitamin preparation without carotenoids (the composition of the remaining products could not be established). The majority of those taking carotenoids started the supplementation later than the recommended minimum of 10 weeks[90] before holidays (≤ 3 weeks: 48.5%; 1-2 months: 21.2%; > 2 months: 30.3%). Vitamin preparations without carotenoids were usually taken over a longer time period.

Among the departing air passengers who had visited a solarium within 4 weeks preceding their holidays (54/533), almost three-quarters (72.2%) did so with the intent of preparing the skin for the sun and thereby preventing sunburn. For the same purpose, 3.6% of respondents at the travel clinic planned to go to a tanning salon before the vacation.

Whereas there was no association between sex and taking dietary supplements, females were more likely than males to pre-tan in the solarium (OR_{adj}: 2.42, 95% CI: 1.22-4.83). Age and skin type had no impact on preparing the skin for the sun ahead of holidays.

5.4.4 Sun protection at the holiday destination

In Survey 1, almost all (97.4%) air passengers had sunscreen in their luggage. Other sun protective items included sunglasses (93.8%), sunhat (63.6%), and clothes with integrated UV protection (4.1%).

In Survey 2, 79.0% of air passengers stated they had practically always applied sunscreen on sunny vacation days, while only 38.9% and 34.0% said that they had stayed in the shade around noon and had worn a sunhat most of the time, respectively. Even among travellers with sparse hair or a bald head, the latter proportion was slightly below 50%. Compared to individuals with skin type III&IV, individuals with skin type I&II were more likely to have usually sought shade around noon (OR_{adj}: 1.69, 95% CI: 1.07-2.68) and to have worn protective headgear (OR_{adj}: 1.76, 95% CI: 1.09-2.86). Significant predictors for the routine use of sunscreen were age > 35 years (OR_{adj}: 2.63, 95% CI: 1.36-5.06) and female sex (OR_{adj}: 2.30, 95% CI: 1.30-4.07). Conversely, females were underrepresented among regular hat wearers (OR_{adj}: 0.45, 95% CI: 0.28-0.73).

In Survey 3, all respondents declared to protect themselves from the sun at the holiday destination (Figure 5-2).

Data of all surveys combined, most sunscreen users applied sunscreen with a medium to very high SPF (SPF < 15: 1.7%; SPF 15-20: 8.1%; SPF 25-30: 44.4%; SPF ≥ 40: 38.3%; no data: 7.5%). However, 15.2% of those applying a sunscreen with SPF ≥ 15 stated to reduce the SPF on average by half (range: factor 1.2-5) after a few days of sun exposure. Multivariate testing revealed an association between using a SPF ≥ 30, female sex (OR_{adj}: 1.76, 95% CI: 1.29-2.40), and age 18-35 years (OR_{adj}: 2.25, 95% CI: 1.53-3.31). The pursuit of a suntan decreased the odds of choosing a SPF ≥ 40 (OR_{adj}: 0.62, 95% CI: 0.36-1.08).

In Survey 1 and Survey 3, most hat wearers (63.0%) wore a baseball cap and merely 34.3% chose a sunhat with a brim that additionally shades ears and neck (type of headgear was not assessed in Survey 2).

5.4.5 Sunburn experience

In Survey 2, 44.4% of air passengers had suffered from sunburn during their holiday stay (29.2% of these described the sunburn(s) as painful). The body parts most often affected were the face (56.9%), neck and shoulder girdle (27.1%), décolleté (27.1%), upper extremities (24.3%), and trunk (16.0%).

Age 18-35 years, spending holidays in the Caribbean (Cancun, Punta Cana), *not wearing a sunhat*, and *only sometimes using sunscreen* were associated with significantly increased odds of sunburn. Moreover, there was a tendency towards an elevated sunburn risk in males and respondents who never sought shade around noon (Table 5-3). Notably, even among vacationers who claimed they had virtually always applied sunscreen the sunburn rate was as high as 39.1% (independent of the sunscreen's SPF).

Table 5-2 Characteristics of the study population

	Survey 1		**Survey 2**		**Survey 3**	
	n (%)	mean (range)	n (%)	mean (range)	n (%)	mean (range)
Total	533 (100)		324 (100)		308 (100)	
Sex						
Male	200 (37.5)		120 (37.4)		140 (45.5)	
Female	333 (62.5)		203 (62.7)		168 (54.6)	
Age (years)		46.2 (18-81)		51.3 (20-84)		40.1 (19-79)
18-35	149 (28.0)		55 (17.0)		153 (49.7)	
> 35	384 (72.0)		263 (81.2)		155 (50.3)	
No data	-		6 (1.9)		-	
Nationality						
Swiss	178 (33.4)		99 (30.6)		251 (81.5)	
French	226 (42.4)		141 (43.5)		1 (0.3)	
German	110 (20.6)		70 (21.6)		30 (9.7)	
Other	19 (3.6)		10 (3.1)		26 (8.4)	
No data	-		4 (1.2)		-	
Skin type						
Fair (I&II)	266 (49.9)		159 (49.1)		98 (31.8)	
Medium (III&IV)	263 (49.3)		164 (50.6)		210 (68.2)	
No data	4 (0.8)		1 (0.3)		-	
Density of head hair						
Dense	486 (91.2)		283 (87.4)		269 (87.3)	
Sparse	22 (4.1)		13 (4.0)		21 (6.8)	
Bald	20 (3.8)		22 (6.8)		17 (5.5)	
No data	5 (0.9)		6 (1.9)		1 (0.3)	
Holiday destination*						
Southern Europe	59 (11.1)		156 (48.2)		-	
North Africa	287 (53.9)		77 (23.8)		4 (1.3)	
Central and Southern Africa	-		-		85 (27.6)	
North America	-		-		4 (1.3)	
Central and South America	187 (35.1)		91 (28.1)		81 (26.3)	
Southeast Asia	-		-		71 (23.1)	
Other Asia	-		-		26 (8.4)	
Australia and Oceania	-		-		2 (0.7)	
Journey across several continents	-		-		35 (11.4)	
Duration of holiday stay (days)		9.5 (6-90)		12.9 (6-180)		50.3 (7-365)
< 14	500 (93.8)		269 (83.0)		92 (29.9)	
15-30	32 (6.0)		42 (13.0)		114 (37.0)	
> 30	1 (0.2)		13 (4.0)		102 (33.1)	
Holiday activities						
Sightseeing/culture	269 (50.5)		Not assessed		298 (96.8)	
Water activities	474 (88.9)		Not assessed		212 (68.8)	
Other outdoor activities	238 (44.7)		Not assessed		243 (78.9)	
Sunbathing	474 (88.9)		Not assessed		158 (51.3)	

*Flight destinations of participants in Survey 1 and Survey 2: Southern Europe: Fuerteventura, Gran Canaria, and Tenerife (28°N, Canary Islands, Spain); North Africa: Marrakech (32°N, Morocco), Hurghada (27°N, Egypt), and Sharm el-Sheikh (28°N, Egypt); Central America: Cancun (21°N, Mexico) and Punta Cana (19°N, Dominican Republic)

Table 5-3 Multivariate logistic regression analysis for the occurrence of sunburn during the preceding holiday

	Cases: at least one sunburn during the preceding holiday Controls: no sunburn during the preceding holiday				
	Cases	Controls	OR_{adj}	(95% CI)	p-value
Sex					
Female	79	120	1.00	Referent	
Male	61	57	1.68	(0.99-2.85)	0.05
Age group					
> 35 years	103	160	1.00	Referent	
18-35 years	37	17	2.37	(1.19-4.73)	0.01
Skin type					
Fair (I/II)	69	88	1.00	Referent	
Medium (III/IV)	71	89	0.83	(0.50-1.39)	0.49
Holiday destination					
Southern Europe (Canary Islands)	56	94	1.00	Referent	
North Africa	32	44	1.23	(0.66-2.31)	0.51
Central America (Caribbean)	52	39	2.85	(1.58-5.14)	0.001
Seeking shade around noon					
Virtually always on sunny days	51	72	1.00	Referent	
Only sometimes	45	69	1.10	(0.61-1.97)	0.75
Never	44	36	1.87	(0.96-3.64)	0.06
Wearing a sunhat					
Virtually always on sunny days	36	71	1.00	Referent	
Only sometimes	21	18	1.96	(0.84-4.57)	0.12
Never	83	88	2.29	(1.31-4.02)	0.004
Applying sunscreen					
Virtually always on sunny days	99	154	1.00	Referent	
Only sometimes	32	9	5.01	(2.14-11.72)	0.0002
Never	9	14	1.19	(0.46-3.08)	0.72

CI, confidence interval; OR_{adj}, odds ratio adjusted for all variables listed in the table

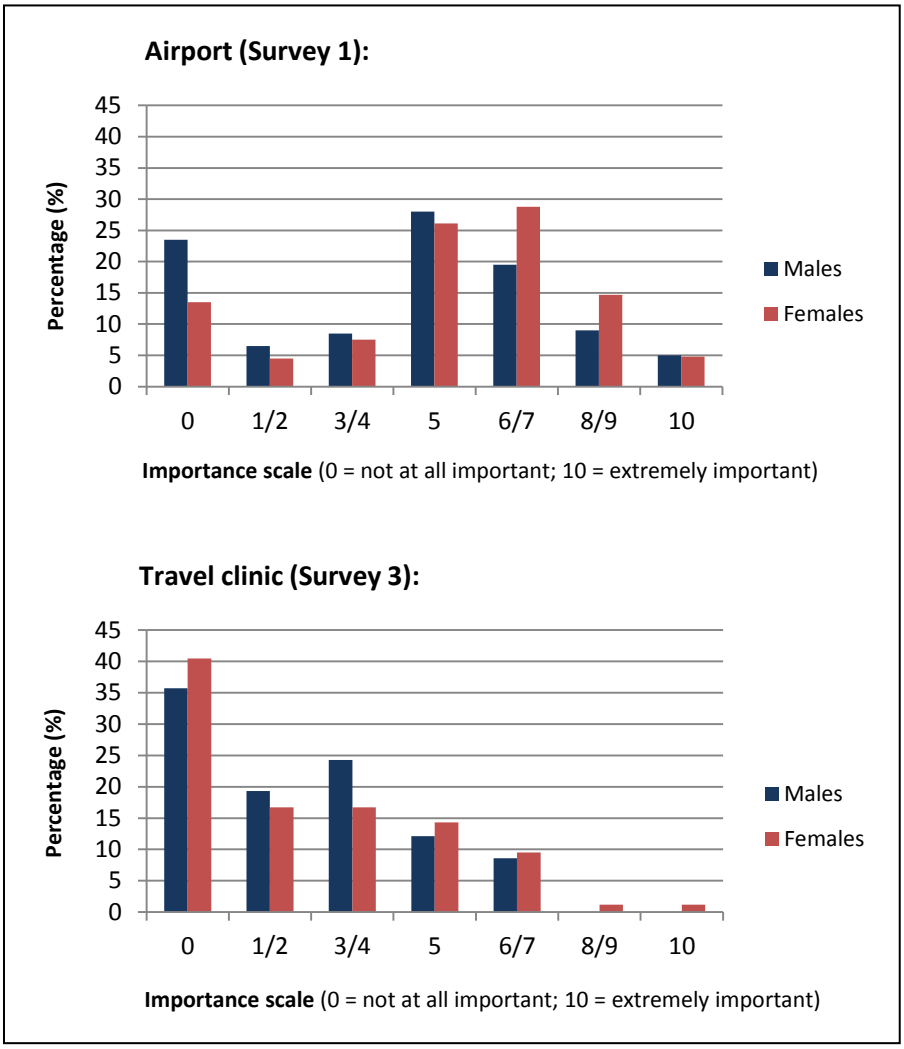


Figure 5-1 Vacationers' attitude towards getting a holiday tan *(Question: "On a scale from 0 to 10, how important is it to you to acquire a suntan during your holidays? 0= not at all important; 10= extremely important")*

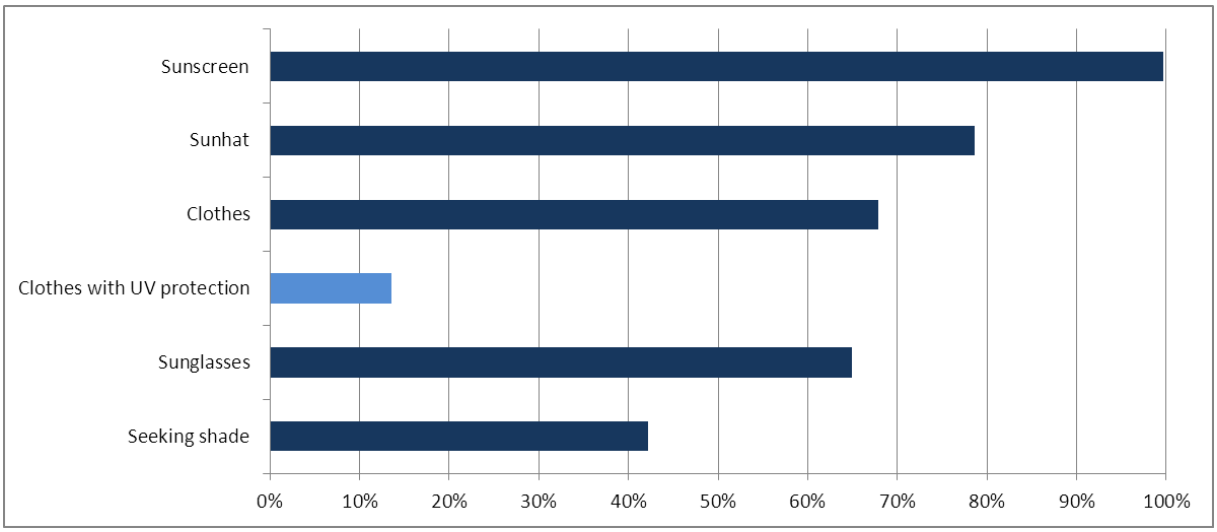


Figure 5-2 Intended sun protective measures of vacationers interviewed at the travel clinic, Survey 3 *(Question: "What sun protective measures do you intend to take during your holidays?" No given response options)*

5.5 Discussion

Whereas vacationers interviewed at the airport represented typical sun worshippers with a high motivation to tan, interviewees at the travel clinic rather planned nature or culture trips without emphasis on sunbathing but involving various other outdoor activities. Given the prolonged sun exposure, either intentional or accidental, and the high UV intensity at the holiday destination, respondents in both study settings share a considerable risk of experiencing sun damage.

The vacationers seemed to be aware of the sun's hazardous effects, since the vast majority used sunscreen. Nevertheless, wearing a sunhat and protective clothing as well as seeking shade were clearly less common sun protection methods, as has been likewise described by other authors.[205-208]

With 44% of returning air passengers having suffered from sunburn during their holidays, the assessed sunburn rate was alarmingly high. Yet it is in accordance with sunburn rates above 30% in beachgoers surveyed during a single day at public beaches in Honolulu (Hawaii, USA)[209] and Galveston (Texas, USA).[208,210] Petersen et al. even reported a sunburn rate of 100% among 25 sun seekers observed throughout a 1-week sun holiday at Tenerife (Canary Islands, Spain).[66] Considering that the melanoma risk increases substantially with an increasing number of sunburns (regardless of what age they are acquired at), these findings are of major public health concern.[211]

Our study and others revealed young adults as a group particularly prone to sunburn, presumably because they have the greatest pursuit of a tan, therefore spend the longest time in the sun, and take the fewest precautions.[65,206]

Not wearing a sunhat more than doubled the risk of experiencing sunburn. Wide-brimmed hats provide reasonable protection to the scalp, face, and neck and could at least partly have prevented the large proportion of sunburns described on these sites.[78]

Albeit sporadic sunscreen users were more likely to suffer from sunburn than routine users, in the latter group too almost four out of ten got sunburnt during their holiday stay. Reasons for sunscreen failure include incomplete coverage of sun-exposed skin, insufficient amount of sunscreen applied, disregard of reapplying the product after swimming and sweating, and overestimation of the protection duration.[210,212,213] Some vacationers reduced the sunscreen's SPF by up to the factor five after a few holiday days, though the natural skin protection afforded by tanning and stratum corneum thickening upon repeated UV (B) exposure is equivalent to a SPF of no more than two and takes at least 1 to 2 weeks to develop.[214,215]

A worrying number of respondents sought to build up natural skin protection before holidays by pre-tanning in the solarium, ignoring that a tan induced by UVA-rich sunlamps is essentially not protective against subsequent sun exposure but per se associated with cellular damage that may result in skin carcinogenesis.[202,203]

Taking dietary supplements containing carotenoids has indeed proven effective in modestly increasing the skin's photoprotective capacities and thereby the erythema threshold. However, the achievement of relevant protection requires at least 10 weeks of supplementation with relatively high doses (for nutrients other than carotenoids the scientific evidence is not conclusive).[90] Since most surveyed travellers started the intake of carotenoids only shortly before their sun holiday, they were unlikely to reap any benefits.

When interpreting our findings, some strengths and limitations of the study need to be considered. Using face-to-face interviews, we attained good quality and completeness of collected data as well as a very high participation rate. On the other hand, due to the lack of anonymity towards the interviewer, we cannot rule out some degree of social desirability bias. Difficulties in correct self-assessment of sunburn may also lead to underestimation of the true incidence rate.[216] A further drawback of self-reported data is inaccuracy due to poor

recall. Nonetheless, we believe that this marginally affected our results since the study setting allowed us to keep recall periods very short.

In conclusion, the observed sunburn rate among vacationers returning from holiday destinations in the tropics or subtropics was alarmingly high. Future skin cancer prevention programs should reveal widespread misconceptions in terms of preparing the skin for the sun, and emphasize adequate sun protective behaviour. Moreover, it should be pointed out that there is no healthy suntan as all tanning is a manifestation of DNA photodamage.[217]

Beside campaigns at community level, pre-travel health advice ought to raise the issue of sun protection at least among travellers most at risk of suffering adverse effects of UVR (e.g. fair-skinned individuals, travellers with children, immunocompromised patients, persons taking photosensitising drugs).[218,219]

Chapter 6

PROJECT IV

Skin cancer prevention, tanning, and vitamin D:

a content analysis of print media in Germany and Switzerland

Daphne Reinau, Christoph R. Meier, Ralf Blumenthal, Christian Surber

Submitted for publication

6.1 Abstract

Background Newspapers and magazines are a major source of health information for the general public.

Objectives To gain insight into the content and quality of press coverage related to skin cancer prevention.

Methods We conducted a comprehensive content analysis of print media articles pertaining to skin cancer prevention, solaria, and vitamin D published in Germany and Switzerland between the years 2012 and 2013.

Results Overall, 2103 articles were included for analysis. Articles reporting on sun protection (n=1287) most commonly recommended applying sunscreen (95.2%), followed by wearing appropriate clothing (60.4%), seeking shade (59.3%), and wearing protective headgear (44.6%). Of the articles reporting on skin cancer detection (n=267), 64.8% fostered skin self-examinations, and 59.9% recommended regular dermatological screening by a health professional. Articles focusing on solaria (n=315) preponderantly mentioned potential adverse health effects. Yet 5.1% and 7.0% advocated indoor tanning to enhance physical appearance and cutaneous vitamin D photosynthesis, respectively. For the latter purpose, exposure to solar or artificial ultraviolet radiation was also promoted in 83.1% of the articles focusing on vitamin D (n=320), with 12% of these not mentioning any precaution measures. In total, 26.8% of all analysed articles contained misleading or erroneous statements mostly related to sunscreen use and vitamin D issues.

Conclusions Print media can serve as powerful education tools to foster skin cancer prevention. However, misleading or erroneous reports may negatively impact sun-safe behaviour. In this context, the media coverage of vitamin D gives special cause for concern.

6.2 Introduction

Skin cancer represents the most frequent malignancy in Caucasian populations,[28] although it is largely preventable by minimising exposure to solar and artificial ultraviolet radiation (UVR).[7,103] Common barriers to primary prevention (sun protection, avoidance of indoor tanning) include lack of awareness, perceived inconvenience, the pursuit of a tanned skin as well as largely unsubstantiated concerns about the safety of sunscreens and insufficient UVR-mediated vitamin D synthesis.[220-223]

Print media are a major source of health information for the general public,[224-227] playing a crucial role in raising knowledge, shaping attitudes, and potentially modifying behaviours regarding sun protection and tanning.[228,229] Considering that skin cancer is readily detectable and highly curable at an early stage, the popular press is moreover indispensable for the widespread communication of secondary prevention strategies (skin self-examinations, dermatological screening).[230] Hence, newspapers and magazines can serve as inexpensive, powerful education tools to foster skin cancer prevention on multiple levels. However, misleading or erroneous reports hold the danger to create confusion and may even negatively impact sun-safe behaviour. In this context, particular mention must be made of unbalanced statements promoting intentional UVR exposure to enhance cutaneous vitamin D photosynthesis, albeit sufficient amounts of the vitamin can be obtained from diet, supplements, and incidental protected sun exposure.[21]

To gain a detailed insight into the content and quality of press coverage pertaining to skin cancer prevention and related topics (solaria, vitamin D), we conducted a comprehensive analysis of respective print media articles published in Germany and Switzerland over a one-year period between 2012 and 2013.

6.3 Methods

6.3.1 Sample selection

Two professional media monitoring agencies prospectively identified print media articles pertaining to skin cancer prevention, solaria, and vitamin D published in Germany and Switzerland over a period of 12 months between 2012 and 2013. The monitoring programmes covered the content from several thousand daily and weekly newspapers, general interest, special interest, and specialist magazines. The complex search profiles

included terms like ‘skin cancer’, ‘malignant melanoma (CMM)’, ‘nonmelanoma skin cancer (NMSC)’, ‘sun protection’, ‘sunscreen’, ‘UV filters’, ‘solarium’, and ‘vitamin D’, as well as corresponding synonyms.

We entirely read all retrieved articles and excluded them from further analysis if they focused on portrayal of individual skin cancer patients, cancer statistics, therapy (skin cancer, sunburn), ‘sun allergy’, or photosensitising substances. We did not consider articles with fewer than four relevant sentences, medical press, reader’s letters, announcements and reports of events, and advertisements for specific products or institutions.

6.3.2 Coding procedure

Using a standardized coding sheet, one author (DR) assessed the articles’ descriptive characteristics (primary topic, publication source, length, authorship, target audience), content (presence or absence of pre-defined information), and quality (correct, misleading, or erroneous information). Articles were defined as ‘misleading’ if they contained at least one statement that could lead readers to false conclusions without being demonstrably wrong (e.g. ambiguous wording, omission of important facts), and as ‘erroneous’ if they contained at least one statement that was factually incorrect according to the current state of science. All statements coded as misleading or erroneous were re-evaluated by a second author (CS).

6.3.3 Statistical analysis

We summarised the extracted data using descriptive statistics. Where appropriate, we calculated frequency distributions separately by the articles’ primary topic (i.e. skin cancer primary prevention, secondary prevention, solaria, and vitamin D).

In addition, we set up a multivariate logistic regression model to examine potential associations between the quality of the articles (outcome: misleading or erroneous information) and selected predictor variables. These comprised the articles’ country of publication, publication source, circulation, length, and authorship. Odds ratios (OR) were adjusted for all variables in the model and are presented with the corresponding 95% confidence interval (CI).

All analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC) and statistical significance was defined at the alpha-level of 0.05.

6.4 Results

Table 6-1 displays the characteristics of the 2103 articles included for analysis. The seasonal frequency of media coverage by primary topic is illustrated in Fig. 6-1.

6.4.1 Primary prevention

In the 1396 articles on primary prevention, the most frequently cited adverse effects of UVR exposure were sunburn (64.8%) and skin cancer (61.7% [CMM: 18.6%; NMSC: 14.0%; not specified: 41.5%]), followed by premature skin ageing (28.4%) and eye disorders (5.3%). Person groups and areas at increased risk of suffering UV damage were named in 54.2% and 16.0% of the texts, respectively (Fig. 6-2). Only a few articles pointed out that UVR may penetrate into the shade (12.9%), through clouds (8.5%), window glass (7.1%), and the water surface (2.6%). No more than 3.1% mentioned the UV Index (UVI) as a measure of the current or forecast UVR intensity at a given time and location.[231]

Artificial tanning was discouraged in 10.7% of articles on primary prevention, and 2.7% stated that a suntan is a manifestation of cutaneous photodamage. On the other hand, 6.0% and 2.0% associated a tanned skin with terms like “attractive” and “healthy”, respectively.

Specific sun protection recommendations were made in 1287 articles (Table 6-2 and Fig. 6-3). Of these, 22.3% exclusively suggested the use of sunscreen.

6.4.2 Secondary prevention

Of the 267 articles on secondary prevention, 64.8% recommended skin self-examinations to detect early signs of skin cancer. However, 89.6% of these did not explain how to perform self-examination, and 11.0% did not describe skin cancer symptoms. The recommendations regarding skin cancer screening by a health professional differed between Germany and Switzerland, with 66.2% of German and 23.1% of Swiss articles on secondary prevention advocating routine dermatological screening for the general adult population.

6.4.3 Solaria

Of the 315 articles focusing on solaria, 93.3% mentioned potential adverse health effects (skin cancer: 87.9%; premature skin ageing: 16.5%; skin burn: 15.6%; eye disorders: 14.6%). Yet 7.0% and 5.1% promoted artificial tanning to enhance cutaneous vitamin D synthesis and physical appearance, respectively.

6.4.4 Vitamin D

Of the 320 articles focusing on vitamin D, 83.1% recommended UVR exposure to achieve healthy vitamin D levels (5.9% encouraged the use of solaria). Of these, 12.0% neither stated that UVR may present a hazard to health nor that vitamin D photosynthesis requires only a relatively small amount of UVR. Furthermore, 17.5% of all vitamin D articles emphasised that sunscreens may limit or even completely block vitamin D photosynthesis.

6.4.5 Quality of information

In total, 26.8% of all analysed articles contained misleading or erroneous information (misleading statements: 22.4%; erroneous statements: 10.9%). Table 6-3 shows the frequency of inaccuracies by topic and some illustrative examples along with our comments.

According to the multivariate model, articles published in general interest and special interest magazines were about twice as likely to contain misleading or erroneous information as articles published in daily or weekly newspapers (OR: 2.02, 95% CI: 1.43-2.85 and OR: 1.87, 95% CI: 1.18-2.96, respectively). Furthermore, the odds of misleading or erroneous information were increased for articles authored by health professionals compared to articles authored by journalists (OR: 2.14, 95% CI: 1.41-3.24) and for long and medium articles compared to short articles (OR: 11.97, 95% CI: 6.17-23.22 and OR: 5.47, 95% CI: 4.13-7.23, respectively). The country of publication and the circulation did not significantly influence the articles' quality.

Table 6-1 Characteristics of the analysed print media articles

	Number of articles (%)
Total	2103 (100.0)
Primary topic	
Primary skin cancer prevention	1396 (66.4)*
Secondary skin cancer prevention	267 (12.7)*
Solaria	315 (15.0)
Vitamin D	320 (15.2)
Country of publication	
Germany	1866 (88.7)
Switzerland	237 (11.3)
Publication source	
Daily and weekly newspapers	1643 (78.1)
General interest magazines	314 (14.9)
Special interest magazines	129 (6.1)
Other	17 (0.8)
Circulation	
< 25 000	598 (28.4)
25 000- 99 999	718 (34.1)
100 000 - 199 999	408 (19.4)
≥ 200 000	373 (17.7)
Unknown	6 (0.3)
Article length	
Short (approx. < ½ page)	723 (34.4)
Medium (approx. ½ - 1 ½ page)	1322 (62.9)
Long (approx. > 1 ½ page)	58 (2.8)
Authorship	
Journalist	1609 (76.5)
Health professional	125 (5.9)
Unknown	369 (17.6)
Target audience	
General public	1753 (83.4)
Parents	214 (10.2)
Children and adolescents	57 (2.7)
Other	79 (3.8)

*195 articles reported on primary and secondary prevention and were counted in both categories.

Table 6-2 Frequency of specific sun protection recommendations

	Number of articles (%)
Any sun protection recommendation	**1287 (100.0)**
Sunscreen	**1225 (95.2)**
Recommendation of specific (minimum) SPF	492 (38.2)
Reference to regular reapplication	397 (30.8)
Reference to amount of application	322 (25.0)
Broad-spectrum sunscreen	240 (18.6)
Water-resistant sunscreen	127 (9.9)
Clothing	**777 (60.4)**
With integrated UV protection	213 (16.6)
Made of tightly-woven fabric	104 (8.1)
Made of dark fabric	76 (5.9)
Made of synthetic fabric	35 (2.7)
Shade	**763 (59.3)**
Sun avoidance around noon	523 (40.6)
Protective head gear	**574 (44.6)**
Wide-brimmed or with neck flaps	155 (12.0)
Sun glasses	**354 (27.5)**
With UV protection	150 (11.7)
With wrap-around design or large lenses	26 (2.0)
Systemic sun protection	**45 (3.5)**
Diet (e.g. carrots, tomatoes)	29 (2.3)
Dietary supplements (e.g. beta-carotene tablets)	25 (1.9)

SPF, Sun Protection Factor

Table 6-3 Frequency and illustrative examples of misleading or erroneous media statements by topic of inaccuracy

Topic of inaccuracy	Number of articles (%)*	Examples (Original quotes from the articles translated into English)	Comment
Sunscreen: application	139 (24.6)	*The sunscreen only grants protection once a day which is not prolonged by repeated application. That just promotes buying!*	Although the reapplication of sunscreen does not extend the provided protection time[‡], it is indispensable to compensate for initial underapplication and to replace sunscreen that may have been removed by sweat, water, towelling, or friction with clothing or sand.[87] (Statement rated as misleading)
Sunscreen: SPF	137 (24.3)	*You can calculate how long you can sunbathe without danger. UVB protection factor multiplied by your own natural protection time.*	Under laboratory conditions (2mg sunscreen/cm^2 skin, no abrasion), the protection time[†] of sunscreen-protected skin can be calculated by multiplying the sunscreen's SPF with the natural protection time of the unprotected skin (dependent on the skin phototype).[84] Under real-world conditions, the protection time of sunscreen-protected skin is usually much shorter, because consumers apply insufficient amounts of sunscreen (typically < 1 mg/cm^2) and fail to reapply the product after swimming and sweating.[210,212,213] (Statement rated as misleading)
		SPF 20 is enough. It already absorbs 95% of all UVB rays. It is absurd to believe that SPF 40 protects you double as well as SPF 20. An additional protection is hardly measurable with sunscreens with a higher factor - they are just more expensive.	Sunscreens with SPF 20 and SPF 40 filter out 95.0% and 97.5% of the erythemogenic UVR, respectively. Hence, the UVR dose that penetrates into the skin and is responsible for UV damage is halved between SPF 20 and SPF 40 (5% versus 2.5%), i.e. the protection doubles between SPF 20 and SPF 40.[86] (Statement rated as erroneous)
Sunscreen: labelling (excl. SPF)	60 (10.6)	*All sunscreen products nowadays guarantee a protection from UVA- and UVB rays*	In Europe, adequate UVA protection is only guaranteed, if a sunscreen is labelled with the UVA logo.[86]  (Statement rated as erroneous)
Sunscreen: safety	67 (11.9)	*Traditional sunscreens contain chemicals that are known to be toxic.*	Before their approval, UV filters have to pass a thorough safety evaluation including studies on acute toxicity, (sub)chronic toxicity, reproductive toxicity, genotoxicity, photogenotoxicity, carcinogenicity, irritation, sensitization, phototoxicity, and photosensitation.[232] (Statement rated as erroneous)
Sunscreen: other	21 (3.7)	*Sunscreens protect you from sunburn, but not from skin cancer.*	Evidence from randomised controlled trials suggests that regular sunscreen use prevents cutaneous squamous cell carcinoma (including actinic keratosis)[79,233] and malignant melanoma.[80] (Statement rated as erroneous)
Protective clothing	49 (8.7)	*Clothing with UV-protection is good, but so is thin cotton clothing.*	Clothes with integrated UV absorbers are an excellent means of photoprotection. However, the protection provided by thin clothes made of cotton is limited.[72] (Statement rated as misleading)

Table 6-3 continued

Topic of inaccuracy	Number of articles (%)*	Examples (Original quotes from the articles translated into English)	Comment
Systemic sun protection	45 (8.0)	*Someone who is going on holiday to a sunny place should start eating fruit and vegetables with plenty of beta-carotene 4 weeks beforehand at the latest.*	Beta-carotene has proven effective in modestly increasing the skin's photoprotective capacities. Yet the achievement of relevant protection requires the intake of relatively high doses (~10mg/day) over at least 10 weeks.[88] (Statement rated as misleading)
Sunbathing	94 (16.7)	*You should only lie in direct sun for as long as you don't get sunburnt.*	Significant molecular and cellular skin damage occurs already at suberythemal UVR doses.[234] (Statement rated as misleading)
Suntan	43 (7.6)	*Tanned skin is the best light protector.*	The natural skin protection afforded by tanning upon repeated UVR exposure is very modest (~SPF 2).[214] Furthermore, tanning always comes at the cost of DNA photodamage.[217] (Statement rated as erroneous)
Solarium	43 (7.6)	*Modern sun studios have got tanning beds that are, thanks to new legislation, designed to maximise the healthy effect of the sun as well as the nice tan-effect, without damaging the skin.*	Irrespective of regulations, solaria users are exposed to high levels of UVR which increase their risk of skin cancer and premature skin ageing.[235,236] (Statement rated as erroneous)
		By systematic pre-tanning in the solarium with professional advice, it is possible to heighten the natural protection of the skin and reduce the risk of getting sunburnt.	A tan induced by UVA-rich solaria is essentially not protective against subsequent sun exposure, but per se associated with cutaneous photodamage.[203] (Statement rated as erroneous)
Vitamin D	120 (21.3)	*Due to vitamin D being produced in the skin, sunbathing at the beach or in the garden is highly recommendable. In winter the solarium is an alternative.*	Since UVR is a human carcinogen, prolonged sun exposure and solaria should be avoided. Adequate vitamin D levels can be obtained from short incidental sun exposure, diet, or oral supplements.[21,236] (Statement rated as erroneous)
		Already a SPF of 10 is enough to practically paralyse vitamin D production.	Sunscreens do not completely block UVR, but permit the transmission of a fraction of UVB equal to 1/SPF (i.e. 1/10 or 10% for a SPF 10 sunscreen). Moreover, consumers usually apply less sunscreen than has been used for the SPF determination. In real-life situations, regular sunscreen use does not lead to decreased vitamin D levels.[237,238] (Statement rated as erroneous)
Other	71 (12.6)	*Research has shown that people who work mostly outside, like gardeners or farmers, are less likely to contract skin cancer.*	According to two recent meta-analyses, outdoor workers are at increased risk of developing nonmelanoma skin cancer.[55,56] (Statement rated as erroneous)

SPF, Sun Protection Factor; UVR, ultraviolet radiation

*100% corresponds to the 564 articles containing misleading or erroneous information. Articles with several inaccurate statements on different topics were counted in all corresponding categories.

† Time of UVR exposure until the occurrence of sunburn

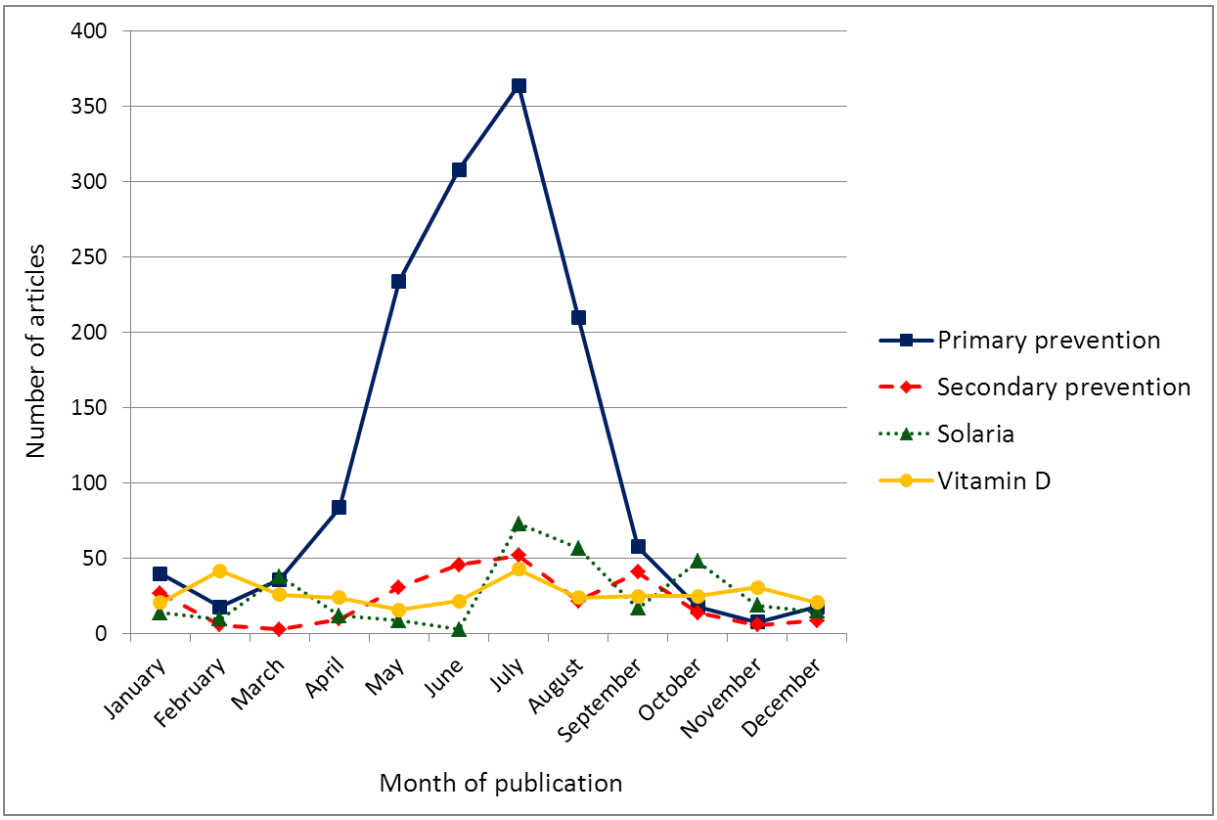


Figure 6-1 Seasonal print media coverage of skin cancer prevention, solaria, and vitamin D

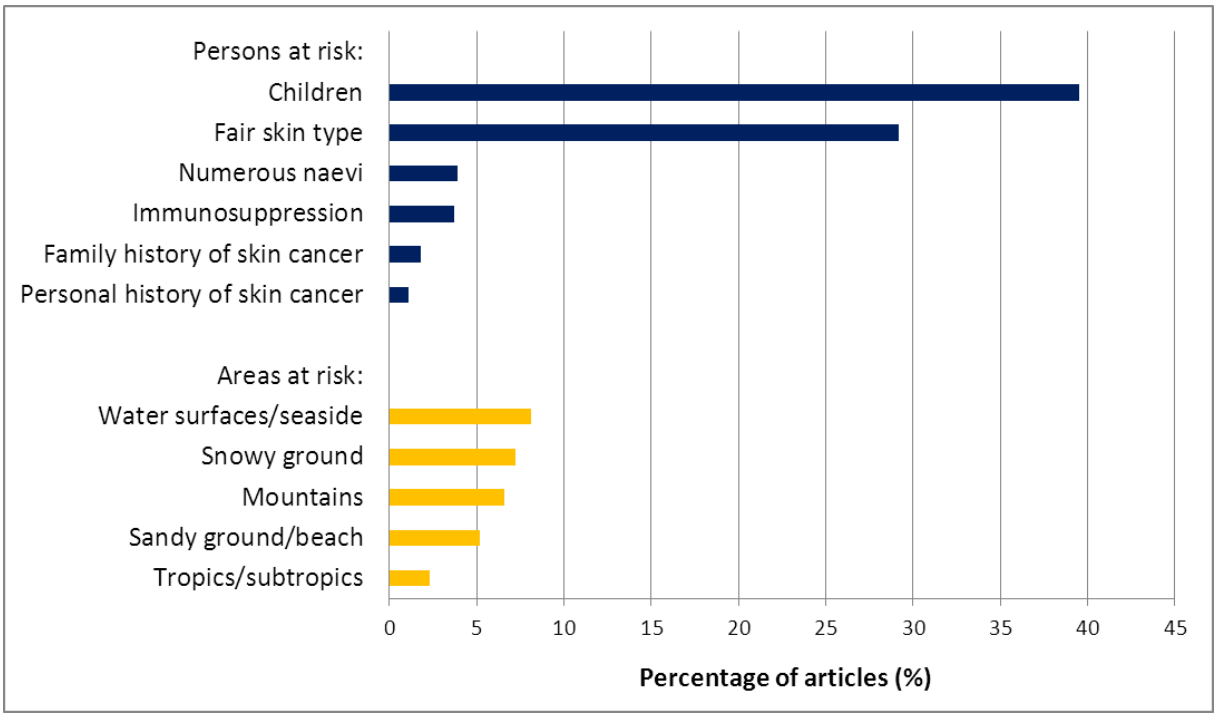


Figure 6-2 Frequency of references to person groups and areas at increased risk of suffering UV damage in articles on primary prevention (n=1396).

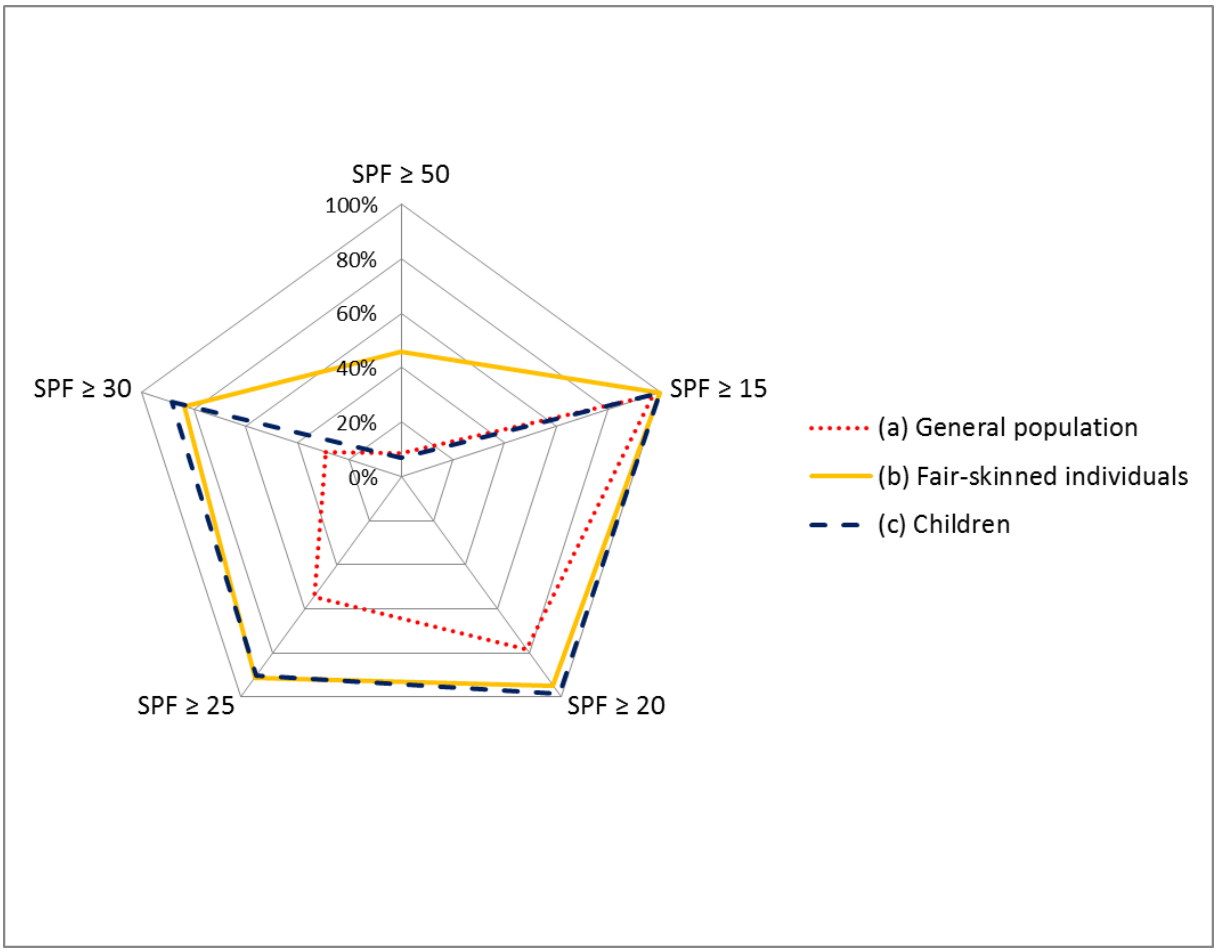


Figure 6-3 Minimum Sun Protection Factor (SPF) of sunscreens recommended in articles on primary prevention (a) for the general population (adults of unspecified skin type), (b) for fair-skinned individuals (Fitzpatrick skin type I/II), and (c) for children (100% corresponds to all articles stating a [minimum] SPF for the respective target group).

6.5 Discussion

The present study represents to our knowledge the most comprehensive content analysis of skin cancer-related print media to date and provides a unique insight into the way prevention messages issued by health organisations reach the public.

Before the 1930s, the association between UVR exposure and skin cancer was rarely mentioned in the popular press and virtually unknown to the general population.[108] Yet in the meantime, skin cancer primary prevention by UVR protection has become a frequently covered media topic, particularly during the summer months.

However, although we identified individual well written and informative reports, the information content of the analysed articles in general was rather limited. Few authors reported that adequate UVR protection does not merely prevent sunburn and skin cancer, but also premature skin ageing and eye disorders. Person groups and situations at increased risk of suffering UV damage were not routinely mentioned, and the UVI as a communication tool of UVR intensity was hardly ever explained. Hence, it is not surprising that the awareness and understanding of the UVI in Germany as well as in Switzerland was found to be very low.[239,240]

The use of sunscreen was by far the most common and- in many cases- the sole sun protection recommendation made, even though seeking shade and covering up with clothing are assigned a more important role in the hierarchy of photoprotective strategies.[72,73] Moreover, only a minority of articles contained detailed advice about what kind of sunscreen (sun protection factor [SPF], UVA protection, water resistance), clothing (fabric properties), and headgear (wide brim, neck flaps) best to use, and about how to apply sunscreen properly (amount and timing of application, reapplication). The recommended SPFs differed substantially, ranging from 10 to 50+ for the general population (adults of unspecified skin type). This reflects in part the diverging SPF recommendations published by national and international cancer control and health agencies. To name a few examples, the Swiss Cancer League generally advises SPF ≥15,[241] the Swiss Federal Office of Public Health as well as the German Cancer Aid recommend SPF ≥20,[242,243] and the European Skin Cancer Foundation suggests SPF ≥25.[244]

Paradoxically, a noteworthy number of articles on skin cancer primary prevention promoted a suntanned skin as attractive or healthy, albeit it is well established that all tanning is a manifestation of DNA photodamage.[217]

Skin cancer secondary prevention by skin self-examinations and dermatological screening receives relatively little attention in the press. Accordingly, a representative telephone survey in Germany revealed that in 2011 less than half of the adult population was aware that persons with statutory health insurance above the age of 35 years are entitled to a biennial skin cancer screening by a trained physician.[245] In Switzerland, routine skin cancer screening is neither generally recommended nor refunded by the health insurance, which accounts for the country differences in the media coverage of this topic.

Despite the widely recognised health risks linked to indoor tanning, several newspapers and magazines still release articles which encourage the visit to solaria in order to acquire a tan and to boost vitamin D photosynthesis. Aside from recommending active exposure to a carcinogen, these articles ignore that tanning devices usually emit predominantly UVA, whereas the action spectrum for vitamin D formation lies in the UVB range.[202]

Compared to solaria, natural sunlight is very efficient in inducing cutaneous vitamin D synthesis. Maximum vitamin D concentrations are already reached after exposure of a relatively small skin surface to solar UVR doses well below the minimal erythema dose. Thus, incidental protected sun exposure usually results in vitamin D levels considered sufficient to maintain musculoskeletal health and potentially to prevent extra-skeletal disorders associated with vitamin D deficiency (e.g. certain internal cancers and autoimmune diseases). Alternatively, diet and oral supplements constitute non-carcinogenic, readily available sources of the vitamin - facts the media often fail to acknowledge.[21,22]

Recent evidence from Australia suggests that concurrent with an increase in media coverage of vitamin D,[246,247] an increasing proportion of the population reduces sun protection practices due to concerns about vitamin D insufficiency.[248] In view of the numerous vitamin D articles unsupportive for UVR protection identified in our study, a similar decline in skin cancer preventive behaviours may be expected in Central Europe.

On the whole, the quality of information across all articles included in our content analysis gives rise to concern, with more than every fourth text containing misleading or erroneous statements. Most ascertained inaccuracies pertained to the use of sunscreens, particularly to their correct application and the meaning and implication of the labelled SPF, followed by

vitamin D issues. It should be noted that uncertainties about these topics do not only prevail among journalists, but also among the journalists' sources, namely dermatologists and other health professionals. This explains the somewhat elusive finding that articles authored by health professionals were not of better quality than articles authored by journalists.

In summary, the data reported herein provide a broad picture of skin cancer prevention and vitamin D messages made available to the public through German and Swiss print media. The delivered information was generally rather superficial and in a considerable number of newspaper and magazine articles misleading or factually incorrect. The latter is partly rooted in persistent misconceptions regarding UVR protection which prevail in the medical community and are subsequently adopted by journalists. To assist the media in disseminating sound skin cancer prevention strategies, health organisations should formulate consistent, easily understandable recommendations based on the current state of science. The uneasy relationship between UVR protection and adequate vitamin D synthesis ought to be proactively addressed, since unbalanced reports on this issue may seriously undermine the longstanding efforts of sun safety campaigns.

Chapter 7

PROJECT V

Epidemiology of basal cell carcinoma in the UK: incidence, lifestyle factors, and comorbidities

Daphne Reinau, Christian Surber, Susan S. Jick, Christoph R. Meier

British Journal of Cancer 2014; 111: 203-6

7.1 Abstract

Background Little is known about the epidemiology of basal cell carcinoma (BCC).

Objectives To estimate UK BCC incidence rates and to characterise lifestyle factors and comorbidities of affected patients.

Methods Using the Clinical Practice Research Datalink, we calculated annual incidence rates. In a case-control analysis, we examined lifestyle factors and comorbidities.

Results Incidence rose significantly between 2000 and 2011. BCC risk was increased in alcohol drinkers (slightly) and immunocompromised patients, but reduced in smokers and individuals with abnormal weight.

Conclusions BCC places a growing public health burden. Lifestyle factors do not play a major role in pathogenesis, but immunosuppression is important.

7.2 Introduction

Cutaneous basal cell carcinoma (BCC) represents the most common malignancy in Caucasian populations, and the incidence is rising.[28] Nevertheless, it is often omitted from official cancer statistics, as little is known about the true extent of the disease. Cancer registries, if at all, only include histologically confirmed tumours and do not take into account the substantial proportion of BCCs diagnosed clinically without histology.[29]

BCC is primarily caused by heavy episodic and chronic sun exposure.[7] Predisposing factors include fair skin type, immunosuppression, and certain genetic disorders (e.g. albinism, Gorlin syndrome, xeroderma pigmentosum).[249] Data on the relationship between BCC, other diseases, and lifestyle factors are limited.

Using the Clinical Practice Research Datalink (CPRD), we aimed at estimating BCC incidence in the UK and at characterising affected patients regarding lifestyle factors and comorbidities.

7.3 Methods

7.3.1 Data source

The CPRD is a large primary care database containing computerised longitudinal patient records for about 6% of the UK population. Available data include demographics, lifestyle factors, medical diagnoses, and prescribed drugs. Numerous studies have demonstrated the completeness and high validity of the records.[250,251]

7.3.2 Study design

We calculated incidence rates (IRs) of BCC in adults between 2000 and 2011, stratified by age, sex, and year of diagnosis.

Using a case-control design, we compared alcohol consumption, smoking status, BMI, and selected comorbidities present before diagnosis between patients with incident BCC and a disease-free control group.

7.3.3 Study population

We identified all patients aged 18 years or older in the CPRD with a BCC first-time diagnosis between 2000 and 2011.

Patients with less than three years of history in the CPRD before diagnosis as well as those with a record of albinism, Gorlin syndrome, or xeroderma pigmentosum were excluded.

For the case-control analysis, we randomly selected a group of controls (patients with no recorded BCC) matched 1:1 to BCC cases on age, sex, general practice, calendar time, and years of history in the database. The same exclusion criteria were applied to controls as to cases.

7.3.4 Statistical analysis

We calculated crude IRs as the number of new BCC cases during the study period divided by the total number of person-years at risk (person-years of all adult individuals at risk in the CPRD between start of the study period and end of follow-up, i.e. the day of first BCC diagnosis, death, leaving the practice, or the end of the study period, whichever came first). We also computed directly age-standardised incidence rates (ASRs, reference: European

standard population 1976) and standardised rate ratios (SRRs) to compare rates between sexes and over time.

For comparison of alcohol consumption (non, current, ex; units per week), smoking status (non, current, ex; cigarettes per day), BMI (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m^2), and comorbidities (Table 7-1) between cases and controls, we conducted conditional logistic regression analyses and presented relative risk estimates as odds ratios (ORs) with 95% confidence intervals (CIs).

We controlled for confounding by running a multivariate model incorporating all examined lifestyle factors and the number of general practitioner visits in the year before diagnosis (marker for medical attention). Comorbidities were not included, as they were only thought to descriptively characterise the study population.

Analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC). Statistical significance was defined at the alpha-level of 0.05.

7.4 Results

7.4.1 UK incidence rates

We identified 57 123 adults with a BCC first-time diagnosis between 2000 and 2011. The overall crude IR and ASR were 201.7 (95% CI: 200.1-203.4) and 151.8 (95% CI: 150.5-153.1) per 100 000 person-years, respectively. BCC incidence sharply increased with increasing age. Although men had a higher aggregate risk than women (SRR: 1.27, 95% CI: 1.25-1.29), BCC was more common among the latter in individuals younger than 55 years (Supplementary Table 7-1).

BCC incidence rose over time in both sexes and in all age groups except in those under 30 years, with an overall increase of 39% between 2000 and 2011 (SRR: 1.39, 95% CI: 1.33-1.45, Fig. 7-1).

7.4.2 Lifestyle factors

The case-control analysis comprised 57 121 cases and the same number of matched controls (mean age 69.5 years [standard deviation: 13.3 years], 51.3% males). Current alcohol drinkers had a slightly elevated BCC risk compared with non-drinkers. However, the risk only marginally increased with increasing number of alcohol units consumed per week. Smokers

had a significantly reduced BCC risk compared with non-smokers. The lowest risk was observed in current heavy smokers (≥ 40 cigarettes per day), indicating a negative dose-response relationship between smoking and BCC. Individuals with a BMI outside the normal range (BMI < 18.5 or ≥ 25) were less likely to develop BCC than normal-weight individuals (Table 7-2 & Supplementary Table 7-2).

7.4.3 Comorbidities

Compared with controls, BCC cases were significantly more likely to have a medical history of rheumatoid arthritis (RA), inflammatory bowel disease (IBD), extra-cutaneous malignancies, solid organ transplantation, and various skin disorders. On the other hand, they were less likely to have been diagnosed with chronic obstructive pulmonary disease (COPD), diabetes mellitus, schizophrenia, and dementia. The prevalences of the remaining examined comorbidities were equally distributed between the two groups (Table 7-1).

Table 7-1 Distribution of comorbidities among basal cell carcinoma cases and their matched controls

	BCC cases (n= 57 121), n (%)	**BCC-free controls** (n= 57 121), n (%)	**OR crude (95%CI)**
Diseases of internal organs			
COPD	2663 (4.7)	2922 (5.1)	0.90 (0.86-0.96)
Diabetes mellitus	5009 (8.8)	5709 (10.0)	0.86 (0.83-0.90)
Hypertension	22235 (38.9)	21807 (38.2)	1.04 (1.01-1.06)
Gout	3660 (6.4)	3483 (6.1)	1.06 (1.01-1.11)
Rheumatoid arthritis	1571 (2.8)	1322 (2.3)	1.20 (1.11-1.29)
Inflammatory bowel disease	729 (1.3)	589 (1.0)	1.24 (1.11-1.39)
Depression	8784 (15.4)	8758 (15.3)	1.00 (0.97-1.04)
Schizophrenia	271 (0.5)	381 (0.7)	0.71 (0.61-0.83)
Dementia	672 (1.2)	945 (1.7)	0.70 (0.63-0.77)
Malignancies (excl. skin cancer)	5247 (9.2)	4015 (7.0)	1.35 (1.29-1.41)
Solid organ transplantation	205 (0.4)	41 (0.1)	5.10 (3.63-7.16)
Skin diseases			
Atopic dermatitis	3761 (6.6)	3305 (5.8)	1.16 (1.10-1.22)
Seborrhoeic dermatitis	3514 (6.2)	2686 (4.7)	1.34 (1.27-1.41)
Skin mycoses	8560 (15.0)	7263 (12.7)	1.22 (1.18-1.27)
Bacterial skin infections	3948 (6.9)	3388 (5.9)	1.18 (1.13-1.24)
Warts	5462 (9.6)	3642 (6.4)	1.58 (1.51-1.65)
Herpes infection	6923 (12.1)	6236 (10.9)	1.13 (1.09-1.17)
Psoriasis	2480 (4.3)	2319 (4.1)	1.07 (1.01-1.14)
Rosacea	2346 (4.1)	1671 (2.9)	1.43 (1.34-1.53)
Cutaneous malignant melanoma	810 (1.4)	332 (0.6)	2.46 (2.16-2.80)

BCC, basal cell carcinoma; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio

Table 7-2 Distribution of lifestyle factors among basal cell carcinoma cases and their matched controls

	BCC cases (n= 57 121), n (%)	BCC-free controls (n= 57 121), n (%)	OR crude (95%CI)	OR adjusted* (95%CI)
Alcohol status				
Non	8592 (15.0)	9442 (16.5)	1.00 (ref.)	1.00 (ref.)
Ex	1069 (1.9)	1193 (2.1)	1.00 (0.92-1.09)	0.96 (0.87-1.05)
Current	42640 (74.7)	40552 (71.0)	1.18 (1.14-1.22)	1.19 (1.15-1.23)
Unknown	4820 (8.4)	5934 (10.4)	0.87 (0.82-0.91)	1.05 (0.99-1.11)
Smoking status				
Non	28058 (49.1)	26439 (46.3)	1.00 (ref.)	1.00 (ref.)
Ex	19607 (34.3)	19033 (33.3)	0.98 (0.95-1.00)	0.91 (0.89-0.94)
Current	6999 (12.3)	8359 (14.6)	0.78 (0.75-0.80)	0.77 (0.74-0.80)
Unknown	2457 (4.3)	3290 (5.8)	0.65 (0.62-0.70)	0.92 (0.86-0.99)
BMI (kg m^{-2})				
12.0-18.4	868 (1.5)	910 (1.6)	0.86 (0.79-0.95)	0.86 (0.78-0.95)
18.5-24.9	20522 (35.9)	18591 (32.6)	1.00 (ref.)	1.00 (ref.)
25.0-29.9	19849 (34.8)	19246 (33.7)	0.93 (0.91-0.96)	0.90 (0.87-0.92)
30.0-60.0	8907 (15.6)	10072 (17.6)	0.80 (0.78-0.83)	0.73 (0.70-0.75)
Unknown	6975 (12.2)	8302 (14.5)	0.73 (0.70-0.76)	0.89 (0.85-0.94)

BCC, basal cell carcinoma; BMI, body mass index; CI, confidence interval; OR, odds ratio

*Adjusted for alcohol status, smoking status, BMI, and number of general practitioner visits 1 year before BCC diagnosis.

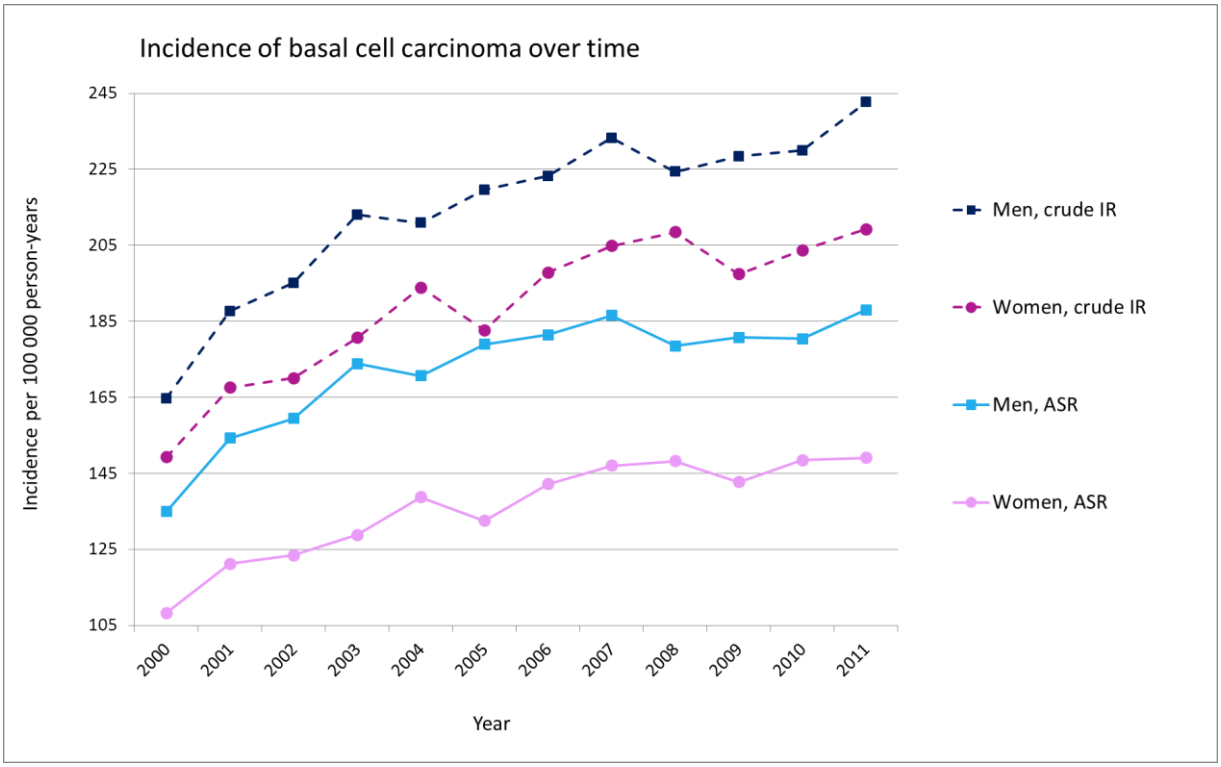


Figure 7-1 Sex-specific crude incidence rates (IRs) and age-standardised incidence rates (ASRs) of basal cell carcinoma first-time diagnoses in the UK from 2000 to 2011 (reference: European standard population)

Supplementary Table 7-1 Age- and sex-specific UK incidence rates of basal cell carcinoma first-time diagnoses in adults over the period from 2000 to 2011

Age group (years)	Men			Women		
	BCC cases (n)	py at risk	IR per 100 000 py (95% CI)	BCC cases (n)	py at risk	IR per 100 000 py (95% CI)
18-19	8	472 967.1	1.7 (0.5-2.9)	9	453 846.0	2.0 (0.7-3.3)
20-24	24	1 077 585.9	2.2 (1.3-3.1)	28	1 027 304.4	2.7 (1.7-3.7)
25-29	56	987 497.7	5.7 (4.2-7.2)	77	965 955.8	8.0 (6.2-9.8)
30-34	131	1 056 162.3	12.4 (10.3-14.5)	161	1 100 486.9	14.6 (12.4-16.9)
35-39	283	1 248 365.8	22.7 (20.0-25.3)	444	1 319 158.0	33.7 (30.5-36.8)
40-44	579	1 348 309.7	42.9 (39.4-46.4)	809	1 402 096.4	57.7 (53.7-61.7)
45-49	1004	1 298 042.3	77.4 (72.6-82.1)	1215	1 327 712.4	91.5 (86.4-96.7)
50-54	1539	1 221 494.5	126.0 (119.7-132.3)	1689	1 247 616.9	135.4 (128.9-141.8)
55-59	2367	1 175 869.2	201.3 (193.2-209.4)	2226	1 211 082.9	183.8 (176.2-191.4)
60-64	3343	1 045 868.0	319.6 (308.8-330.5)	2866	1 086 617.9	263.8 (254.1-273.4)
65-69	4077	843 986.9	483.1 (468.2-497.9)	3173	912 955.8	347.6 (335.5-359.7)
70-74	4572	692 657.0	660.1 (640.9-679.2)	3646	811 821.9	449.1 (434.5-463.7)
75-79	4662	535 792.0	870.1 (845.1-895.1)	3807	711 274.4	535.2 (518.2-552.2)
80+	6641	601 304.5	1104.4 (1077.9-1131.0)	7687	1 135 271.9	677.1 (662.0-692.2)
ASR			172.1 (170.1-174.0)			135.4 (133.7-137.1)

ASR, age-standardised incidence rate (reference: European standard population); BCC, basal cell carcinoma; CI, confidence interval; IR, incidence rate; py, person-years

Supplementary Table 7-2 Distribution of alcohol and smoking status among basal cell carcinoma cases and their matched controls, stratified by alcohol units consumed per week and cigarettes smoked per day.

	BCC cases	**BCC-free controls**	**OR crude (95%CI)**	**OR adjusted* (95%CI)**
	n (%)	n (%)		
Alcohol status				
Non	8592 (15.0)	9442 (16.5)	1.00 (ref.)	1.00 (ref.)
Current				
1-4 units/week	10878 (19.0)	10569 (18.5)	1.16 (1.11-1.20)	1.16 (1.11-1.21)
5-9 units/week	6397 (11.2)	5811 (10.2)	1.24 (1.18-1.30)	1.26 (1.20-1.32)
10-14 units/week	5622 (9.8)	5011 (8.8)	1.27 (1.21-1.34)	1.29 (1.22-1.36)
15-24 units/week	3518 (6.2)	3296 (5.8)	1.22 (1.15-1.29)	1.25 (1.18-1.33)
25+ units/week	2644 (4.6)	2480 (4.3)	1.22 (1.14-1.30)	1.27 (1.18-1.36)
Units/week unknown	13581 (23.8)	13385 (23.4)	1.13 (1.08-1.17)	1.13 (1.09-1.18)
Smoking status				
Non	28058 (49.1)	26439 (46.3)	1.00 (ref.)	1.00 (ref.)
Current				
1-9 cigarettes/day	1409 (2.5)	1674 (2.9)	0.78 (0.73-0.84)	0.75 (0.70-0.81)
10-19 cigarettes/day	1883 (3.3)	2266 (4.0)	0.77 (0.72-0.82)	0.77 (0.72-0.83)
20-39 cigarettes/day	1304 (2.3)	1680 (2.9)	0.71 (0.66-0.77)	0.70 (0.65-0.76)
40+ cigarettes/day	104 (0.2)	142 (0.3)	0.67 (0.52-0.87)	0.66 (0.51-0.86)
Cigarettes/day unknown	2299 (4.0)	2597 (4.6)	0.82 (0.77-0.87)	0.82 (0.77-0.87)

BCC, basal cell carcinoma; CI, confidence interval; OR, odds ratio. 1 alcohol unit= 10 mL of pure ethanol.

*Adjusted for alcohol status, smoking status, BMI, and number of general practitioner visits 1 year before BCC diagnosis.

7.5 Discussion

The observed BCC incidence in the UK is considerably high, particularly in the elderly. Projecting the crude IR in the CPRD population to the total UK population aged 18 years or older, we estimate that approximately 110 000 adults developed BCC for the first time in 2011 alone. Taking into account the ageing of the UK population and the increasing IRs over the last decade, BCC places a growing burden on the National Health Service.

In accordance with three large cohort studies,[252-254] we observed an elevated BCC risk in alcohol drinkers. Several mechanisms have been suggested to explain how alcohol may initiate and promote skin carcinogenesis. These comprise impairment of the immune system, poor nutritional status as well as photosensitising and direct mutagenic effects of acetaldehyde, the primary oxidative metabolite of ethanol.[255,256] Nonetheless, the detected association between alcohol intake and BCC risk was weak and there was no evidence of a clear dose-response relationship. Two US surveys reported an increased prevalence and severity of sunburns in alcohol drinkers. Thus, alcohol consumption could also be a marker for willingness to take health risks including excessive sun exposure, which then increases the risk of BCC, rather than being a causal factor for BCC itself.[257,258]

A meta-analysis of 11 case-control and 3 cohort studies[259] and two subsequently published individual studies (a case-control study and a study based on two cohorts)[260,261] found that smoking was not related to an increased BCC risk. Some of these studies[253,261-263] and our results even suggest a lower risk for smokers, which seems paradoxical in view of the carcinogenic effects of cigarette smoke. Aside from non-causal explanations (cigarette smoking may for example be associated with a lower socioeconomic status and less opportunities to go on sunny holidays), an underlying mechanism might be an attenuated cutaneous inflammatory response to ultraviolet radiation in smokers, possibly by nicotine altering prostaglandin metabolism.[264]

The relationship between overweight and a decreased BCC risk has already been reported by others.[265-268] It has been proposed that obese individuals engage less in physical activity, therefore spend less time outdoors, and wear less revealing clothing, which leads to reduced sun exposure of the skin. The same might be true for underweight people.

The analysis of comorbidities revealed significant associations between BCC and diseases related to iatrogenic or non-iatrogenic immunosuppression (RA, IBD, organ transplantation,

malignancies, skin infections, seborrhoeic dermatitis). Beside specific photosensitising and oncogenic effects of certain immunosuppressive drugs, it is believed that impaired immune surveillance facilitates unrestricted growth of cancer-initiated cells.[69] The increased risk of non-melanoma skin cancer in organ transplant recipients has been extensively discussed in the literature, and regular dermatological examinations are an integral part of post-transplant care.[67] Evidence of a heightened susceptibility in other immunocompromised populations such as RA and IBD patients has been growing only recently, but skin cancer screening should be considered likewise in these individuals.[269,270]

A plausible reason for the overrepresentation of rosacea and cutaneous malignant melanoma among BCC cases is the role of sun exposure in the pathogenesis of all three diseases, even though we cannot rule out some degree of detection and misclassification bias.

Considering the strong correlation between a history of tobacco smoking and COPD, the slightly reduced BCC risk of these patients most likely underscores the protective effect of smoking discussed above.

Similar to our observations, a few other studies also found inverse associations of non-melanoma skin cancer with diabetes mellitus, schizophrenia, and dementia. Suggested explanations include again confounding by sun exposure (possibly mediated by its role in vitamin D synthesis), detection bias, and complex biological mechanisms such as the maintenance of insulin-like growth factor-1 receptor activity (important in the response of keratinocytes to ultraviolet radiation) through exogenous insulin in diabetics.[271-273]

In conclusion, the presented incidence rates highlight the growing burden of BCC in the UK. Along with sun exposure, immunosuppression is an important factor in tumour pathogenesis, whereas lifestyle factors do not appear to play a major role.

Chapter 8

PROJECT VI

Nonsteroidal anti-inflammatory drugs and the risk of nonmelanoma skin cancer

Daphne Reinau, Christian Surber, Susan S. Jick, Christoph R. Meier

International Journal of Cancer 2014 [Epub ahead of print]

8.1 Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been assigned a promising role in the chemoprevention of various malignancies. However, epidemiological data on the association between NSAID use and nonmelanoma skin cancer (NMSC) are limited. To explore whether patients regularly exposed to systemic NSAIDs are at a reduced risk of basal cell carcinoma (BCC) or squamous cell carcinoma (SCC), we conducted a population-based case-control analysis using the Clinical Practice Research Datalink, a United Kingdom primary care database. We identified 65 398 patients with incident BCC and 7864 patients with incident SCC diagnosed between 1995 and 2013 and matched 1 and 4 NMSC-free controls to each BCC and SCC case, respectively, on age, sex, general practice, calendar time, and years of history in the database. We compared prior NSAID exposure between cases and controls using multivariate conditional logistic regression analyses controlling for several potential confounders. Overall, we found no association between NSAID use and BCC, but when looking exclusively at users of single NSAID substances there was a suggestion of a reduced BCC risk in regular users of aspirin and ibuprofen (adjusted odds ratio [OR_{adj}]: 0.92, 95% confidence interval [CI]: 0.85-0.99 and OR_{adj}: 0.61, 95% CI: 0.48-0.78, respectively). The risk of SCC was slightly decreased in regular users of any NSAIDs (OR_{adj}: 0.89, 95% CI: 0.82-0.97), with the strongest risk reduction observed in current users of coxibs (OR_{adj}: 0.77, 95% CI: 0.62-0.95). These findings provide evidence that patients predisposed to NMSC might benefit from chemoprevention with NSAIDs.

8.2 Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs in pain management, representing a structurally diverse group of substances with anti-inflammatory and analgesic properties.[274] NSAIDs have been assigned a potential role in the chemoprevention of various malignancies including basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (SCC), which are collectively referred to as nonmelanoma skin cancer (NMSC).[94,275-277] Although the precise mechanism of anti-tumorigenic activity is unknown, the inhibition of cyclooxygenase (COX) enzymes and the subsequent decrease in prostaglandin synthesis is thought to be of key importance. Unlike the COX-1 isoenzyme, which is constitutively expressed, the COX-2 isoenzyme is usually undetectable in normal skin, but inducible by ultraviolet radiation (UVR) and multiple other inflammatory stimuli. COX-2 activity has been shown to be up-regulated in a high percentage of UV-induced skin tumours and has been associated with fundamental processes in cancer development such as cell proliferation, angiogenesis, and suppression of apoptosis.[278-280]

In mouse models, pharmacological inhibition of COX-2 by orally or topically administered NSAIDs has proven effective in reducing UV-carcinogenesis.[281-285] In humans, the NSAID diclofenac is successfully used in the topical treatment of actinic keratosis, which is considered a SCC precursor lesion.[286] However, human data on the systemic use of NSAIDs in the chemoprevention of NMSC are limited. Two small double-blind placebo-controlled randomised trials[287,288] suggested a protective effect of oral celecoxib (200 mg twice daily for 9 and 24 months, respectively) on the risk of developing NMSC. The study populations, however, consisted of specific subsets of high-risk patients with multiple actinic keratoses or basal cell nevus syndrome, and NMSC was not a primary endpoint in one trial.[287] Published observational studies examining associations between NSAID use and NMSC yielded inconsistent results. Most were based on a small number of cases, NSAID exposure was primarily self-reported, and information on timing and duration of use was often not available.

To further investigate whether patients regularly exposed to systemically administered NSAIDs are at an altered risk of NMSC, we conducted a large population-based case-control analysis using data from the Clinical Practice Research Datalink (CPRD), a well-validated United Kingdom (UK) primary care database.

8.3 Methods

8.3.1 Data source

In the UK healthcare system, primary care physicians (general practitioners [GPs]) play a key role as gatekeepers. Secondary care is provided at the request of and with full disclosure to the GP. As a result, GP records contain a patient's virtually complete medical history. The CPRD (formerly known as General Practice Research Database [GPRD]) is a large UK primary care database which has been widely used in epidemiological research and which has been described in detail elsewhere.[251,289,290] It was set up in 1987 and contains computerised GP records from some 12 million patients who are representative of the UK population with respect to age, sex, socioeconomic class, and region of residence.[289,290] The available information includes anonymised longitudinal data on patients' demographics, lifestyle factors, medical diagnoses (captured as 'Read codes' [coded thesaurus of clinical terms]), and prescribed drugs (captured as 'Gemscript codes' [coded thesaurus of medicines]). Prescriptions are generated by computer, thus ensuring that they are recorded in the database. The completeness and high validity of CPRD records have been demonstrated in numerous studies.[250,291,292]

8.3.2 Study design

Using a case-control design, we compared prior exposure to systemic NSAIDs between patients with incident BCC and a NMSC-free control group, as well as between patients with incident SCC and a NMSC-free control group.

The study was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA database research.

8.3.3 Study population

We identified all patients in the CPRD with an incident first-time diagnosis of NMSC (i.e. a Read code of BCC or SCC) between age 18 and 89 years and between January 1, 1995 and December 31, 2013.

The validity of BCC Read codes has recently been investigated and documented in a study on The Health Improvement Network (THIN) database, a UK primary care database similar in

structure and content to the CPRD with some overlap in that a considerable number of practices contribute data to both schemes.[293]

As SCC may also occur in organs other than the skin, we excluded cases with site-unspecific SCC Read codes unless there was at least one additional record within 30 days before or after the unspecific SCC Read code indicating that the tumour affected the skin (i.e. a record of a consultation with a dermatologist, a skin lesion, or skin surgery). To validate this procedure we further conducted a sensitivity analysis restricted to patients with a skin-specific SCC Read code who had at least one additional record of a consultation with a dermatologist within 30 days before or after the SCC Read code.

We excluded all patients with less than 3 years of history in the CPRD before the first NMSC diagnosis to increase the likelihood of including incident rather than prevalent cases, and to allow time for exposure opportunity. We further excluded those with a prior record of any other malignancy, solid organ transplantation, human immunodeficiency virus infection, alcoholism, naevoid basal cell carcinoma syndrome, xeroderma pigmentosum, or albinism.

Within the CPRD, we randomly selected one NMSC-free control patient for each BCC case, and four NMSC-free control patients for each SCC case (i.e. control patients had neither a record of BCC nor SCC at any time), matched to cases on age, sex, general practice, calendar time, and years of history in the database. The same exclusion criteria were applied to controls as to cases.

8.3.4 NSAID exposure and covariates

To account for some lag time between the onset of NMSC and the recorded diagnosis, we captured all exposure and covariate information one year preceding the date of the first NMSC record, i.e. the index date was a priori defined as the date of the first recording of BCC or SCC minus 365 days.

By means of Gemscript codes, we assessed prescriptions for systemic NSAIDs and categorised exposure according to NSAID class (acetylsalicylic acid [aspirin, primarily ≤ 325 mg], non-aspirin COX-1/COX-2 inhibitors [non-aspirin NSAIDs], and selective COX-2 inhibitors [coxibs]). In addition, we analysed frequently prescribed non-aspirin NSAIDs (i.e. diclofenac, ibuprofen, and naproxen) separately.

Patients were classified by timing of use (current users: last prescription ≤ 1 year before the index date; past users: last prescription > 1 year before the index date) and by duration of

use based on the number of prescriptions (Rx) before the index date (short-term users: 1-9 Rx; medium-term users: 10-29 Rx; long-term users: $\geq$ 30 Rx). The reference group was defined as patients without any NSAID prescription before the index date (never users).

For both cases and controls, we determined the prevalence of selected lifestyle factors, comorbidities, and concomitant medications, as well as the number of GP visits in the year prior to the index date (see statistical analysis).

8.3.5 Statistical analysis

We evaluated the association between NSAID use, covariates, and the occurrence of NMSC using conditional logistic regression analyses. Relative risk estimates were calculated as odds ratios (ORs) with 95% confidence intervals (CIs).

To control for confounding we set up two multivariate models. Model 1 a priori included covariates known from the literature to be associated with NMSC and/or NSAID use (lifestyle factors: smoking, alcohol consumption, body mass index [BMI]; comorbidities: cerebro- and cardiovascular diseases, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, psoriasis; comedication: systemic glucocorticoids, other immunosuppressive drugs, photosensitising and phototoxic drugs). We did not include further comorbidities (congestive heart failure, diabetes mellitus, chronic obstructive pulmonary disease, lupus erythematodes, migraine, peptic ulcer, renal diseases) and concomitant medications (proton pump inhibitors, insulin, acetaminophen, opioids), since they did not alter the ORs for the association between NSAIDs and NMSC by more than 10% when tested one by one. Model 2 contained the same variables as Model 1, but additionally the number of GP visits in the year prior to the index date was added as a marker for a patient's medical attention and overall health status.

In a supplementary sensitivity analysis we investigated the association between predefined NSAID classes and active substances and the risk of NMSC by exclusively examining the subsets of patients who received only one type of NSAID (mono users).

All analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC) and statistical significance was defined at the alpha-level of 0.05.

8.4 Results

8.4.1 Characteristics of the study population

The study population comprised 65 398 cases with incident BCC (mean age: 66.8 years, standard deviation [SD]: ± 13.1 years) and the same number of matched controls, and 7864 cases with incident SCC (mean age: 73.6 years, SD: ± 10.8 years) and 31 456 matched controls. The mean time of active history in the database for BCC and SCC patients was 11.4 years (SD ± 5.0 years) and 13.7 years (SD ± 5.3 years), respectively. Further key characteristics of the cases and their matched controls are summarised in Table 8-1.

8.4.2 NSAIDs and the risk of BCC

There was no evidence for a reduced BCC risk in association with systemic NSAID use in the main analysis by NSAID class (Table 8-2). However, when non-aspirin NSAIDs were examined separately by active substance, long-term use of ibuprofen was associated with a statistically significant small BCC risk reduction (OR: 0.85, 95% CI: 0.77-0.94, see Table 8-3).

When we restricted the analysis to mono users (sensitivity analysis), the BCC risk for long-term ibuprofen use was further decreased (OR: 0.61, 95% CI: 0.48-0.78). BCC risk was also slightly reduced among current and long-term mono users of aspirin, but elevated among current and long-term mono users of coxibs (Table 8-4).

8.4.3 NSAIDs and the risk of SCC

The main analysis by NSAID class revealed a weakly decreased SCC risk in current as well as long-term users of aspirin and non-aspirin NSAIDs. For current and long-term use of coxibs, the SCC risk reduction was more pronounced, though statistical significance was reached only for current use (OR: 0.77, 95% CI: 0.62-0.95, see Table 8-2). When non-aspirin NSAIDs were examined separately by active substance, the analyses for current, medium-term, and long-term use of diclofenac, ibuprofen, and naproxen all yielded point estimates lower than 1, but the decrease in SCC risk was only statistically significant for current use of naproxen (OR: 0.84, 95% CI: 0.70-0.99, see Table 8-3).

The sensitivity analysis restricted to mono users did not markedly alter the results of the main analysis (data not shown).

In the sensitivity analysis restricted to SCC patients with a skin-specific SCC Read code and a recorded dermatologist consultation within 30 days before or after the SCC diagnosis, the ORs for ever, current, and long term use of aspirin, non-aspirin NSAIDs, and coxibs were consistently below 1.0 and lower than in the analysis including all SCC cases (Table 8-5).

Table 8-1 Characteristics of the study population

	Basal cell carcinoma				Squamous cell carcinoma			
	Cases, n (%) (n= 65398)	**Controls, n (%)** (n= 65398)	**OR crude (95%CI)**	**OR adjusted (95%CI)***	**Cases, n (%)** (n=7864)	**Controls, n (%)** (n=31456)	**OR crude (95%CI)**	**OR adjusted (95%CI)***
Sex								
Male	32648 (49.9)	32648 (49.9)	NA	NA	4552 (57.9)	18208 (57.9)	NA	NA
Female	32750 (50.1)	32750 (50.1)	NA	NA	3312 (42.1)	13248 (42.1)	NA	NA
Age (years)								
< 50	7383 (11.3)	7387 (11.3)	NA	NA	266 (3.4)	1076 (3.4)	NA	NA
50-59	10389 (15.9)	10399 (15.9)	NA	NA	582 (7.4)	2345 (7.5)	NA	NA
60-69	16715 (25.6)	16705 (25.5)	NA	NA	1514 (19.3)	6055 (19.3)	NA	NA
70-79	19225 (29.4)	19260 (29.5)	NA	NA	2800 (35.6)	11258 (35.8)	NA	NA
≥ 80	11686 (17.9)	11647 (17.8)	NA	NA	2702 (34.4)	10722 (34.1)	NA	NA
Alcohol consumption								
Non	9953 (15.2)	11214 (17.2)	1.00 (ref.)	1.00 (ref.)	1399 (17.8)	5836 (18.6)	1.00 (ref.)	1.00 (ref.)
Ex	835 (1.3)	952 (1.5)	1.00 (0.91-1.11)	1.01 (0.91-1.11)	178 (2.3)	778 (2.5)	0.96 (0.81-1.15)	0.95 (0.80-1.13)
Current	47241 (72.2)	44722 (68.4)	1.21 (1.18-1.25)	1.22 (1.18-1.26)	5666 (72.1)	21955 (69.8)	1.09 (1.01-1.16)	1.11 (1.04- 1.19)
Unknown	7369 (11.3)	8510 (13.0)	0.96 (0.91-1.00)	1.05 (0.99-1.10)	621 (7.9)	2887 (9.2)	0.88 (0.79-0.98)	0.96 (0.84-1.08)
Smoking status								
Non	33292 (50.9)	31281 (47.8)	1.00 (ref.)	1.00 (ref.)	3604 (45.8)	13976 (44.4)	1.00 (ref.)	1.00 (ref.)
Ex	19057 (29.1)	18811 (28.8)	0.95 (0.93-0.98)	0.93 (0.91-0.96)	3032 (38.6)	12570 (40.0)	0.93 (0.88-0.98)	0.90 (0.85- 0.95)
Current	8214 (12.6)	9879 (15.1)	0.77 (0.75-0.80)	0.77 (0.74-0.80)	963 (12.3)	3699 (11.8)	1.01 (0.93-1.10)	1.01 (0.93-1.10)
Unknown	4835 (7.4)	5427 (8.3)	0.81 (0.77-0.84)	0.96 (0.91-1.02)	265 (3.4)	1211 (3.9)	0.83 (0.71- 0.96)	1.04 (0.88-1.23)
BMI (kg m^{-2})								
12.0-18.4	815 (1.3)	857 (1.3)	0.86 (0.78-0.95)	0.89 (0.81-0.98)	122 (1.6)	510 (1.6)	0.87 (0.71-1.06)	0.84 (0.69-1.04)
18.5-24.9	22746 (34.8)	20510 (31.4)	1.00 (ref.)	1.00 (ref.)	2804 (35.7)	10189 (32.4)	1.00 (ref.)	1.00 (ref.)
25.0-29.9	21898 (33.5)	21285 (32.6)	0.92 (0.90-0.95)	0.90 (0.88-0.93)	2837 (36.1)	11239 (35.7)	0.91 (0.86-0.97)	0.91 (0.86-0.97)
30.0-60.0	9682 (14.8)	11248 (17.2)	0.77 (0.75-0.80)	0.74 (0.72-0.77)	1271 (16.2)	5775 (18.4)	0.80 (0.74-0.86)	0.77 (0.71-0.83)
Unknown	10257 (15.7)	11498 (17.6)	0.78 (0.75-0.81)	0.86 (0.83-0.90)	830 (10.6)	3743 (11.9)	0.79 (0.72-0.86)	0.88 (0.80- 0.98)
GP visits (1 year prior to ID)								
0-1	9827 (15.0)	12068 (18.5)	1.00 (ref.)	1.00 (ref.)	595 (7.6)	3133 (10.0)	1.00 (ref.)	1.00 (ref.)
2-4	13818 (21.1)	14379 (22.0)	1.23 (1.18-1.27)	1.21 (1.16-1.25)	1057 (13.4)	5213 (16.6)	1.11 (0.99-1.24)	1.10 (0.98-1.23)
5-9	17412 (26.6)	17103 (26.2)	1.34 (1.30-1.39)	1.32 (1.27-1.37)	1805 (23.0)	8075 (25.7)	1.27 (1.14-1.41)	1.26 (1.13-1.40)
≥10	24341 (37.2)	21848 (33.4)	1.52 (1.47-1.58)	1.51 (1.45-1.57)	4407 (56.0)	15035 (47.8)	1.74 (1.57-1.93)	1.71 (1.53-1.90)
Comorbidities								
Ischemic stroke/ TIA	3807 (5.8)	4049 (6.2)	0.93 (0.89-0.98)	0.91 (0.86-0.95)	666 (8.5)	2848 (9.1)	0.93 (0.85-1.01)	0.88 (0.80-0.96)
Ischemic heart disease	9236 (14.1)	8943 (13.7)	1.04 (1.01-1.08)	1.00 (0.96-1.03)	1515 (19.3)	5896 (18.7)	1.04 (0.97-1.11)	0.97 (0.91-1.04)
IBD	799 (1.2)	693 (1.1)	1.16 (1.04-1.28)	1.07 (0.96-1.19)	128 (1.6)	330 (1.1)	1.57 (1.28-1.93)	1.22 (0.98-1.51)
Psoriasis	2576 (3.9)	2560 (3.9)	1.01 (0.95-1.06)	1.00 (0.94-1.06)	399 (5.1)	1407 (4.5)	1.14 (1.02- 1.28)	1.08 (0.96-1.21)
Rheumatoid arthritis	1246 (1.9)	1095 (1.7)	1.14 (1.05-1.24)	1.01 (0.92-1.11)	193 (2.5)	634 (2.0)	1.23 (1.04-1.44)	0.69 (0.57-0.85)
Osteoarthritis	13913 (21.3)	13020 (19.9)	1.10 (1.07-1.13)	1.08 (1.05-1.11)	2248 (28.6)	8507 (27.0)	1.09 (1.03-1.16)	1.06 (1.00-1.12)
Comedication								
Immunosuppressants	1023 (1.6)	771 (1.2)	1.33 (1.21-1.47)	1.25 (1.12-1.39)	268 (3.4)	432 (1.4)	2.54 (2.18-2.97)	2.60 (2.15- 3.14)
Systemic glucocorticoids	11641 (17.8)	11468 (17.5)	1.02 (0.99-1.05)	0.96 (0.93-0.99)	1921 (24.4)	6993 (22.2)	1.14 (1.07-1.21)	1.00 (0.94-1.07)
Photosensitising or phototoxic drugs**	25820 (39.5)	24565 (37.6)	1.10 (1.07-1.12)	1.05 (1.03-1.08)	3795 (48.3)	14159 (45.0)	1.16 (1.10-1.22)	1.05 (0.99-1.11)

BMI, body mass index; CI, confidence interval; GP, general practitioner; IBD, inflammatory bowel disease; ID, index date; NA, not applicable;

OR, odds ratio; TIA, transient ischemic attack.

*Adjusted for alcohol consumption, smoking status, BMI, number of GP visits in the year prior to ID, ischemic stroke/TIA, ischemic heart disease, IBD, psoriasis, rheumatoid arthritis, osteoarthritis, immunosuppressants, systemic glucocorticoids , and photosensitising or phototoxic drugs.

** Antibiotics (quinolones, sulphonamides, tetracyclines), diuretics, ACE inhibitors, nifedipine, amiodarone, carbamazepine, lamotrigine, azathioprine, isotretinoin, acitretin, St. John's wort

Table 8-2 Non-steroidal anti-inflammatory drugs and the risk of nonmelanoma skin cancer by drug class

Use of NSAIDs by drug class	Basal cell carcinoma					Squamous cell carcinoma				
	Cases, n (%) (n= 65398)	Controls, n (%) (n= 65398)	OR crude (95%CI)	OR adjusted (95%CI)* Multivariate Model 1	OR adjusted (95%CI)** Multivariate Model 2	Cases, n (%) (n=7864)	Controls, n (%) (n=31456)	OR crude (95%CI)	OR adjusted (95%CI)* Multivariate Model 1	OR adjusted (95%CI)** Multivariate Model 2
Never use of NSAIDs	19 197 (29.4)	19 918 (30.5)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1701 (21.6)	7104 (22.6)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Any NSAIDs										
Ever use	46201 (70.7)	45480 (69.5)	1.06 (1.04-1.09)	1.05 (1.02-1.08)	1.00 (0.98-1.03)	6163 (78.4)	24352 (77.4)	1.06 (1.00-1.13)	1.04 (0.97-1.11)	0.98 (0.91-1.04)
Current use	23153 (35.4)	22293 (34.1)	1.09 (1.06-1.12)	1.08 (1.05-1.11)	1.01 (0.98-1.04)	3130 (39.8)	12873 (40.9)	1.02 (0.95-1.09)	0.98 (0.91-1.06)	0.90 (0.83-0.97)
Past use	23048 (35.2)	23187 (35.5)	1.04 (1.01-1.07)	1.03 (1.00-1.06)	1.00 (0.97-1.03)	3033 (38.6)	11479 (36.5)	1.11 (1.04-1.19)	1.09 (1.01-1.17)	1.04 (0.97-1.12)
1-9 Rx	25662 (39.2)	25183 (38.5)	1.06 (1.03-1.09)	1.05 (1.02-1.08)	1.01 (0.98-1.04)	2754 (35.0)	10630 (33.8)	1.09 (1.01-1.16)	1.07 (1.00-1.15)	1.02 (0.95-1.09)
10-29 Rx	9058 (13.9)	8920 (13.6)	1.06 (1.02-1.10)	1.04 (1.00-1.08)	0.98 (0.95-1.02)	1219 (15.5)	4768 (15.2)	1.07 (0.98-1.17)	1.03 (0.94-1.12)	0.94 (0.86-1.03)
≥30 Rx	11481 (17.6)	11377 (17.4)	1.06 (1.02-1.10)	1.04 (1.00-1.08)	0.98 (0.94-1.02)	2190 (27.9)	8954 (28.5)	1.02 (0.95-1.10)	0.97 (0.89-1.06)	0.89 (0.82-0.97)
Aspirin										
Ever use	17708 (27.1)	17510 (26.8)	1.06 (1.03-1.09)	1.05 (0.02-1.09)	0.99 (0.95-1.02)	3137 (39.9)	12532 (39.8)	1.05 (0.98-1.13)	1.03 (0.95-1.11)	0.94 (0.87-1.01)
Current use	13052 (20.0)	13026 (19.9)	1.05 (1.01-1.09)	1.04 (1.00-1.08)	0.97 (0.94-1.01)	2185 (27.8)	9190 (29.2)	1.00 (0.93-1.08)	0.97 (0.89-1.05)	0.88 (0.81-0.96)
Past use	4656 (7.1)	4484 (6.9)	1.09 (1.04-1.14)	1.08 (1.02-1.13)	1.02 (0.97-1.07)	952 (12.1)	3342 (10.6)	1.20 (1.09-1.32)	1.16 (1.05-1.28)	1.07 (0.96-1.18)
1-9 Rx	5938 (9.1)	5582 (8.5)	1.11 (1.06-1.16)	1.10 (1.05-1.15)	1.02 (0.98-1.07)	865 (11.0)	3153 (10.0)	1.15 (1.05-1.27)	1.11 (1.01-1.23)	1.01 (0.91-1.11)
10-29 Rx	4990 (7.6)	4964 (7.6)	1.05 (1.00-1.10)	1.03 (0.99-1.09)	0.97 (0.93-1.02)	762 (9.7)	3115 (9.9)	1.02 (0.93-1.13)	0.99 (0.89-1.10)	0.90 (0.82-1.00)
≥30 Rx	6780 (10.4)	6964 (10.7)	1.02 (0.97-1.06)	1.01 (0.96-1.06)	0.95 (0.91-1.00)	1510 (19.2)	6264 (19.9)	1.01 (0.93-1.10)	0.97 (0.89-1.07)	0.90 (0.82-0.99)
Non-aspirin NSAIDs										
Ever use	40199 (61.5)	39267 (60.0)	1.07 (1.04-1.10)	1.05 (1.03-1.08)	0.96 (0.92-1.00)	5151 (65.5)	20274 (64.5)	1.07 (1.00-1.14)	1.04 (0.97-1.11)	0.98 (0.91-1.05)
Current use	11904 (18.2)	11105 (17.0)	1.12 (1.08-1.16)	1.10 (1.06-1.14)	1.03 (0.99-1.06)	1223 (15.6)	4851 (15.4)	1.06 (0.97-1.15)	1.02 (0.94-1.11)	0.92 (0.85-1.01)
Past use	28295 (43.3)	28162 (43.1)	1.05 (1.02-1.08)	1.04 (1.01-1.07)	1.00 (0.97-1.03)	3928 (50.0)	15423 (49.0)	1.07 (1.00-1.15)	1.05 (0.98-1.12)	1.00 (0.93-1.07)
1-9 Rx	29832 (45.6)	29144 (44.6)	1.07 (1.04-1.10)	1.06 (1.03-1.09)	1.01 (0.99-1.04)	3662 (46.6)	14286 (45.4)	1.08 (1.01-1.15)	1.06 (0.99-1.13)	1.00 (0.93-1.07)
10-29 Rx	6125 (9.4)	5974 (9.1)	1.08 (1.03-1.12)	1.05 (1.00-1.10)	0.99 (0.95-1.04)	832 (10.6)	3348 (10.6)	1.05 (0.95-1.15)	0.99 (0.90-1.09)	0.91 (0.82-1.01)
≥30 Rx	4242 (6.5)	4149 (6.3)	1.07 (1.02-1.13)	1.04 (0.99-1.09)	0.98 (0.93-1.04)	657 (8.4)	2640 (8.4)	1.05 (0.94-1.16)	0.97 (0.87-1.09)	0.90 (0.81-1.01)
Coxibs										
Ever use	5505 (8.4)	5142 (7.9)	1.13 (1.08-1.19)	1.10 (1.05-1.15)	1.03 (0.98-1.08)	958 (12.2)	3701 (11.8)	1.09 (0.99-1.20)	1.03 (0.93-1.13)	0.94 (0.85-1.04)
Current use	1405 (2.2)	1215 (1.9)	1.22 (1.12-1.32)	1.19 (1.09-1.29)	1.09 (1.01-1.19)	125 (1.6)	561 (1.8)	0.93 (0.76-1.15)	0.86 (0.70-1.06)	0.77 (0.62-0.95)
Past use	4100 (6.3)	3927 (6.0)	1.10 (1.05-1.16)	1.07 (1.02-1.13)	1.01 (0.96-1.07)	833 (10.6)	3140 (10.0)	1.12 (1.02-1.24)	1.06 (0.95-1.17)	0.98 (0.88-1.08)
1-9 Rx	4369 (6.7)	4115 (6.3)	1.12 (1.07-1.18)	1.09 (1.04-1.15)	1.03 (0.97-1.08)	757 (9.6)	2898 (9.2)	1.10 (1.00-1.22)	1.05 (0.94-1.16)	0.96 (0.86-1.07)
10-29 Rx	856 (1.3)	778 (1.2)	1.16 (1.05-1.29)	1.12 (1.01-1.24)	1.05 (0.94-1.16)	153 (2.0)	585 (1.9)	1.10 (0.91-1.33)	1.00 (0.82-1.21)	0.91 (0.75-1.11)
≥30 Rx	280 (0.4)	249 (0.4)	1.19 (1.00-1.42)	1.15 (0.96-1.37)	1.08 (0.91-1.29)	48 (0.6)	218 (0.7)	0.93 (0.68-1.28)	0.84 (0.61-1.16)	0.77 (0.56-1.07)

CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; Rx, prescriptions.

Current use: last prescription ≤ 1 year before the index date (i.e. ≤ 2 years before the recorded cancer diagnosis) ; past use: last prescription > 1 year before the index date (i.e. > 2 years before the recorded cancer diagnosis)

*Adjusted for body mass index, smoking status, alcohol status, ischemic stroke/ transient ischemic attack, ischemic heart disease, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, psoriasis, systemic glucocorticoids, other immunosuppressants, and photosensitising or phototoxic drugs. ** Additionally adjusted for the number of general practitioner visits in the year before the index date.

Table 8-3 Non-aspirin non-steroidal anti-inflammatory drugs and the risk of nonmelanoma skin cancer by active substance

Use of non-aspirin NSAIDs by active substance	Basal cell carcinoma					Squamous cell carcinoma				
	Cases, n (%) (n= 65398)	**Controls, n (%)** (n= 65398)	**OR crude (95%CI)**	**OR adjusted (95%CI)*** Multivariate Model 1	**OR adjusted (95%CI)**** Multivariate Model 2	**Cases, n (%)** (n=7864)	**Controls, n (%)** (n=31456)	**OR crude (95%CI)**	**OR adjusted (95%CI)*** Multivariate Model 1	**OR adjusted (95%CI)**** Multivariate Model 2
Never use of NSAIDs	19 197 (29.4)	19 918 (30.5)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1701 (21.6)	7104 (22.6)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Diclofenac										
Ever use	23773 (36.4)	22840 (34.9)	1.09 (1.06-1.13)	1.08 (1.04-1.11)	1.02 (0.99-1.05)	3175 (40.4)	12229 (38.9)	1.10 (1.02-1.17)	1.06 (0.99-1.14)	0.99 (0.92-1.07)
Current use	5401 (8.3)	5058 (7.7)	1.12 (1.07-1.17)	1.10 (1.05-1.15)	1.02 (0.97-1.06)	509 (6.5)	2016 (6.4)	1.06 (0.95-1.19)	1.03 (0.92-1.16)	0.92 (0.82-1.04)
Past use	18372 (28.1)	17782 (27.2)	1.09 (1.05-1.12)	1.07 (1.04-1.10)	1.02 (0.99-1.06)	2666 (33.9)	10213 (32.5)	1.10 (1.03-1.19)	1.07 (0.99-1.15)	1.01 (0.93-1.09)
1-9 Rx	19864 (30.4)	19126 (29.3)	1.09 (1.06-1.12)	1.08 (1.04-1.11)	1.02 (0.99-1.06)	2606 (33.1)	9938 (31.6)	1.11 (1.03-1.19)	1.08 (1.00-1.16)	1.00 (0.93-1.08)
10-29 Rx	2395 (3.7)	2317 (3.5)	1.09 (1.02-1.16)	1.06 (1.00-1.13)	1.00 (0.94-1.07)	333 (4.2)	1366 (4.3)	1.03 (0.90-1.18)	0.97 (0.85-1.11)	0.90 (0.78-1.03)
≥30 Rx	1514 (2.3)	1397 (2.1)	1.14 (1.06-1.23)	1.11 (1.03-1.20)	1.05 (0.97-1.14)	236 (3.0)	925 (2.9)	1.08 (0.92-1.26)	1.01 (0.86-1.19)	0.94 (0.80-1.10)
Ibuprofen										
Ever use	23824 (36.4)	23347 (35.7)	1.07 (1.04-1.10)	1.05 (1.02-1.09)	1.00 (0.97-1.04)	3140 (39.9)	12546 (39.9)	1.05 (0.98-1.13)	1.02 (0.95-1.10)	0.96 (0.89-1.03)
Current use	4065 (6.2)	3827 (5.9)	1.11 (1.06-1.17)	1.09 (1.04-1.15)	1.02 (0.97-1.07)	438 (5.6)	1711 (5.4)	1.07 (0.95-1.21)	1.05 (0.93-1.19)	0.95 (0.84-1.07)
Past use	19759 (30.2)	19520 (29.9)	1.06 (1.03-1.09)	1.05 (1.01-1.08)	1.00 (0.97-1.03)	2702 (34.4)	10835 (34.4)	1.05 (0.97-1.13)	1.02 (0.95-1.10)	0.96 (0.89-1.03)
1-9 Rx	21120 (32.3)	20659 (31.6)	1.07 (1.04-1.10)	1.06 (1.02-1.09)	1.01 (0.97-1.04)	2721 (34.6)	10850 (34.5)	1.05 (0.98-1.13)	1.03 (0.95-1.11)	0.96 (0.89-1.04)
10-29 Rx	1949 (3.0)	1807 (2.8)	1.13 (1.06-1.21)	1.11 (1.03-1.19)	1.05 (0.98-1.13)	292 (3.7)	1132 (3.6)	1.08 (0.94-1.25)	1.02 (0.89-1.19)	0.94 (0.81-1.09)
≥30 Rx	755 (1.2)	881 (1.4)	0.90 (0.81-1.00)	0.89 (0.80-0.98)	0.85 (0.77-0.94)	127 (1.6)	564 (1.8)	0.95 (0.77-1.16)	0.92 (0.75-1.13)	0.86 (0.70-1.06)
Naproxen										
Ever use	8939 (13.7)	8706 (13.3)	1.08 (1.04-1.12)	1.05 (1.01-1.10)	1.00 (0.96-1.04)	1194 (15.2)	4710 (15.0)	1.07 (0.98-1.17)	1.03 (0.94-1.12)	0.95 (0.87-1.05)
Current use	1707 (2.6)	1602 (2.5)	1.12 (1.04-1.20)	1.09 (1.02-1.18)	1.01 (0.94-1.09)	190 (2.4)	831 (2.6)	0.96 (0.81-1.14)	0.93 (0.78-1.10)	0.84 (0.70-0.99)
Past use	7232 (11.1)	7104 (10.9)	1.07 (1.03-1.11)	1.05 (1.00-1.09)	0.99 (0.95-1.04)	1004 (12.8)	3879 (12.3)	1.09 (1.00-1.20)	1.05 (0.95-1.16)	0.98 (0.89-1.08)
1-9 Rx	7886 (12.1)	7676 (11.7)	1.08 (1.04-1.12)	1.06 (1.01-1.10)	1.00 (0.96-1.04)	1037 (13.2)	4058 (12.9)	1.08 (0.98-1.18)	1.04 (0.94-1.14)	0.97 (0.88-1.06)
10-29 Rx	693 (1.1)	649 (1.0)	1.12 (1.01-1.25)	1.08 (0.96-1.21)	1.02 (0.91-1.14)	101 (1.3)	416 (1.3)	1.02 (0.82-1.28)	0.95 (0.76-1.20)	0.89 (0.70-1.12)
≥30 Rx	360 (0.6)	381 (0.6)	0.99 (0.86-1.15)	0.96 (0.82-1.11)	0.91 (0.78-1.06)	56 (0.7)	236 (0.8)	1.00 (0.74-1.35)	0.94 (0.70-1.28)	0.88 (0.65-1.20)

CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; Rx, prescriptions.

Current use: last prescription ≤ 1 year before the index date (i.e. ≤ 2 years before the recorded cancer diagnosis) ; past use: last prescription > 1 year before the index date (i.e. > 2 years before the recorded cancer diagnosis)

*Adjusted for body mass index, smoking status, alcohol status, ischemic stroke/ transient ischemic attack, ischemic heart disease, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, psoriasis, systemic glucocorticoids, other immunosuppressants, and photosensitising or phototoxic drugs. ** Additionally adjusted for the number of general practitioner visits in the year before the index date.

Table 8-4 Non-steroidal anti-inflammatory drugs (NSAIDs) and the risk of basal cell carcinoma: sensitivity analysis restricted to patients who received only one type of NSAID (mono users).

Use of NSAIDs	Basal cell carcinoma (sensitivity analysis)				
	Cases, n (%) (n=65398)	**Controls, n (%)** (n= 65398)	**OR crude (95%CI)**	**OR adjusted (95%CI)*** Multivariate Model 1	**OR adjusted (95%CI)**** Multivariate Model 2
Never use of NSAIDs	19197 (29.4)	19918 (30.5)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Aspirin mono use					
Ever	5258 (8.0)	5579 (8.5)	0.99 (0.94-1.03)	0.99 (0.95-1.04)	0.94 (0.90-0.99)
Current	4016 (6.1)	4275 (6.5)	0.98 (0.93-1.03)	0.99 (0.94-1.04)	0.93 (0.89-0.98)
Long-term (≥30 Rx)	1902 (2.9)	2091 (3.2)	0.95 (0.89-1.02)	0.97 (0.90-1.04)	0.92 (0.85-0.99)
Diclofenac mono use					
Ever	5579 (8.5)	5313 (8.1)	1.10 (1.05-1.14)	1.08 (1.04-1.13)	1.05 (1.01-1.10)
Current	1369 (2.1)	1219 (1.9)	1.17 (1.08-1.27)	1.15 (1.06-1.24)	1.07 (0.99-1.16)
Long-term (≥30 Rx)	242 (0.4)	213 (0.3)	1.18 (0.98-1.42)	1.15 (0.96-1.39)	1.10 (0.91-1.33)
Ibuprofen mono use					
Ever	5907 (9.0)	5983 (9.2)	1.03 (0.99-1.07)	1.02 (0.98-1.06)	0.99 (0.95-1.04)
Current	1176 (1.8)	1081 (1.7)	1.13 (1.04-1.23)	1.12 (1.03-1.22)	1.06 (0.97-1.15)
Long-term (≥30 Rx)	103 (0.2)	168 (0.3)	0.64 (0.50-0.82)	0.62 (0.49-0.80)	0.61 (0.48-0.78)
Naproxen mono use					
Ever	1158 (1.8)	1186 (1.8)	1.02 (0.93-1.11)	1.00 (0.92-1.09)	0.98 (0.90-1.07)
Current	283 (0.4)	273 (0.4)	1.08 (0.91-1.27)	1.08 (0.91-1.28)	1.02 (0.86-1.20)
Long-term (≥30 Rx)	54 (0.1)	67 (0.1)	0.84 (0.59-1.20)	0.84 (0.59-1.21)	0.81 (0.56-1.16)
Coxibs mono use					
Ever	470 (0.7)	397 (0.6)	1.25 (1.09-1.43)	1.22 (1.06-1.40)	1.16 (1.01-1.33)
Current	148 (0.2)	112 (0.2)	1.38 (1.08-1.77)	1.35 (1.05-1.73)	1.25 (0.97-1.60)
Long-term (≥30 Rx)	19 (0.0)	7 (0.0)	2.84 (1.19-6.76)	2.76 (1.16-6.60)	2.52 (1.05-6.02)

CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; Rx, prescriptions.

Current use: last prescription ≤ 1 year before the index date (i.e. ≤ 2 years before the recorded cancer diagnosis)

*Adjusted for body mass index, smoking status, alcohol status, ischemic stroke/ transient ischemic attack, ischemic heart disease, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, psoriasis, systemic glucocorticoids, other immunosuppressants, and photosensitising or phototoxic drugs.

** Additionally adjusted for the number of general practitioner visits in the year before the index date.

Table 8-5 Non-steroidal anti-inflammatory drugs and the risk of squamous cell carcinoma (SCC): sensitivity analysis restricted to patients with a skin-specific SCC Read code and a dermatologist consultation within 30 days before or after SCC diagnosis.

Use of NSAIDs	Squamous cell carcinoma (sensitivity analysis)				
	Cases, n (%) (n= 1741)	**Controls, n (%)** (n= 6964)	**OR crude (95%CI)**	**OR adjusted (95%CI)*** Multivariate Model 1	**OR adjusted (95%CI)**** Multivariate Model 2
Never use of NSAIDs	339 (19.5)	1352 (19.4)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Any NSAIDs					
Ever use	1402 (80.5)	5612 (80.6)	1.00 (0.88-1.14)	0.97 (0.84-1.12)	0.91 (0.78-1.05)
Current use	677 (38.9)	2837 (40.7)	0.95 (0.82-1.11)	0.92 (0.78-1.08)	0.83 (0.71-0.98)
Long-term use (≥30 Rx)	520 (29.9)	2211 (31.8)	0.93 (0.79-1.09)	0.90 (0.73-1.05)	0.81 (0.67-0.97)
Aspirin					
Ever use	707 (40.6)	2966 (42.6)	0.94 (0.81-1.10)	0.92 (0.78-1.09)	0.84 (0.70-0.99)
Current use	480 (27.6)	2089 (30.0)	0.91 (0.77-1.07)	0.89 (0.74-1.06)	0.80 (0.67-0.97)
Long-term use (≥30 Rx)	357 (20.5)	1576 (22.6)	0.89 (0.75-1.06)	0.87 (0.72-1.07)	0.80 (0.66-0.98)
Non-aspirin NSAIDs					
Ever use	1186 (68.1)	4671 (67.1)	1.02 (0.88-1.17)	0.98 (0.84-1.14)	0.92 (0.79-1.06)
Current use	249 (14.3)	980 (14.1)	1.02 (0.84-1.23)	0.95 (0.78-1.15)	0.85 (0.70-1.04)
Long-term use (≥30 Rx)	162 (9.3)	633 (9.1)	1.03 (0.82-1.28)	0.90 (0.71-1.14)	0.84 (0.66-1.06)
Diclofenac					
Ever use	757 (43.5)	3019 (43.4)	1.00 (0.86-1.16)	0.95 (0.81-1.12)	0.89 (0.76-1.04)
Current use	97 (5.6)	371 (5.3)	1.04 (0.81-1.35)	0.97 (0.75-1.27)	0.87 (0.67-1.14)
Long-term use (≥30 Rx)	60 (3.5)	220 (3.2)	1.09 (0.79-1.50)	0.96 (0.69-1.33)	0.88 (0.63-1.22)
Ibuprofen					
Ever use	720 (41.4)	2837 (40.7)	1.02 (0.87-1.18)	0.98 (0.83-1.15)	0.91 (0.77-1.07)
Current use	81 (4.7)	352 (5.1)	0.92 (0.70-1.21)	0.88 (0.66-1.16)	0.78 (0.59-1.03)
Long-term use (≥30 Rx)	30 (1.7)	131 (1.9)	0.91 (0.60-1.39)	0.86 (0.56-1.32)	0.81 (0.53-1.24)
Naproxen					
Ever use	298 (17.1)	1136 (16.3)	1.05 (0.87-1.27)	1.00 (0.82-1.21)	0.92 (0.76-1.12)
Current use	51 (2.9)	222 (3.2)	0.92 (0.66-1.28)	0.87 (0.62-1.22)	0.76 (0.54-1.08)
Long-term use (≥30 Rx)	11 (0.6)	58 (0.8)	0.76 (0.39-1.47)	0.65 (0.33-1.28)	0.62 (0.32-1.22)
Coxibs					
Ever use	268 (15.4)	1018 (14.6)	1.06 (0.87-1.27)	0.97 (0.80-1.19)	0.89 (0.73-1.09)
Current use	21 (1.2)	91 (1.3)	0.92 (0.56-1.52)	0.81 (0.49-1.34)	0.71 (0.43-1.17)
Long-term use (≥30 Rx)	15 (0.9)	69 (1.0)	0.87 (0.49-1.54)	0.75 (0.42-1.35)	0.69 (0.39-1.25)

CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; Rx, prescriptions.

Current use: last prescription ≤ 1 year before the index date (i.e. ≤ 2 years before the recorded cancer diagnosis)

*Adjusted for body mass index, smoking status, alcohol status, ischemic stroke/ transient ischemic attack, ischemic heart disease, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, psoriasis, systemic glucocorticoids, other immunosuppressants, and photosensitising or phototoxic drugs.

** Additionally adjusted for the number of general practitioner visits in the year before the index date.

8.5 Discussion

The study reported herein represents a large case-control analysis examining the relationship between systemic NSAID use and the risk of NMSC. Our results suggest that regular exposure to aspirin and non-aspirin NSAIDs may moderately reduce the risk of NMSC, in particular the risk of SCC. Among non-aspirin NSAIDs, the observed protective effect was most pronounced for ibuprofen (BCC) and naproxen (SCC). Coxibs led to a marked risk reduction in SCC, but on the other hand seemed to increase the risk of BCC. These findings are broadly consistent with the findings from a comparable population-based case-control study conducted in Denmark, which linked data from a prescription database (Aarhus University database) to data from Danish medical registries, including 13 316 BCC cases and 1974 SCC cases.[294] The hypothesis that NSAIDs decrease the risk of NMSC is also supported by several smaller studies in the field, although most of them were not able to distinguish between different NSAID classes and substances, or the respective groups were not large enough to allow meaningful inferences.[295-300]

The greater inverse association between NSAID use and SCC as compared to BCC, especially for the use of NSAIDs with weak (diclofenac) or strong (coxibs) COX-2 selectivity, is consistent with observations from laboratory studies showing that COX-2 overexpression is much more prevalent in SCC and its precursor lesions than in BCC.[279,301] The observed risk reduction in association with aspirin and ibuprofen (both weakly COX-1 selective) on the development of BCC may possibly be attributed for the most part to COX-2 independent mechanisms, such as COX-1 inhibition and regulation of genes involved in inflammatory responses and apoptosis.[302]

Irrespective of NMSC subtype, NSAID class or substance, odds ratios statistically significantly different from 1.0 were exclusively obtained for current and long-term medication use, which suggests a possible drug effect. According to the available epidemiological literature on the effects of NSAIDs on major internal cancers, 5 to 10 years of NSAID exposure might be needed for protection to become apparent, and protection is rapidly lost after prophylaxis is stopped.[302,303]

It is noteworthy that the NSAID-associated decrease in NMSC risk became more pronounced after adjusting for the number of GP visits in the year prior to the index date (multivariate Model 2). Patients who frequently consulted their GP, i.e. patients who tended to be more concerned about their health or who were chronically sick, were more likely to receive

NSAID prescriptions than patients who rarely consulted their GP. At the same time, they had more opportunity to have their NMSC detected, since NMSC is typically a visual diagnosis that causes mild symptoms which *per se* do not often prompt patients to seek medical advice. Hence, although the real NMSC incidence is potentially higher in non-NSAID users, the proportion of actually diagnosed tumours may be larger in NSAID users due to their more intense contact with health care providers.

Another aspect that could have biased the inverse associations between NSAID use and NMSC towards the null is the well-documented phototoxicity of these agents.[304] In the case of the somewhat unexpected elevated BCC risk among regular coxibs users, the phototoxic effects may have mitigated any purported anti-cancer effects. Thus, skin cancer chemoprevention with NSAIDs may merely appear suitable for patients who consistently comply with adequate sun protection measures.

Although this observational study was based on data from a high-quality primary care database, several limitations need to be considered when interpreting our results. Most importantly, we were not able to control for potential confounding or effect modification by sun exposure, skin constitutional factors, and socioeconomic status in the regression analyses, since these parameters are not available in the CPRD. We were also not in a position to analyse the anatomic localisation of the tumours. Furthermore, we could not avert some degree of outcome and exposure misclassification. With regard to the outcome, we inevitably missed a number of NMSC cases, since - as already discussed above- some patients may have remained undiagnosed during the study period. On the other hand, we cannot rule out clinical misdiagnoses of NMSC in patients who did not undergo biopsy. With regard to NSAID exposure, the CPRD records may not be complete, since they usually do not include over-the-counter (OTC) preparations of these drugs. However, a previous CPRD study demonstrated that patients with no recorded NSAID prescriptions (alleged non-users) indeed rarely use OTC NSAIDs on a regular basis.[305] Moreover, prescriptions in the patient records do not necessarily reflect actual drug use, as there is no information on whether the prescriptions were redeemed and whether the drugs were actually taken as advised by the GP. Since such misclassification is likely to occur at random and unlikely to be related to the case-control status of the patients or to the type of drugs used, it may have biased our results towards the null. Finally, we cannot exclude the possibility of chance findings.

In summary, our findings provide additional evidence that long-term continuous use of NSAIDs is associated with a moderately reduced risk of NMSC.

Chapter 9

FINAL DISCUSSION AND OUTLOOK

The six projects presented within this thesis provide a multifaceted perspective on the prevention of skin cancer. The main results of each individual project have been discussed in detail in the respective discussion sections. In the following, more general aspects of the findings and their relevance for future approaches to skin cancer prevention will be considered. Moreover, forthcoming research needs will be addressed.

Exposure to UVR emitted from the sun as well as from artificial sources is widely acknowledged as the most important modifiable risk factor for all major skin cancers, whereas in contrast to other malignancies, alcohol consumption and tobacco smoking play a subordinate role. Nonetheless, alcohol intake has been associated with a slightly elevated risk of BCC (see Project V) and CMM.[306-308] The relationship between alcohol intake and SCC has only been investigated in a small number of patients and requires further study.[252] Smoking has not or even inversely been associated with BCC (see Project V) and CMM,[261] but according to a recent meta-analysis it appears to increase the risk of SCC.[259] Although these data are derived from observational studies and can therefore not reliably establish causation, they suggest that limiting alcohol consumption or smoking cessation may to some extent reduce the risk of contracting particular types of cutaneous tumours.

Given the paramount importance of UVR in skin cancer pathogenesis, the efforts of primary prevention campaigns have commonly focused on promoting sun safety and on discouraging the use of solaria. Research on skin cancer prevention shows that among the general population, the last decades of campaigning have resulted in a reasonable level of knowledge about adverse health effects of extensive sun exposure and about sun protection.[309] However, there may still be considerable room for improvement in sun-related knowledge of specific high-risk subpopulations such as school children (see Project I) and outdoor workers (see Project II).

Despite the increasing awareness about the hazards associated with excessive UVR exposure, many people do not yet engage in adequate sun protective behaviour when out in the sun. This applies in particular to males, adolescents and young adults, individuals with less sun-sensitive skin types, individuals with low educational background, and outdoor workers (see Projects I-III).[114,126] Furthermore, people often solely rely on the use of sunscreen (see Projects I & III), even though seeking shade and wearing protective clothing are assigned a more important role in the hierarchy of photoprotective strategies.[72,73] The

latter circumstance may have been influenced in part by the popular media, which are a main source of health information for the public and primarily emphasise sunscreens as photoprotection means while neglecting the significance of seeking shade and covering up (see Project IV). Against this background, it is not surprising that sunburn rates remain high (see Projects I-III) and skin cancer places a growing burden on health services (see Project V).

The apparent gap between knowledge and actual behaviour is founded on various barriers to UV protection, of which presumably the most important is the desire for tanned skin. Although it is known that a suntan comes at the cost of DNA damage,[217] it is generally associated with healthiness and physical attractiveness, promoted by the media (see Project IV), and strived for by large segments of the population (see Projects II & III).[221,310-312] In addition to the cosmetic aspect, tanning may be driven by reinforcing effects on mood thought to be related to UVR-induced cutaneous endorphin release.[313] In terms of skin cancer prevention, the widespread pursuit of a tan is not only perturbing in that it negatively impacts sun safety, but also in that it fosters the regular use of solaria, especially among young women who express the greatest appeal of a tanned appearance (see Project III).[314]

Further identified barriers to UV protection include the perceived hassle of planning activities in the shade, of wearing protective clothing (e.g. discomfort in the heat, unfashionable look, costs), and of using sunscreens (e.g. time consuming application, unpleasant skin feel, costs) as well as largely unsubstantiated concerns about the safety of UV filters and insufficient UVR-mediated vitamin D synthesis.[221,312,315]

In order to improve people's sun protective behaviour in the long-term, effective programmes to prevent skin cancer ought to specifically address the above-mentioned barriers.

Considering the strong social norms regarding tanned skin as desirable, changing attitudes towards tanning presents one of the greatest challenges in the combat against skin cancer.[316] As intentional tanners may view the hazard of photoageing as more 'real' and serious than the hazard of skin cancer,[221] education messages focussed on appearance-related harms of UVR exposure offer a promising approach to foster primary preventive behaviours in this person group,[317] and are potentially more effective than messages focussed on health-related harms.[318] Yet at present, the mass media only occasionally mention photoageing as a negative consequence of UVR exposure (see Project IV) and

people seem to be much less sensitised to the risk of photoageing as compared to the risk of UV-induced cutaneous malignancies (see Project III).

A safe option for obtaining a tan is the use of topical self-tanners. Nonetheless, the promotion of these sunless tanning products is controversial, since they do not contribute to shift social norms around tanned skin and are unlikely to reduce UV exposure in the majority of tan seekers.[319,320]

Legal bans on commercial solariums have the potential to dramatically reduce harms from indoor tanning. Brazil was the first country in the world to issue a complete solarium ban in 2009, followed by Australia where virtually nationwide a similar ban will come into effect by the end of 2014.[321,322] Whether such indoor tanning legislation positively affects attitudes and beliefs about tanning and eventually leads to the anticipated reduction in skin cancer rates or whether it simply results in more intense outdoor tanning needs to be evaluated in future research.[320]

Increasing opportunities for sun protection in outdoor settings such as parks, public swimming pools, sports facilities, schoolyards, and certain workplaces can facilitate sun protective behaviours and ideally make them the default choice. This may include the provision of shade through building structures or strategic planting of trees as well as the supply of personal protective items (e.g. sunhats, sunscreen) free of charge or at affordable prices. Advances in textile and sunscreen technology resulting in more fashionable, comfortable to wear UV clothing and non-greasy, easy to apply sunscreens are likely to further enhance people's compliance with sun protection measures.[223,320,323]

In addition to highlighting the benefits of sun protection, assiduous efforts should be made to assure the public about the safety of sunscreens, which is time and again questioned by the popular press (see Project IV) and other sources. Much of this concern stems from *in vitro* and animal studies without relevance to everyday use in humans, and a favourable safety profile exits for commonly used organic and inorganic UV filters regardless of particle size.[324-326]

In recent years, unbalanced media reports (see Project IV) and advertisements of the solarium industry encouraging intentional exposure to solar and artificial UVR in order to enhance cutaneous vitamin D photosynthesis have emerged as a new threat to skin cancer prevention.[248,327] Ironically, the groups most receptive to such messages are those at the lowest risk of vitamin D deficiency, i.e. healthy, fair-skinned adolescents and young adults

with a great pursuit of a tan. In the future, successful skin cancer campaigning will not get around proactively addressing the uneasy relationship between UVR protection and vitamin D, thereby emphasising that adequate levels of the vitamin can be obtained from incidental protected sun exposure, diet, and oral supplements.[21]

Since skin cancers are multifactorial disorders and the complete avoidance of UVR exposure is usually neither desirable nor achievable, primary preventive measures beyond sun protection are needed to reduce the incidence of these tumours in high-risk patients, for example in chronically immunosuppressed individuals (see Project V) and persons with certain genetic diseases or extensive premalignant actinic skin damage.[94] Retinoids have proven effective in the systemic chemoprevention of NMSC, although the type of retinoid to choose, the dosage, and the duration of the treatment have not uniformly been established and the long-term use of the drugs is limited by substantial adverse side effects.[328] A number of other potential agents for the chemoprevention of both NMSC and CMM have yielded promising results in preclinical studies, but their clinical efficacy and safety remains to be determined.[93-97] For the thorough evaluation of these parameters, large prospective RCTs are warranted. Unfortunately, the implementation of such trials faces several practical, ethical, and financial constraints, which are often difficult to overcome. Observational studies are generally easier to realise, and may provide first, albeit not conclusive insights into the suitability of candidate compounds for skin cancer chemoprevention in clinical practice. Longitudinal electronic health record databases including the CPRD can serve as valuable data sources for such studies offering an effective approach to test hypotheses from preclinical settings in large samples of patients, under real-life conditions, and with a reasonable period of follow-up. However, a major limitation of health record databases for the investigation of potential skin cancer chemopreventive agents is the fact that they usually do not contain information on important relevant confounders such as the patients' skin constitutional factors and previous exposure to UVR (see Project VI). Taken together, research into skin cancer chemoprevention is still in its infancy and has to deal with significant obstacles, but the identification of new effective, safe, and accessible chemopreventive compounds could mark a milestone in the control of the disease in predisposed patients.

Aside from primary prevention, secondary prevention represents an integral part of the overall endeavour to reduce the burden of skin cancer. There are first indications of the effectiveness of population-wide skin cancer screening,[104-106] and in patients with a

heightened susceptibility to the disease regular dermatological examinations belong to the standard medical care.[67,329] Increased press coverage of skin cancer secondary prevention could contribute to encouraging people to attend appropriate screening programmes and to better familiarising the population with early signs of malignant skin lesions that necessitate a consultation with a trained physician (see Project IV).

As the Australian experience demonstrates, successful skin cancer prevention programmes should use multi-component strategies, which need to be sustained over the long term.[110] Beside broad mass media campaigns, these ought to comprise comprehensive interventions targeted at specific subsets of the population. Based on systematic reviews of the scientific literature, there is now sufficient evidence of effectiveness to recommend the latter in child care centres, in primary and middle schools, in outdoor occupational settings (see Project II) as well as in outdoor recreational and tourism settings. However, more research is required to identify the elements of interventions which are most effective in eliciting the envisaged changes in risk behaviours.[128,330]

To learn from and improve on existing interventions, the formal evaluation of prevention programmes is essential. This implies that along with trends in sun-related knowledge, attitudes, and behaviour, in a given population sunburn rates, skin cancer incidence and skin cancer mortality need to be closely monitored over time. Yet to date, the lack of systematic NMSC surveillance in many regions impedes the measuring of intervention impacts on this important health outcome linked to excessive UVR exposure. Electronic health record databases may substantially contribute to the better monitoring of incidence trends of NMSC, as they also contain data on the considerable proportion of these tumours not reported to cancer registries (see Project V).[320]

In conclusion, tackling the major public health issue of skin cancer necessitates concerted efforts of many partners across various sectors, including state and local governments, health agencies, clinicians, scientists, sun protection industry, schools, child care centres, employers, the media, and funding bodies. Prevention initiatives have to move from purely imparting knowledge to inspiring actual changes in risk behaviours. Photoprotective messages ought to be constantly updated to the most current state of science, ensuring the dissemination of adequate and consistent information.[315,320] Moreover, protection measures beyond the use of sunscreens should be further emphasised.

Considering the limited success of therapy, in particular with respect to metastatic CMM, prevention will continue to play a key role in reducing morbidity and mortality from skin cancer. And last but not least, investments in skin cancer prevention show strong potential for long-term savings in health care costs.[32]

Chapter 10

SYNOPSIS

- Exposure to solar and artificial UVR is the most important modifiable risk factor for skin cancer. Hence, primary prevention campaigns commonly focus on promoting sun protection and on discouraging the use of solaria.
- Over the last decades, a number of interventions to prevent skin cancer have significantly improved people's knowledge about adverse health effects of UVR and about sun protection.
- However, the impact of prevention efforts on people's sun protective behaviour has been modest, sunburn rates remain high, and skin cancer incidence continues to rise in many countries.
- Important barriers to adequate UV protection comprise the widespread desire for tanned skin, the perceived hassle of planning activities in the shade, of wearing protective clothing, and of applying sunscreen as well as largely unsubstantiated concerns about the safety of UV filters and insufficient UVR-mediated vitamin D synthesis.
- To address these barriers and tackle the major public health issue of skin cancer, concerted efforts of many partners across various sectors are needed, including governments, health agencies, clinicians, scientists, sun protection industry, schools, child care centres, employers, the media, and funding bodies.
- In patients highly predisposed to skin cancer, systemic chemoprevention can be considered. Yet to date, the clinical use of available chemopreventive agents is limited by substantial adverse side effects.
- Secondary prevention of skin cancer plays a key role in reducing morbidity and mortality from the disease and should be further fostered.

APPENDIX

Project I: Self-administered questionnaire

Fragebogen zur Untersuchung des Sonnenschutzverhaltens von Primarschülerinnen und Primarschülern

1. **Ich bin ein**

☐ ☐

2. **Ich bin _____ Jahre alt**

3. **Meine Augen sind**

Blau ☐ Braun ☐ Grün ☐

4. **Meine Haare sind**

Schwarz ☐ Blond ☐ Braun ☐ Rot-Blond ☐

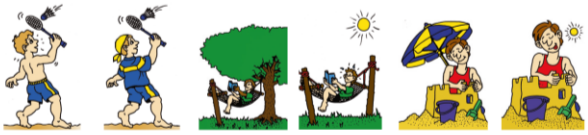
5. **Die Sonne kann für mich gefährlich sein?**

☐ Ja ☐ Nein ☐ Weiss nicht

6. **Ich kann mich vor der Sonne schützen.**

☐ Ja ☐ Nein ☐ Weiss nicht

7. **Auf welchen Bildern ist das Kind gut vor der Sonne geschützt?**



☐ ☐ ☐ ☐ ☐ ☐

Zürich, Frühjahr 2012 (post-test)

krebsliga schweiz

8. Was fehlt dem Bub um sich vor der Sonne zu schützen?

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

9. Wenn die Sonne scheint gehe ich in den Schatten.

☐ Ja ☐ Ja, manchmal ☐ nein ☐ Weiss nicht

10. Ich creme mich im Sommer selber mit Sonnencreme ein.

☐ Ja ☐ Nein ☐ Weiss nicht

11. Ich habe im letzten Jahr einen Sonnenbrand gehabt.

☐ Ja ☐ Nein ☐ Weiss nicht

12. Mama und Papa sagen wie ich mich vor der Sonne schützen kann.

☐ Ja ☐ Nein ☐ Weiss nicht

13. In der Schule lerne ich, wie ich mich vor der Sonne schützen kann.

☐ Ja ☐ Nein ☐ Weiss nicht

14. Mama oder Papa cremen mich im Sommer mit Sonnencreme ein.

☐ Ja ☐ Nein ☐ Weiss nicht

15. Ich habe letztes Jahr am Sonnenschutz-Parcours in meiner Schule mitgemacht.

☐ Ja ☐ Nein ☐ Ich kann mich nicht mehr erinnern

Zürich, Frühjahr 2012 (post-test)

krebsliga schweiz

Project III: Questionnaires for standardised face-to-face interviews

Fragebogen zur Untersuchung des Sonnenschutzverhaltens von Reisenden in die Tropen und Subtropen am Flughafen Basel

Datum Interview:

……..

Studieninformation und Teilnahmezustimmung:

Der Studienteilnehmer/ die Studienteilnehmerin wurde mündlich über Ziel und Inhalt der Studie informiert und hat sich zur Studienteilnahme bereit erklärt

☐ Ja ☐ Nein

Angaben zur Person:

1. Geschlecht: ☐ männlich ☐ weiblich

2. Hauttyp: ☐ Hauttyp 1 oder 2 ☐ Hauttyp 3 oder 4

3. Kopfhaar: ☐ Dicht ☐ Licht ☐ Glatze ☐ Nicht beurteilbar

4. Geburtsjahrgang: ……..

5. Nationalität: ……

6. Leiden Sie manchmal an Sonnenallergie? ☐ Ja ☐ Nein

Angaben zur Reise:

7. Zieldestination (Land): ……

8. Geplante Aufenthaltsdauer: ……...

9. Art der Reise:

☐ Privat (Urlaub) → direkt weiter bei Frage 10.b
☐ Beruflich

10. Sind folgende Aktivitäten an der Zieldestination geplant?

	Ja	Nein
a) Arbeit im Freien	☐	☐
b) Safari, Trekking	☐	☐
c) Wasseraktivitäten (z.B. Baden, Schnorcheln, Tauchen)	☐	☐
d) Andere Outdoor-Sportart (z.B. Wandern, Tennis, Golf)	☐	☐
e) Besichtigung "Land und Leute", Kulturstätten	☐	☐
f) Sonnenbaden	☐	☐

Sonnenbräune:

11. a) Auf einer Skala von 0-10, wie wichtig ist es für Sie, während Ihrem Aufenthalt an der Zieldestination Sonnenbräune zu erlangen („braun" zu werden)?

0= völlig unwichtig; 10= sehr wichtig

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

b) *Falls angegebener Skalenwert ≥ 5:* Nehmen Sie einen Sonnenbrand in Kauf, um danach braun zu werden?

☐ Ja ☐ Nein

Vorbereitung auf die Sonne:

12. Haben Sie in den letzten 4 Wochen ein Solarium besucht?

☐ Ja ☐ Nein → direkt weiter bei Frage 14

13. Wenn ja, mit welcher Absicht? *(Auswahlantworten nicht vorgeben)*

☐ Erlangen des „Ferienteints" / um braun zu werden
☐ Vorbeugung Sonnenbrand/Hautkrebs/Hautalterung
☐ Vorbeugung Sonnenallergie
☐ Vitamin D- Bildung
☐ Anderes:……..

14. Haben Sie Ihre Haut durch die Einnahme von bestimmten Nahrungsmitteln oder Nahrungsergänzungsmitteln („Sonnenkapseln") auf die Sonnenexposition vorbereitet?

☐ Nein → direkt weiter bei Frage 17
☐ Ja, mit folgenden Nahrungsmitteln: ……..
☐ Ja, mit folgenden Nahrungsergänzungsmitteln: ……..

15. Wie lange vor Ferienbeginn haben Sie mit der regelmässigen Einnahme dieser Nahrungsmittel/Nahrungsergänzungsmittel begonnen? *(Auswahlantworten nicht vorgeben)*

☐ Vor mehr als 2 Monaten
☐ Vor 1-2 Monaten
☐ Vor 2-3 Wochen
☐ Vor weniger als 2 Wochen

16. Wie häufig haben Sie die Nahrungsmittel/Nahrungsergänzungsmittel während dieser Zeitspanne eingenommen? *(Auswahlantworten nicht vorgeben)*

☐ Täglich
☐ An mindestens 4 Tagen pro Woche
☐ An weniger als 4 Tagen pro Woche

Sonnenschutz:

17. Haben Sie Sonnencreme im Gepäck?

☐ Ja
☐ Nein, das kaufe ich an der Zieldestination → direkt weiter bei Frage 19
☐ Nein, ich verwende keine Sonnencreme → direkt weiter bei Frage 19

18. Welchen Lichtschutzfaktor (LSF) hat diese Sonnencreme?

LSF: …… ☐ Ich weiss es nicht

Falls verschiedene Sonnencremen mit unterschiedlichem LSF im Gepäck sind: Weshalb? *(Auswahlantworten nicht vorgeben)*

☐ Höchster LSF am Anfang der Reise, dann Reduktion
☐ Hoher LSF für die Kinder
☐ Hoher LSF fürs Gesicht
☐ Anderes: .....

19. Haben Sie einen Sonnenhut (oder Kopftuch) im Gepäck?

☐ Ja
☐ Nein, das kaufe ich an der Zieldestination → direkt weiter bei Frage 21
☐ Nein, ich trage keinen Sonnenhut → direkt weiter bei Frage 21

20. Welche Art von Sonnenhut?

☐ Hut mit Krempe ☐ Schirmmütze
☐ Hut mit Nackenschutz ☐ Kopftuch ☐ Anderes: ……

21. Haben Sie eine Sonnenbrille im Gepäck?

☐ Ja
☐ Nein, das kaufe ich an der Zieldestination
☐ Nein, ich trage keine Sonnenbrille

22. Haben Sie Kleidung mit speziell eingearbeitetem UV-Schutz im Gepäck?

☐ Ja ☐ Nein

Fragebogen zur Untersuchung des Sonnenschutzverhaltens von Heimkehrenden aus den Tropen und Subtropen am Flughafen Basel

Datum Interview:

……..

Studieninformation und Teilnahmezustimmung:

Der Studienteilnehmer/ die Studienteilnehmerin wurde mündlich über Ziel und Inhalt der Studie informiert und hat sich zur Studienteilnahme bereit erklärt

☐ Ja ☐ Nein

Angaben zur Person:

1. Geschlecht: ☐ männlich ☐ weiblich

2. Hauttyp: ☐ Hauttyp 1 oder 2 ☐ Hauttyp 3 oder 4

3. Kopfhaar: ☐ Dicht ☐ Licht ☐ Glatze ☐ Nicht beurteilbar

4. Geburtsjahrgang: ……..

5. Nationalität: ……

Angaben zur Reise:

6. Reisedestination (Land): ……..

7. Aufenthaltsdauer: ……...

Sonnenbrand:

8. Haben Sie während Ihrem Aufenthalt an der Reisedestination einen Sonnenbrand erlitten?
Sonnenbrand = Durch die Sonne verursachte Rötung der Haut, die mindestens 24 Stunden anhält (nicht zwingend schmerzhaft!)
☐ Ja
☐ Nein → weiter bei Frage 11

9. Welche Beschreibung trifft auf den Sonnenbrand zu?
Falls auf der Reise mehrere Sonnenbrände erlitten wurden: Welche Beschreibung trifft auf den schlimmsten Sonnenbrand zu?

☐ Leichte Rötung der Haut, nicht schmerzhaft
☐ Schmerzhafte Rötung der Haut
☐ Rötung der Haut mit Blasenbildung

10. Welche Körperteile waren vom Sonnenbrand betroffen? *(Auswahlantworten nicht vorgeben)*

☐ Gesicht	☐ Dékolleté	☐ Obere Extremitäten
☐ Ohren	☐ Rücken	☐ Untere Extremitäten
☐ Kopfhaut	☐ Bauch	
☐ Nacken	☐ Schultergürtel	

Sonnenschutz:

11. Haben Sie während Ihrem Aufenthalt an der Zieldestination Sonnencreme verwendet?

☐ Nein, nie → direkt weiter bei Frage 13
☐ Ja, manchmal
☐ Ja, bei schönem Wetter (fast) immer

12. Welchen Lichtschutzfaktor (LSF) hatte diese Sonnencreme?

LSF: …… ☐ Ich weiss es nicht

Falls Sonnencremes mit verschiedenen LSF: Weshalb?

☐ Höchster LSF am Anfang der Reise, dann Reduktion
☐ Hoher LSF für die Kinder
☐ Hoher LSF fürs Gesicht
☐ Anderes: .....

13. Haben Sie während Ihrem Aufenthalt an der Zieldestination einen Sonnenhut oder eine vergleichbare Kopfbedeckung getragen?

☐ Nein, nie
☐ Ja, manchmal
☐ Ja, bei schönem Wetter (fast) immer

14. Haben Sie sich während Ihrem Aufenthalt an der Zieldestination über Mittag im Schatten aufgehalten?

☐ Nein, nie
☐ Ja, manchmal
☐ Ja, bei schönem Wetter (fast) immer

Fragebogen zur Untersuchung des Sonnenschutzverhaltens von Reisenden am Tropen- und Public Health-Institut Basel (Swiss TPH)

Datum Interview:

……..

Studieninformation und Teilnahmezustimmung:

Der Studienteilnehmer/ die Studienteilnehmerin wurde mündlich über Ziel und Inhalt der Studie informiert und hat sich zur Studienteilnahme bereit erklärt

☐ Ja ☐ Nein

Angaben zur Person:

1. Geschlecht: ☐ männlich ☐ weiblich

2. Hauttyp: ☐ Hauttyp 1 oder 2 ☐ Hauttyp 3 oder 4

3. Kopfhaar: ☐ Dicht ☐ Licht ☐ Glatze ☐ Nicht beurteilbar

4. Geburtsjahrgang: ……..

5. Nationalität: ……

6. Leiden Sie manchmal an Sonnenallergie? ☐ Ja ☐ Nein

Angaben zur Reise:

7. Zieldestination (Land): ……

8. Geplantes Abreisedatum: ……..

9. Geplante Aufenthaltsdauer: ……...

10. Art der Reise:

☐ Privat (Urlaub) → direkt weiter bei Frage 11 b)
☐ Beruflich

11. Sind folgende Aktivitäten an der Zieldestination geplant?

	Ja	Nein
a) Arbeit im Freien	☐	☐
b) Safari, Trekking	☐	☐
c) Wasseraktivitäten (z.B. Baden, Schnorcheln, Tauchen)	☐	☐
d) Andere Outdoor-Sportart (z.B. Wandern, Tennis, Golf)	☐	☐
e) Besichtigung “Land und Leute”, Kulturstätten	☐	☐
f) Sonnenbaden	☐	☐

Sonnenbräune:

12. a) Auf einer Skala von 0-10, wie wichtig ist es für Sie, während Ihrem Aufenthalt an der Zieldestination Sonnenbräune zu erlangen („braun“ zu werden)?

0= völlig unwichtig; 10= sehr wichtig

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

b) *Falls angegebener Skalenwert ≥ 5:* Nehmen Sie einen Sonnenbrand in Kauf, um danach braun zu werden?

☐ Ja ☐ Nein

Vorbereitung auf die Sonne:

13. Bereiten Sie Ihre Haut bereits vor der Abreise auf die hohe Sonnenexposition an der Zieldestination vor?

☐ Ja
☐ Nein → direkt weiter bei Frage 17

14. Wie bereiten Sie Ihre Haut auf die Sonne vor? *(Auswahlantworten nicht vorgeben)*

☐ Vorbräunen im Solarium → direkt weiter bei Frage 17
☐ Einnahme bestimmter Nahrungsmittel, nämlich……...
☐ Einnahme bestimmter Nahrungsergänzungsmittel, nämlich……..
☐ Anderes, nämlich……. → direkt weiter bei Frage 17

15. Wie lange vor Ferienbeginn planen Sie mit der regelmässigen Einnahme dieser Nahrungsmittel/Nahrungsergänzungsmittel zu beginnen? *(Auswahlantworten nicht vorgeben)*

☐ Mehr als 2 Monate vor Abreise
☐ 1-2 Monate vor Abreise
☐ 2-3 Wochen vor Abreise
☐ Weniger als 2 Wochen vor Abreise
☐ Ich weiss es noch nicht

16. Wie häufig planen Sie die Nahrungsmittel/Nahrungsergänzungsmittel während dieser Zeitspanne einzunehmen? *(Auswahlantworten nicht vorgeben)*

☐ Täglich
☐ An mindestens 4 Tagen pro Woche
☐ An weniger als 4 Tagen pro Woche
☐ Ich weiss es noch nicht

Sonnenschutz:

17. Planen Sie sich an der Zieldestination vor der Sonne zu schützen?

☐ Ja ☐ Nein → direkt weiter bei Frage 19

18. Welche Sonnenschutzmassnahmen treffen Sie?

Mehrere Antworten möglich. Auswahlantworten nicht vorgeben.
Fällt eine der aufgeführten Auswahlantworten spontan: präzisierende Frage hinter dem Pfeil stellen!

☐ Sonnencreme → mit welchem Lichtschutzfaktor (LSF)?

LSF: …….. ☐ Weiss nicht

Falls mehr als ein LSF genannt wird: Begründung?

☐ Hoher LSF am Anfang der Reise, dann Reduktion
☐ Hoher LSF für mitreisende Kinder
☐ Hoher LSF fürs Gesicht
☐ Anderes: .....

☐ Kopfbedeckung → Welche Art von Kopfbedeckung?

☐ Hut mit Krempe ☐ Schirmmütze
☐ Hut mit Nackenschutz ☐ Kopftuch
☐ Weiss nicht ☐ Anderes: …….

☐ Sonnenbrille

☐ Kleidung → Welche Art von Kleidung?

☐ Schulterbedeckendes Shirt ☐ Langärmeliges Shirt
☐ Lange Hosen ☐ Kleidung mit speziell eingearbeitetem UV-Schutz

☐ Schattenstrukturen (Sonnenschirm, Sonnensegel, Bäume)

☐ Mittagssonne meiden

☐ Anderes: ……..

Abschliessende Frage: „Wenden Sie noch weitere Sonnenschutzmethoden an?“
Wenn dies verneint wird → weiter bei Frage 19

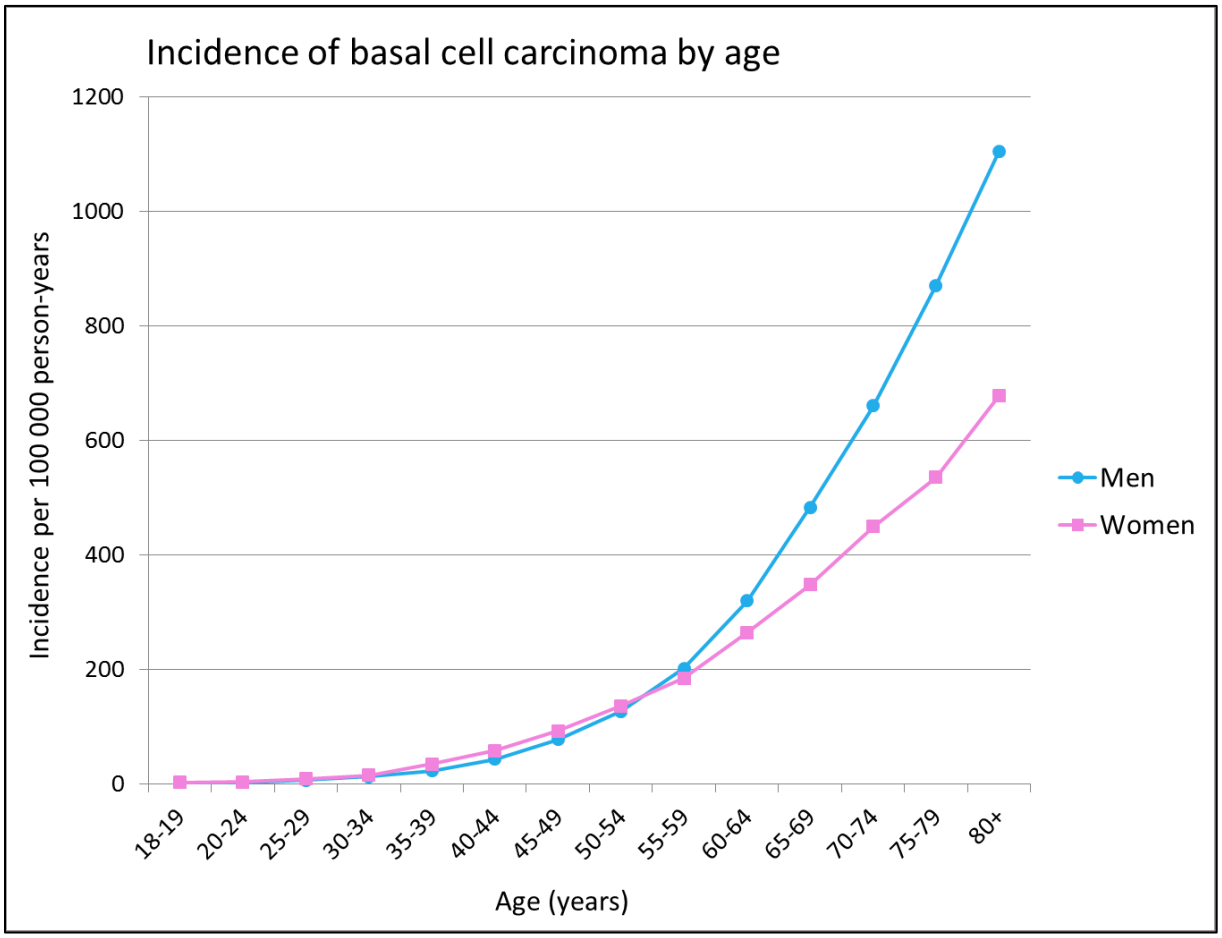
Kenntnisse:

19. Welche negativen Auswirkungen von Sonnenstrahlung auf den Menschen sind Ihnen bekannt? *(Auswahlantworten nicht vorgeben)*

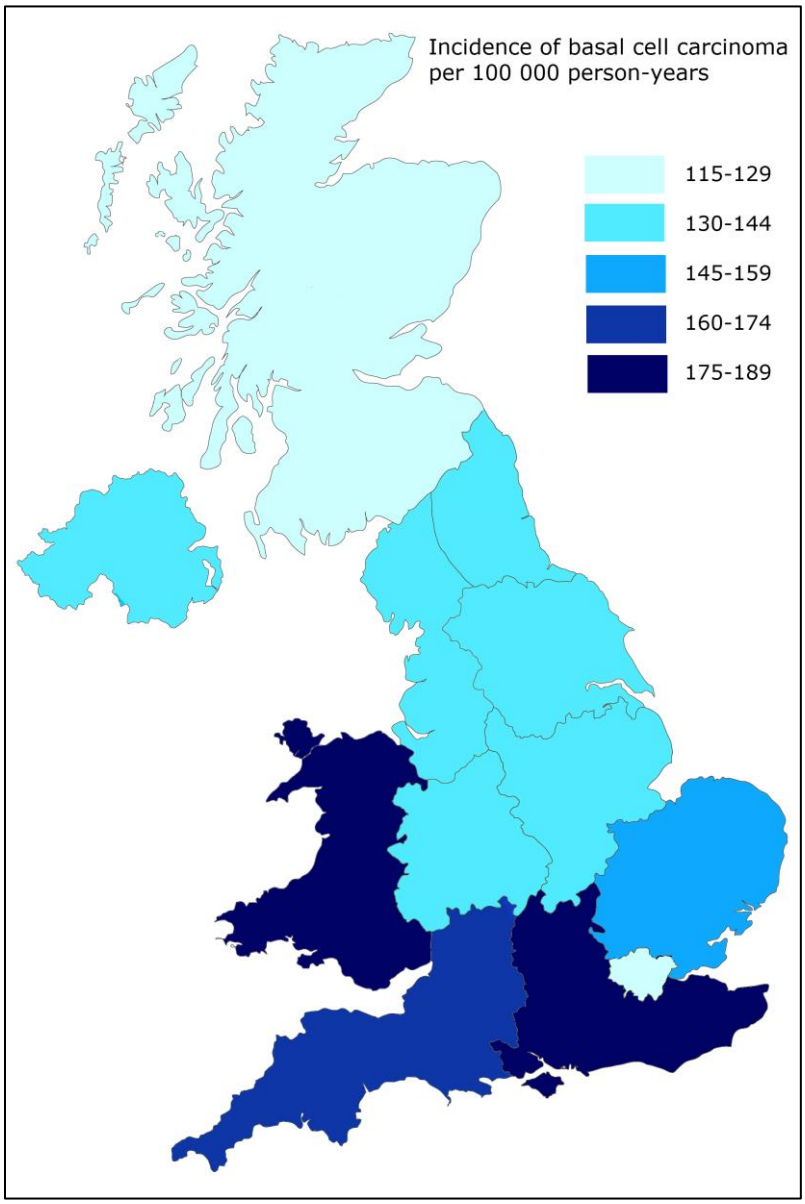
☐ Sonnenbrand
☐ Sonnenallergie
☐ Aktinische Keratose, Morbus Bowen
☐ Hautkrebs (nicht spezifiziert)
☐ Schwarzer Hautkrebs
☐ Heller/weisser Hautkrebs
☐ Vorzeitige Hautalterung
☐ Pigmentflecken/ Sonnenflecken/ Altersflecken
☐ Augenschäden (nicht spezifiziert)
☐ Photokeratitis/Photokonjunktivitis („Schneeblindheit“)
☐ Grauer Star (Katarakt)
☐ Andere Augenschäden (spezifiziert): …….
☐ Immunsuppression
☐ Hitzeerkrankungen (Sonnenstich, Hitzschlag, Hitzeerschöpfung, Dehydration, Kopfschmerzen, Übelkeit, …)
☐ Anderes: ……

Abschliessende Frage: „Kennen Sie noch weitere negative Auswirkungen?“

Project V: Unpublished supplementary material



UK incidence rates of basal cell carcinoma first-time diagnoses by age in adults over the period from 2000 to 2011



UK incidence rates of basal cell carcinoma first-time diagnoses by region in adults over the period from 2000 to 2011 (age-standardised to the European standard population)

REFERENCES

1 Diffey BL. What is light? *Photodermatol Photoimmunol Photomed* 2002; **18**: 68-74.

2 Honigsmann H. Erythema and pigmentation. *Photodermatol Photoimmunol Photomed* 2002; **18**: 75-81.

3 Gruber-Wackernagel A, Byrne SN, Wolf P. Polymorphous Light Eruption: Clinic Aspects and Pathogenesis. *Dermatol Clin* 2014; **32**: 315-34.

4 Santoro FA, Lim HW. Update on photodermatoses. *Semin Cutan Med Surg* 2011; **30**: 229-38.

5 Polefka TG, Meyer TA, Agin PP *et al.* Effects of solar radiation on the skin. *J Cosmet Dermatol* 2012; **11**: 134-43.

6 El Ghissassi F, Baan R, Straif K *et al.* A review of human carcinogens-part D: radiation. *Lancet Oncol* 2009; **10**: 751-2.

7 Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. *J Photochem Photobiol B* 2001; **63**: 8-18.

8 Ikehata H, Ono T. The mechanisms of UV mutagenesis. *J Radiat Res* 2011; **52**: 115-25.

9 Pfeifer GP, You YH, Besaratinia A. Mutations induced by ultraviolet light. *Mutat Res* 2005; **571**: 19-31.

10 Kusewitt DF, Applegate LA, Ley RD. Ultraviolet radiation-induced skin tumors in a South American opossum (Monodelphis domestica). *Vet Pathol* 1991; **28**: 55-65.

11 Setlow RB, Woodhead AD, Grist E. Animal model for ultraviolet radiation-induced melanoma: platyfish-swordtail hybrid. *Proc Natl Acad Sci U S A* 1989; **86**: 8922-6.

12 Winkelmann RK, Zollman PE, Baldes EJ. Squamous cell carcinoma produced by ultraviolet light in hairless mice. *J Invest Dermatol* 1963; **40**: 217-24.

13 Norval M. The mechanisms and consequences of ultraviolet-induced immunosuppression. *Prog Biophys Mol Biol* 2006; **92**: 108-18.

14 Wang J, Aldabagh B, Yu J *et al.* Role of human papillomavirus in cutaneous squamous cell carcinoma: a meta-analysis. *J Am Acad Dermatol* 2014; **70**: 621-9.

15 Gilchrest BA. Photoaging. *J Invest Dermatol* 2013; **133**: E2-6.

16 Han A, Chien AL, Kang S. Photoaging. *Dermatol Clin* 2014; **32**: 291-9.

17 Situm M, Buljan M, Cavka V *et al.* Skin changes in the elderly people--how strong is the influence of the UV radiation on skin aging? *Coll Antropol* 2010; **34 Suppl 2**: 9-13.

18 Young AR. Acute effects of UVR on human eyes and skin. *Prog Biophys Mol Biol* 2006; **92**: 80-5.

19 Norval M, Lucas RM, Cullen AP *et al.* The human health effects of ozone depletion and interactions with climate change. *Photochem Photobiol Sci* 2011; **10**: 199-225.

20 Oliva MS, Taylor H. Ultraviolet radiation and the eye. *Int Ophthalmol Clin* 2005; **45**: 1-17.

21 Gilchrest BA. Sun exposure and vitamin D sufficiency. *Am J Clin Nutr* 2008; **88**: 570S-7S.

22 Wolpowitz D, Gilchrest BA. The vitamin D questions: how much do you need and how should you get it? *J Am Acad Dermatol* 2006; **54**: 301-17.

23 Reichrath J, Reichrath S. Hope and challenge: the importance of ultraviolet (UV) radiation for cutaneous vitamin D synthesis and skin cancer. *Scand J Clin Lab Invest Suppl* 2012; **243**: 112-9.

24 World Health Organization. How common is skin cancer? (available from http://www.who.int/uv/faq/skincancer/en/index1.html [cited 2014 June 19]).

25 Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. *N Engl J Med* 2005; **353**: 2262-9.

26 Kim RH, Armstrong AW. Nonmelanoma skin cancer. *Dermatol Clin* 2012; **30**: 125-39, ix.

27 Staples MP, Elwood M, Burton RC *et al.* Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. *Med J Aust* 2006; **184**: 6-10.

28 Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. *Br J Dermatol* 2012; **166**: 1069-80.

29 Flohil SC, Proby CM, Forrest AD *et al.* Basal cell carcinomas without histological confirmation and their treatment: an audit in four European regions. *Br J Dermatol* 2012; **167 Suppl 2**: 22-8.

30 Marcil I, Stern RS. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. *Arch Dermatol* 2000; **136**: 1524-30.

31 Madan V, Lear JT, Szeimies RM. Non-melanoma skin cancer. *Lancet* 2010; **375**: 673-85.

32 Gordon LG, Rowell D. Health system costs of skin cancer and cost-effectiveness of skin cancer prevention and screening: a systematic review. *Eur J Cancer Prev* 2014.

33 Guy GP, Ekwueme DU. Years of potential life lost and indirect costs of melanoma and non-melanoma skin cancer: a systematic review of the literature. *Pharmacoeconomics* 2011; **29**: 863-74.

34 Ferlay J SI, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013. (available from http://globocan.iarc.fr [cited 2014 July 1]).

35 Agbai ON, Buster K, Sanchez M *et al.* Skin cancer and photoprotection in people of color: a review and recommendations for physicians and the public. *J Am Acad Dermatol* 2014; **70**: 748-62.

36 Leiter U, Meier F, Schittek B *et al.* The natural course of cutaneous melanoma. *J Surg Oncol* 2004; **86**: 172-8.

37 Eggermont AM, Spatz A, Robert C. Cutaneous melanoma. *Lancet* 2014; **383**: 816-27.

38 Erdmann F, Lortet-Tieulent J, Schuz J *et al.* International trends in the incidence of malignant melanoma 1953-2008--are recent generations at higher or lower risk? *Int J Cancer* 2013; **132**: 385-400.

39 Gass R, Bopp M. Melanom-Mortalität: Trends in der Schweiz. *Praxis* 2005; **94**: 1295-300.

40 Jemal A, Saraiya M, Patel P *et al.* Recent trends in cutaneous melanoma incidence and death rates in the United States, 1992-2006. *J Am Acad Dermatol* 2011; **65**: S17-25 e1-3.

41 Gandini S, Sera F, Cattaruzza MS *et al.* Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur J Cancer* 2005; **41**: 28-44.

42 Gandini S, Sera F, Cattaruzza MS *et al.* Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Eur J Cancer* 2005; **41**: 2040-59.

43 Khalesi M, Whiteman DC, Tran B *et al.* A meta-analysis of pigmentary characteristics, sun sensitivity, freckling and melanocytic nevi and risk of basal cell carcinoma of the skin. *Cancer Epidemiol* 2013; **37**: 534-43.

44 Green AC, Wallingford SC, McBride P. Childhood exposure to ultraviolet radiation and harmful skin effects: epidemiological evidence. *Prog Biophys Mol Biol* 2011; **107**: 349-55.

45 Whiteman DC, Whiteman CA, Green AC. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. *Cancer Causes Control* 2001; **12**: 69-82.

46 Corona R, Dogliotti E, D'Errico M *et al.* Risk factors for basal cell carcinoma in a Mediterranean population: role of recreational sun exposure early in life. *Arch Dermatol* 2001; **137**: 1162-8.

47 Gallagher RP, Hill GB, Bajdik CD *et al.* Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer. I. Basal cell carcinoma. *Arch Dermatol* 1995; **131**: 157-63.

48 English DR, Armstrong BK, Kricker A *et al.* Case-control study of sun exposure and squamous cell carcinoma of the skin. *Int J Cancer* 1998; **77**: 347-53.

49 Gallagher RP, Hill GB, Bajdik CD *et al.* Sunlight exposure, pigmentation factors, and risk of nonmelanocytic skin cancer. II. Squamous cell carcinoma. *Arch Dermatol* 1995; **131**: 164-9.

50 Grodstein F, Speizer FE, Hunter DJ. A prospective study of incident squamous cell carcinoma of the skin in the nurses' health study. *J Natl Cancer Inst* 1995; **87**: 1061-6.

51 Volkmer B, Greinert R. UV and children's skin. *Prog Biophys Mol Biol* 2011; **107**: 386-8.

52 Garcia AM, McLaren CE, Meyskens FL, Jr. Melanoma: is hair the root of the problem? *Pigment Cell Melanoma Res* 2011; **24**: 110-8.

53 Balk SJ, Council on Environmental Health and Section on Dermatology. Ultraviolet radiation: a hazard to children and adolescents. *Pediatrics* 2011; **127**: e791-817.

54 IARC monographs on the evaluation of carcinogenic risks to humans. Solar and ultraviolet radiation. *IARC Monogr Eval Carcinog Risks Hum* 1992; **55**: 1-316.

55 Bauer A, Diepgen TL, Schmitt J. Is occupational solar ultraviolet irradiation a relevant risk factor for basal cell carcinoma? A systematic review and meta-analysis of the epidemiological literature. *Br J Dermatol* 2011; **165**: 612-25.

56 Schmitt J, Seidler A, Diepgen TL *et al.* Occupational ultraviolet light exposure increases the risk for the development of cutaneous squamous cell carcinoma: a systematic review and meta-analysis. *Br J Dermatol* 2011; **164**: 291-307.

57 Whiteman DC, Pavan WJ, Bastian BC. The melanomas: a synthesis of epidemiological, clinical, histopathological, genetic, and biological aspects, supporting distinct subtypes, causal pathways, and cells of origin. *Pigment Cell Melanoma Res* 2011; **24**: 879-97.

58 Fartasch M, Diepgen TL, Schmitt J *et al.* The relationship between occupational sun exposure and non-melanoma skin cancer: clinical basics, epidemiology, occupational disease evaluation, and prevention. *Dtsch Arztebl Int* 2012; **109**: 715-20.

59 Safe Work Australia. Occupational disease indicators. April 2010 (available from http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/340/Occupational_Disease_Indicators_2010_PDF.pdf [cited 2014 July 11]).

60 Albert MR, Ostheimer KG. The evolution of current medical and popular attitudes toward ultraviolet light exposure: part 1. *J Am Acad Dermatol* 2002; **47**: 930-7.

61 Albert MR, Ostheimer KG. The evolution of current medical and popular attitudes toward ultraviolet light exposure: part 2. *J Am Acad Dermatol* 2003; **48**: 909-18.

62 Gormsen E. The impact of tourism on coastal areas. *GeoJournal* 1997; **42**: 39-54.

63 Petersen B, Thieden E, Philipsen PA *et al.* Determinants of personal ultraviolet-radiation exposure doses on a sun holiday. *Br J Dermatol* 2013; **168**: 1073-9.

64 Hiom S. Public awareness regarding UV risks and vitamin D--the challenges for UK skin cancer prevention campaigns. *Prog Biophys Mol Biol* 2006; **92**: 161-6.

65 Manning DL, Quigley P. Sunbathing intentions in Irish people travelling to Mediterranean summer holiday destinations. *Eur J Cancer Prev* 2002; **11**: 159-63.

66 Petersen B, Thieden E, Philipsen PA *et al.* A sun holiday is a sunburn holiday. *Photodermatol Photoimmunol Photomed* 2013; **29**: 221-4.

67 Mudigonda T, Levender MM, O'Neill JL *et al.* Incidence, risk factors, and preventative management of skin cancers in organ transplant recipients: a review of single- and multicenter retrospective studies from 2006 to 2010. *Dermatol Surg* 2013; **39**: 345-64.

68 Dahlke E, Murray CA, Kitchen J *et al.* Systematic review of melanoma incidence and prognosis in solid organ transplant recipients. *Transplant Res* 2014; **3**: 10.

69 Athar M, Walsh SB, Kopelovich L *et al.* Pathogenesis of nonmelanoma skin cancers in organ transplant recipients. *Arch Biochem Biophys* 2011; **508**: 159-63.

70 Hofbauer GF, Bouwes Bavinck JN, Euvrard S. Organ transplantation and skin cancer: basic problems and new perspectives. *Exp Dermatol* 2010; **19**: 473-82.

71 Wheless L, Jacks S, Mooneyham Potter KA *et al.* Skin cancer in organ transplant recipients: More than the immune system. *J Am Acad Dermatol* 2014; **71**: 359-65.

72 Lautenschlager S, Wulf HC, Pittelkow MR. Photoprotection. *Lancet* 2007; **370**: 528-37.

73 Surber C, Ulrich C, Hinrichs B *et al.* Photoprotection in immunocompetent and immunocompromised people. *Br J Dermatol* 2012; **167 Suppl 2**: 85-93.

74 Dirschka T, Kraehn-Senftleben G, Petering H *et al.* Standardisierte Lichtschutzberatung. *onkoderm e.V.* 2011.

75 Moise AF, Aynsley R. Ambient ultraviolet radiation levels in public shade settings. *Int J Biometeorol* 1999; **43**: 128-38.

76 Turnbull DJ, Parisi AV. Effective shade structures. *Med J Aust* 2006; **184**: 13-5.

77 Gies P. Photoprotection by clothing. *Photodermatol Photoimmunol Photomed* 2007; **23**: 264-74.

78 Diffey BL, Cheeseman J. Sun protection with hats. *Br J Dermatol* 1992; **127**: 10-2.

79 van der Pols JC, Williams GM, Pandeya N *et al.* Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 2546-8.

80 Green AC, Williams GM, Logan V *et al.* Reduced melanoma after regular sunscreen use: randomized trial follow-up. *J Clin Oncol* 2011; **29**: 257-63.

81 Hughes MC, Williams GM, Baker P *et al.* Sunscreen and prevention of skin aging: a randomized trial. *Ann Intern Med* 2013; **158**: 781-90.

82 Shaath NA. Ultraviolet filters. *Photochem Photobiol Sci* 2010; **9**: 464-9.

83 Diffey BL, Brown MW. The ideal spectral profile of topical sunscreens. *Photochem Photobiol* 2012; **88**: 744-7.

84 International Standard. Cosmetics - Sun protection test methods - In vivo determination of the sun protection factor (SPF). *ISO 24444* 2010.

85 Commission of the European Communities. Commission Recommendation of 22 September 2006 on the efficacy of sunscreen products and the claims made relating thereto. *Official Journal of the European Union* 2006; **L 265**: 39-43.

86 Osterwalder U, Herzog B. Sun protection factors: world wide confusion. *Br J Dermatol* 2009; **161 Suppl 3**: 13-24.

87 Diffey BL. When should sunscreen be reapplied? *J Am Acad Dermatol* 2001; **45**: 882-5.

88 Stahl W, Sies H. Photoprotection by dietary carotenoids: concept, mechanisms, evidence and future development. *Mol Nutr Food Res* 2012; **56**: 287-95.

89 Afaq F, Katiyar SK. Polyphenols: skin photoprotection and inhibition of photocarcinogenesis. *Mini Rev Med Chem* 2011; **11**: 1200-15.

90 Kopcke W, Krutmann J. Protection from sunburn with beta-Carotene--a meta-analysis. *Photochem Photobiol* 2008; **84**: 284-8.

91 Heinrich U, Moore CE, De Spirt S *et al.* Green tea polyphenols provide photoprotection, increase microcirculation, and modulate skin properties of women. *J Nutr* 2011; **141**: 1202-8.

92 Chang YJ, Myung SK, Chung ST *et al.* Effects of vitamin treatment or supplements with purported antioxidant properties on skin cancer prevention: a meta-analysis of randomized controlled trials. *Dermatology* 2011; **223**: 36-44.

93 Madhunapantula SV, Robertson GP. Chemoprevention of melanoma. *Adv Pharmacol* 2012; **65**: 361-98.

94 Prado R, Francis SO, Mason MN *et al.* Nonmelanoma skin cancer chemoprevention. *Dermatol Surg* 2011; **37**: 1566-78.

95 Chen AC, Halliday GM, Damian DL. Non-melanoma skin cancer: carcinogenesis and chemoprevention. *Pathology* 2013; **45**: 331-41.

96 Francis SO, Mahlberg MJ, Johnson KR *et al.* Melanoma chemoprevention. *J Am Acad Dermatol* 2006; **55**: 849-61.

97 Uzarska M, Czajkowski R, Schwartz RA *et al.* Chemoprevention of skin melanoma: facts and myths. *Melanoma Res* 2013; **23**: 426-33.

98 Boniol M, Autier P, Boyle P *et al.* Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. *BMJ* 2012; **345**: e4757.

99 Colantonio S, Bracken MB, Beecker J. The association of indoor tanning and melanoma in adults: systematic review and meta-analysis. *J Am Acad Dermatol* 2014; **70**: 847-57 e1-18.

100 Wehner MR, Shive ML, Chren MM *et al.* Indoor tanning and non-melanoma skin cancer: systematic review and meta-analysis. *BMJ* 2012; **345**: e5909.

101 Gerber B, Mathys P, Moser M *et al.* Ultraviolet emission spectra of sunbeds. *Photochem Photobiol* 2002; **76**: 664-8.

102 Gies P, Javorniczky J, Henderson S *et al.* UVR emissions from solaria in Australia and implications for the regulation process. *Photochem Photobiol* 2011; **87**: 184-90.

103 Wehner MR, Chren MM, Nameth D *et al.* International Prevalence of Indoor Tanning: A Systematic Review and Meta-analysis. *JAMA Dermatol* 2014.

104 Choudhury K, Volkmer B, Greinert R *et al.* Effectiveness of skin cancer screening programmes. *Br J Dermatol* 2012; **167 Suppl 2**: 94-8.

105 Breitbart EW, Waldmann A, Nolte S *et al.* Systematic skin cancer screening in Northern Germany. *J Am Acad Dermatol* 2012; **66**: 201-11.

106 Katalinic A, Waldmann A, Weinstock MA *et al.* Does skin cancer screening save lives?: an observational study comparing trends in melanoma mortality in regions with and without screening. *Cancer* 2012; **118**: 5395-402.

107 Hamidi R, Peng D, Cockburn M. Efficacy of skin self-examination for the early detection of melanoma. *Int J Dermatol* 2010; **49**: 126-34.

108 Albert MR, Ostheimer KG. The evolution of current medical and popular attitudes toward ultraviolet light exposure: part 3. *J Am Acad Dermatol* 2003; **49**: 1096-106.

109 Blum A, Garbe C, Rassner G. Prävention des malignen Melanoms. *Hautarzt* 1998; **49**: 826-34.

110 Sinclair C, Foley P. Skin cancer prevention in Australia. *Br J Dermatol* 2009; **161 Suppl 3**: 116-23.

111 Makin JK, Warne CD, Dobbinson SJ *et al.* Population and age-group trends in weekend sun protection and sunburn over two decades of the SunSmart programme in Melbourne, Australia. *Br J Dermatol* 2013; **168**: 154-61.

112 Iannacone MR, Youlden DR, Baade PD *et al.* Melanoma incidence trends and survival in adolescents and young adults in Queensland, Australia. *Int J Cancer* 2014.

113 Olsen CM, Williams PF, Whiteman DC. Turning the tide? Changes in treatment rates for keratinocyte cancers in Australia 2000 through 2011. *J Am Acad Dermatol* 2014; **71**: 21-6 e1.

114 Buller DB, Cokkinides V, Hall HI *et al.* Prevalence of sunburn, sun protection, and indoor tanning behaviors among Americans: review from national surveys and case studies of 3 states. *J Am Acad Dermatol* 2011; **65**: S114-23.

115 Oyebanjo E, Bushell F. A critical evaluation of the UK SunSmart campaign and its relevance to Black and minority ethnic communities. *Perspect Public Health* 2014; **134**: 144-9.

116 Krebs H. Sonnenexposition und Sonnenschutz 2011. Früherkennung von Pigmentmalveränderungen. Eine Evaluationsstudie im Auftrag der Krebsliga Schweiz. Zurich 2012.

117 Gallagher RP, Lee TK. Adverse effects of ultraviolet radiation: a brief review. *Prog Biophys Mol Biol* 2006; **92**: 119-31.

118 Mancini AJ. Skin. *Pediatrics* 2004; **113**: 1114-9.

119 Hill D, Dixon H. Promoting sun protection in children: rationale and challenges. *Health Educ Behav* 1999; **26**: 409-17.

120 Reinau D, Meier C, Gerber N *et al.* Sun protective behaviour of primary and secondary school students in North-Western Switzerland. *Swiss Med Wkly* 2012; **142**: w13520.

121 Statistical Office of the Canton of Zurich. Kanton Zürich in Zahlen 2011. Zurich 2011.

122 Alberg AJ, Herbst RM, Genkinger JM *et al.* Knowledge, attitudes, and behaviors toward skin cancer in Maryland youths. *J Adolesc Health* 2002; **31**: 372-7.

123 Horsley L, Charlton A, Waterman C. Current action for skin cancer risk reduction in English schools: pupils' behaviour in relation to sunburn. *Health Educ Res* 2002; **17**: 715-31.

124 Lowe JB, Borland R, Stanton WR *et al.* Sun-safe behaviour among secondary school students in Australia. *Health Educ Res* 2000; **15**: 271-81.

125 Autier P, Boniol M, Dore JF. Sunscreen use and increased duration of intentional sun exposure: still a burning issue. *Int J Cancer* 2007; **121**: 1-5.

126 Kasparian NA, McLoone JK, Meiser B. Skin cancer-related prevention and screening behaviors: a review of the literature. *J Behav Med* 2009; **32**: 406-28.

127 O'Riordan DL, Geller AC, Brooks DR *et al.* Sunburn reduction through parental role modeling and sunscreen vigilance. *J Pediatr* 2003; **142**: 67-72.

128 Saraiya M, Glanz K, Briss PA *et al.* Interventions to prevent skin cancer by reducing exposure to ultraviolet radiation: a systematic review. *Am J Prev Med* 2004; **27**: 422-66.

129 Guide to Community Preventive Services. Preventing skin cancer: primary and middle school interventions. August 2012 (available from: http://www.thecommunityguide.org/cancer/skin/education-policy/primaryandmiddleschools.html [cited 2013 July 29])

130 Buller DB, Borland R. Skin cancer prevention for children: a critical review. *Health Educ Behav* 1999; **26**: 317-43.

131 Quereux G, Nguyen JM, Volteau C *et al.* Prospective trial on a school-based skin cancer prevention project. *Eur J Cancer Prev* 2009; **18**: 133-44.

132 International Commission on Non-Ionizing Radiation Protection. Guidelines on limits of exposure to ultraviolet radiation of wavelengths between 180 nm and 400 nm (incoherent optical radiation). *Health Phys* 2004; **87**: 171-86.

133 Rigel EG, Lebwohl MG, Rigel AC *et al.* Ultraviolet radiation in alpine skiing: magnitude of exposure and importance of regular protection. *Arch Dermatol* 2003; **139**: 60-2.

134 Moehrle M, Dennenmoser B, Garbe C. Continuous long-term monitoring of UV radiation in professional mountain guides reveals extremely high exposure. *Int J Cancer* 2003; **103**: 775-8.

135 Vishvakarman D, Wong JC, Boreham BW. Annual occupational exposure to ultraviolet radiation in central Queensland. *Health Phys* 2001; **81**: 536-44.

136 Hammond V, Reeder AI, Gray A. Patterns of real-time occupational ultraviolet radiation exposure among a sample of outdoor workers in New Zealand. *Public Health* 2009; **123**: 182-7.

137 Gies P, Wright J. Measured solar ultraviolet radiation exposures of outdoor workers in Queensland in the building and construction industry. *Photochem Photobiol* 2003; **78**: 342-8.

138 Gies P, Glanz K, O'Riordan D *et al.* Measured occupational solar UVR exposures of lifeguards in pool settings. *Am J Ind Med* 2009; **52**: 645-53.

139 Milon A, Sottas PE, Bulliard JL *et al.* Effective exposure to solar UV in building workers: influence of local and individual factors. *J Expo Sci Environ Epidemiol* 2007; **18**: 58-68.

140 Bouchardy C, Schuler G, Minder C *et al.* Cancer risk by occupation and socioeconomic group among men--a study by the Association of Swiss Cancer Registries. *Scand J Work Environ Health* 2002; **28 Suppl 1**: 1-88.

141 Beral V, Robinson N. The relationship of malignant melanoma, basal and squamous skin cancers to indoor and outdoor work. *Br J Cancer* 1981; **44**: 886-91.

142 Hakansson N, Floderus B, Gustavsson P *et al.* Occupational sunlight exposure and cancer incidence among Swedish construction workers. *Epidemiology* 2001; **12**: 552-7.

143 Schmid-Kubista KE, Kellner L, Maier H *et al.* Effect of work-related ultraviolet exposure and ophthalmic changes in Austrian farmers: the SVB-UV study. *Ophthalmic Res* 2010; **43**: 201-7.

144 Khoo J, Saw SM, Banerjee K *et al.* Outdoor work and the risk of pterygia: a case-control study. *Int Ophthalmol* 1998; **22**: 293-8.

145 Neale RE, Purdie JL, Hirst LW *et al.* Sun exposure as a risk factor for nuclear cataract. *Epidemiology* 2003; **14**: 707-12.

146 International Commission on Non-Ionizing Radiation Protection. ICNIRP statement - Protection of workers against ultraviolet radiation. *Health Phys* 2010; **99**: 66-87.

147 Thomas BH, Ciliska D, Dobbins M *et al.* A process for systematically reviewing the literature: providing the research evidence for public health nursing interventions. *Worldviews Evid Based Nurs* 2004; **1**: 176-84.

148 Bridges T, Ehrlich A. Assessment of behavior and attitudes concerning sun protection and skin cancer risks in Maryland Watermen. *J Am Acad Dermatol* 2005; **52**: 102.

149 Cioffi J, Wilkes L, Hartcher-O'Brien J. Outdoor workers and sun protection: knowledge and behaviour. *The Australian Journal of Construction Economics and Building* 2003; **2**: 10-4.

150 Garbe C, Buettner PG. Predictors of the use of sunscreen in dermatological patients in Central Europe. *Prev Med* 2000; **31**: 134-9.

151 Green A, Battistutta D, Hart V *et al.* Skin cancer in a subtropical Australian population: incidence and lack of association with occupation. The Nambour Study Group. *Am J Epidemiol* 1996; **144**: 1034-40.

152 Hall DM, McCarty F, Elliott T *et al.* Lifeguards' sun protection habits and sunburns: association with sun-safe environments and skin cancer prevention program participation. *Arch Dermatol* 2009; **145**: 139-44.

153 Hammond V, Reeder AI, Gray AR *et al.* Are workers or their workplaces the key to occupational sun protection? *Health Promot J Austr* 2008; **19**: 97-101.

154 Inaba R, Mirbod SM. Comparison of subjective symptoms and hot prevention measures in summer between traffic control workers and construction workers in Japan. *Ind Health* 2007; **45**: 91-9.

155 Ing SY, Ashbury FD, Marrett LD *et al.* Use of focus group methodology in the development of an Ontario farmers' sun safety survey. *Chronic Dis Can* 2002; **23**: 65-70.

156 Laporte J. Sensibilisation des salariés du bâtiment et des travaux publics au risque solaire: pour une prévention efficace. *Arch Mal Prof Env* 2006; **67**: 828-41.

157 Lewis EC, Mayer JA, Slymen D. Postal workers' occupational and leisure-time sun safety behaviors (United States). *Cancer Causes Control* 2006; **17**: 181-6.

158 Lichte V, Dennenmoser B, Dietz K *et al.* Professional risk for skin cancer development in male mountain guides--a cross-sectional study. *J Eur Acad Dermatol Venereol* 2010; **24**: 797-804.

159 Madgwick P, Houdmont J, Randall R. Sun safety measures among construction workers in Britain. *Occup Med (Lond)* 2011; **61**: 430-3.

160 Maier H, Schmalwieser A, Rohn H *et al. UV-Belastung bei der bäuerlichen Arbeit*, 1st edn. Vienna: SVB (Health Insurance for Farmers). 2009.

161 Marlenga B. The health beliefs and skin cancer prevention practices of Wisconsin dairy farmers. *Oncol Nurs Forum* 1995; **22**: 681-6.

162 Marrett LD, Pichora EC, Costa ML. Work-time sun behaviours among Canadian outdoor workers: results from the 2006 National Sun Survey. *Can J Public Health* 2010; **101**: I19-22.

163 McCool JP, Reeder AI, Robinson EM *et al.* Outdoor workers' perceptions of the risks of excess sun-exposure. *J Occup Health* 2009; **51**: 404-11.

164 Oliveira LM, Glauss N, Palma A. Habits related to sun exposure among physical education teachers working with water activities. *An Bras Dermatol* 2011; **86**: 445-50.

165 Parrott R, Steiner C, Goldenhar L. Georgia's harvesting healthy habits: a formative evaluation. *J Rural Health* 1996; **12**: 291-300.

166 Parrott R, Monahan J, Ainsworth S *et al.* Communicating to Farmers About Skin Cancer. The Behavior Adaptation Model. *Hum Commun Res* 1998; **24**: 386-409.

167 Robinson JD, Silk KJ, Parrott RL *et al.* Healthcare providers' sun-protection promotion and at-risk clients' skin-cancer-prevention outcomes. *Prev Med* 2004; **38**: 251-7.

168 Rosenman KD, Gardiner J, Swanson GM *et al.* Use of skin-cancer prevention strategies among farmers and their spouses. *Am J Prev Med* 1995; **11**: 342-7.

169 Salas R, Mayer JA, Hoerster KD. Sun-protective behaviors of California farm workers. *J Occup Environ Med* 2005; **47**: 1244-9.

170 Scerri L, Aquilina S, Amato GA *et al.* Sun awareness and sun protection practices in Malta. *J Eur Acad Dermatol Venereol* 2002; **16**: 47-52.

171 Schenker MB, Orenstein MR, Samuels SJ. Use of protective equipment among California farmers. *Am J Ind Med* 2002; **42**: 455-64.

172 Shoveller JA, Lovato CY, Peters L *et al.* Canadian National Survey on Sun Exposure & Protective Behaviours: outdoor workers. *Can J Public Health* 2000; **91**: 34-5.

173 Stepanski BM, Mayer JA. Solar protection behaviors among outdoor workers. *J Occup Environ Med* 1998; **40**: 43-8.

174 Unverricht I, Knuschke P. Verhalten von im Freien Beschäftigten gegenüber solarer UV-Strahlung in Beruf und Alltag. *Dermatol Beruf Umwelt* 2007; **4**: 159-66.

175 Weber M, Uller A, Schulmeister K *et al.* Outdoor workers' acceptance of personal protective measures against solar ultraviolet radiation. *Photochem Photobiol* 2007; **83**: 1471-80.

176 Woolley T, Buettner PG, Lowe J. Sun-related behaviors of outdoor working men with a history of non-melanoma skin cancer. *J Occup Environ Med* 2002; **44**: 847-54.

177 Woolley T, Lowe J, Raasch B *et al.* Workplace sun protection policies and employees' sun-related skin damage. *Am J Health Behav* 2008; **32**: 201-8.

178 Andersen PA, Buller DB, Voeks JH *et al.* Testing the Long-Term Effects of the Go Sun Smart Worksite Health Communication Campaign: A Group-Randomized Experimental Study. *J Commun* 2008; **58**: 447-71.

179 Azizi E, Flint P, Sadetzki S *et al.* A graded work site intervention program to improve sun protection and skin cancer awareness in outdoor workers in Israel. *Cancer Causes Control* 2000; **11**: 513-21.

180 Borland RM, Hocking B, Godkin GA *et al.* The impact of a skin cancer control education package for outdoor workers. *Med J Aust* 1991; **154**: 686-8.

181 Buller DB, Andersen PA, Walkosz BJ *et al.* Randomized trial testing a worksite sun protection program in an outdoor recreation industry. *Health Educ Behav* 2005; **32**: 514-35.

182 Dobbinson S, Borland R, Anderson M. Sponsorship and sun protection practices in lifesavers. *Health Promot Int* 1999; **14**: 167-76.

183 Geller AC, Glanz K, Shigaki D *et al.* Impact of skin cancer prevention on outdoor aquatics staff: the Pool Cool program in Hawaii and Massachusetts. *Prev Med* 2001; **33**: 155-61.

184 Girgis A, Sanson-Fisher RW, Watson A. A workplace intervention for increasing outdoor workers' use of solar protection. *Am J Public Health* 1994; **84**: 77-81.

185 Glanz K, Chang L, Song V *et al.* Skin cancer prevention for children, parents, and caregivers: a field test of Hawaii's SunSmart program. *J Am Acad Dermatol* 1998; **38**: 413-7.

186 Glanz K, Maddock JE, Lew RA *et al.* A randomized trial of the Hawaii SunSmart program's impact on outdoor recreation staff. *J Am Acad Dermatol* 2001; **44**: 973-8.

187 Hiemstra M, Glanz K, Nehl E. Changes in sunburn and tanning attitudes among lifeguards over a summer season. *J Am Acad Dermatol* 2012; **66**: 430-7.

188 Lombard D, Neubauer TE, Canfield D *et al.* Behavioral community intervention to reduce the risk of skin cancer. *J Appl Behav Anal* 1991; **24**: 677-86.

189 Malak AT, Yildirim P, Yildiz Z *et al.* Effects of training about skin cancer on farmers' knowledge level and attitudes. *Asian Pac J Cancer Prev* 2011; **12**: 117-20.

190 Mayer JA, Slymen DJ, Clapp EJ *et al.* Promoting sun safety among US Postal Service letter carriers: impact of a 2-year intervention. *Am J Public Health* 2007; **97**: 559-65.

191 Mayer JA, Slymen DJ, Clapp EJ *et al.* Long-term maintenance of a successful occupational sun safety intervention. *Arch Dermatol* 2009; **145**: 88-9.

192 Mullan PB, Gardiner JC, Rosenman K *et al.* Skin cancer prevention and detection practices in a Michigan farm population following an educational intervention. *J Rural Health* 1996; **12**: 311-20.

193 Reding DJ, Fischer VV, Berg RL *et al.* Assessment of Farmers' Acceptance of Veterinarians as Human Health Advocates. *J Agromedicine* 1998; **5**: 291-305.

194 Shani E, Rachkovsky E, Bahar-Fuchs A *et al.* The role of health education versus safety regulations in generating skin cancer preventive behavior among outdoor workers in Israel: an exploratory photosurvey. *Health Promot Int* 2000; **15**: 333-9.

195 Stock ML, Gerrard M, Gibbons FX *et al.* Sun protection intervention for highway workers: long-term efficacy of UV photography and skin cancer information on men's protective cognitions and behavior. *Ann Behav Med* 2009; **38**: 225-36.

196 Parisi A, Kimlin M. Effects of simple measures to reduce the occupational solar UV exposure of outdoor workers. *J Occup Health Safety* 1999; **15**: 267-72.

197 Thieden E, Collins SM, Philipsen PA *et al.* Ultraviolet exposure patterns of Irish and Danish gardeners during work and leisure. *Br J Dermatol* 2005; **153**: 795-801.

198 Rigel DS, Rigel EG, Rigel AC. Effects of altitude and latitude on ambient UVB radiation. *J Am Acad Dermatol* 1999; **40**: 114-6.

199 Oh SS, Mayer JA, Lewis EC *et al.* Validating outdoor workers' self-report of sun protection. *Prev Med* 2004; **39**: 798-803.

200 Glanz K, McCarty F, Nehl EJ *et al.* Validity of self-reported sunscreen use by parents, children, and lifeguards. *Am J Prev Med* 2009; **36**: 63-9.

201 Hall HI, Miller DR, Rogers JD *et al.* Update on the incidence and mortality from melanoma in the United States. *J Am Acad Dermatol* 1999; **40**: 35-42.

202 Woo DK, Eide MJ. Tanning beds, skin cancer, and vitamin D: An examination of the scientific evidence and public health implications. *Dermatol Ther* 2010; **23**: 61-71.

203 Miyamura Y, Coelho SG, Schlenz K *et al.* The deceptive nature of UVA tanning versus the modest protective effects of UVB tanning on human skin. *Pigment Cell Melanoma Res* 2011; **24**: 136-47.

204 Diaz JH, Nesbitt LT, Jr. Sun exposure behavior and protection: recommendations for travelers. *J Travel Med* 2013; **20**: 108-18.

205 Devos SA, Van der Endt JD, Broeckx W *et al.* Sunscreen use and skin protection behaviour on the Belgian beach: a comparison 9 years later. *Eur J Cancer Prev* 2012; **21**: 474-7.

206 Koster B, Thorgaard C, Philip A *et al.* Vacations to sunny destinations, sunburn, and intention to tan: a cross-sectional study in Denmark, 2007-2009. *Scand J Public Health* 2011; **39**: 64-9.

207 O'Riordan DL, Steffen AD, Lunde KB *et al.* A day at the beach while on tropical vacation: sun protection practices in a high-risk setting for UV radiation exposure. *Arch Dermatol* 2008; **144**: 1449-55.

208 McCarthy EM, Ethridge KP, Wagner RF, Jr. Beach holiday sunburn: the sunscreen paradox and gender differences. *Cutis* 1999; **64**: 37-42.

209 O'Riordan DL, Lunde KB, Steffen AD *et al.* Validity of beachgoers' self-report of their sun habits. *Arch Dermatol* 2006; **142**: 1304-11.

210 Wright MW, Wright ST, Wagner RF. Mechanisms of sunscreen failure. *J Am Acad Dermatol* 2001; **44**: 781-4.

211 Dennis LK, Vanbeek MJ, Beane Freeman LE *et al.* Sunburns and risk of cutaneous melanoma: does age matter? A comprehensive meta-analysis. *Ann Epidemiol* 2008; **18**: 614-27.

212 Lademann J, Schanzer S, Richter H *et al.* Sunscreen application at the beach. *J Cosmet Dermatol* 2004; **3**: 62-8.

213 Petersen B, Datta P, Philipsen PA *et al.* Sunscreen use and failures--on site observations on a sun-holiday. *Photochem Photobiol Sci* 2013; **12**: 190-6.

214 Sheehan JM, Potten CS, Young AR. Tanning in human skin types II and III offers modest photoprotection against erythema. *Photochem Photobiol* 1998; **68**: 588-92.

215 Knuschke P, Unverricht I, Aschoff R *et al.* Investigation of the natural skin protection against solar UV radiation in outdoor workers. *Schriftenreihe der Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Forschung, F 1986,* 2010; **ISBN 978-3-88261-121-2**.

216 Petersen B, Thieden E, Lerche CM *et al.* Validation of self-reported erythema: comparison of self-reports, researcher assessment and objective measurements in sun worshippers and skiers. *J Eur Acad Dermatol Venereol* 2013; **27**: 214-9.

217 Miller AJ, Tsao H. New insights into pigmentary pathways and skin cancer. *Br J Dermatol* 2010; **162**: 22-8.

218 Dey P, Collins S, Will S *et al.* Randomised controlled trial assessing effectiveness of health education leaflets in reducing incidence of sunburn. *BMJ* 1995; **311**: 1062-3.

219 Segan CJ, Borland R, Hill DJ. Development and evaluation of a brochure on sun protection and sun exposure for tourists. *Health Educ J* 1999; **58**: 177-91.

220 Dadlani C, Orlow SJ. Planning for a brighter future: a review of sun protection and barriers to behavioral change in children and adolescents. *Dermatol Online J* 2008; **14**: 1.

221 Garside R, Pearson M, Moxham T. What influences the uptake of information to prevent skin cancer? A systematic review and synthesis of qualitative research. *Health Educ Res* 2010; **25**: 162-82.

222 Mahler HI. Reasons for using and failing to use sunscreen: comparison among whites, Hispanics, and Asian/Pacific Islanders in Southern California. *JAMA Dermatol* 2014; **150**: 90-1.

223 McLeod G, Insch A, Henry J. Reducing barriers to sun protection- Application of a holistic model for social marketing. *Australasian Marketing Journal* 2011; **19**: 212-22.

224 Hay J, Coups EJ, Ford J *et al.* Exposure to mass media health information, skin cancer beliefs, and sun protection behaviors in a United States probability sample. *J Am Acad Dermatol* 2009; **61**: 783-92.

225 Meissner HI, Potosky AL, Convissor R. How sources of health information relate to knowledge and use of cancer screening exams. *J Community Health* 1992; **17**: 153-65.

226 O'Keefe GJ, Boyd HH, Brown MR. Who learns preventive health care information from where: cross-channel and repertoire comparisons. *Health Commun* 1998; **10**: 25-36.

227 Schwitzer G, Mudur G, Henry D *et al.* What are the roles and responsibilities of the media in disseminating health information? *PLoS Med* 2005; **2**: e215.

228 Dixon H, Warne C, Scully M *et al.* Agenda-setting effects of sun-related news coverage on public attitudes and beliefs about tanning and skin cancer. *Health Commun* 2014; **29**: 173-81.

229 Kemp GA, Eagle L, Verne J. Mass media barriers to social marketing interventions: the example of sun protection in the UK. *Health Promot Int* 2011; **26**: 37-45.

230 Geller AC, Zhang Z, Sober AJ *et al.* The first 15 years of the American Academy of Dermatology skin cancer screening programs: 1985-1999. *J Am Acad Dermatol* 2003; **48**: 34-41.

231 WHO. Global Solar UV Index: A Practical guide. A joint recommendation of World Health Organization, World Meteorological Organization, United Nations Environment Programme and The International Commission on Non-Ionizing Radiation Protection. *World Health Organization* 2002.

232 Loden M, Beitner H, Gonzalez H *et al.* Sunscreen use: controversies, challenges and regulatory aspects. *Br J Dermatol* 2011; **165**: 255-62.

233 Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. *N Engl J Med* 1993; **329**: 1147-51.

234 Seite S, Fourtanier A, Moyal D *et al.* Photodamage to human skin by suberythemal exposure to solar ultraviolet radiation can be attenuated by sunscreens: a review. *Br J Dermatol* 2010; **163**: 903-14.

235 Autier P, Dore JF, Breitbart E *et al.* The indoor tanning industry's double game. *Lancet* 2011; **377**: 1299-301.

236 Lim HW, James WD, Rigel DS *et al.* Adverse effects of ultraviolet radiation from the use of indoor tanning equipment: time to ban the tan. *J Am Acad Dermatol* 2011; **64**: 893-902.

237 Kannan S, Lim HW. Photoprotection and vitamin D: a review. *Photodermatol Photoimmunol Photomed* 2014; **30**: 137-45.

238 Norval M, Wulf HC. Does chronic sunscreen use reduce vitamin D production to insufficient levels? *Br J Dermatol* 2009; **161**: 732-6.

239 Borner FU, Schutz H, Wiedemann P. The influence of the UV-index on attitudes toward sun exposure in the German population. *J Cancer Educ* 2010; **25**: 643-9.

240 Krebs H. Bekanntheit, Verständnis und Beachtung des UV Index. Eine Evaluationsstudie im Auftrag der Krebsliga Schweiz. Zurich 2008.

241 Krebsliga Schweiz. Sonnenschutz. Eine Information der Krebsliga. Bern 2013 (available from https://assets.krebsliga.ch/downloads/1320.pdf [cited 2014 August 10]).

242 Bundesamt für Gesundheit. Ultraviolette Strahlung. Bern 2013 (available from http://www.bag.admin.ch/uv_strahlung [cited 2014 August 10]).

243 Deutsche Krebshilfe. Die Deutsche Krebshilfe rät: Richtig mit der Sonne umgehen. Bonn 2014 (available from http://www.krebshilfe.de/wir-informieren/ueber-praevention-frueherk/sonne-und-hautkrebs.html [cited 2014 August 10].

244 European Skin Cancer Foundation. Sun protection. Berlin (available from http://www.escf-network.eu/en/patients/prevention/sun-protection.html [cited 2014 August 10]).

245 Augustin M, Stadler R, Reusch M *et al.* Skin cancer screening in Germany - perception by the public. *J Dtsch Dermatol Ges* 2012; **10**: 42-9.

246 Scully M, Wakefield M, Dixon H. Trends in news coverage about skin cancer prevention, 1993-2006: increasingly mixed messages for the public. *Aust N Z J Public Health* 2008; **32**: 461-6.

247 Scully M, Makin J, Maloney S *et al.* Changes in coverage of sun protection in the news: threats and opportunities from emerging issues. *Health Educ Res* 2014; **29**: 378-87.

248 Youl PH, Janda M, Kimlin M. Vitamin D and sun protection: the impact of mixed public health messages in Australia. *Int J Cancer* 2009; **124**: 1963-70.

249 Baxter JM, Patel AN, Varma S. Facial basal cell carcinoma. *BMJ* 2012; **345**: e5342.

250 Herrett E, Thomas SL, Schoonen WM *et al.* Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010; **69**: 4-14.

251 Wood L, Martinez C. The general practice research database: role in pharmacovigilance. *Drug Saf* 2004; **27**: 871-81.

252 Jensen A, Birch-Johansen F, Olesen AB *et al.* Intake of alcohol may modify the risk for non-melanoma skin cancer: results of a large Danish prospective cohort study. *J Invest Dermatol* 2012; **132**: 2718-26.

253 Freedman DM, Sigurdson A, Doody MM *et al.* Risk of basal cell carcinoma in relation to alcohol intake and smoking. *Cancer Epidemiol Biomarkers Prev* 2003; **12**: 1540-3.

254 Fung TT, Hunter DJ, Spiegelman D *et al.* Intake of alcohol and alcoholic beverages and the risk of basal cell carcinoma of the skin. *Cancer Epidemiol Biomarkers Prev* 2002; **11**: 1119-22.

255 Poschl G, Seitz HK. Alcohol and cancer. *Alcohol Alcohol* 2004; **39**: 155-65.

256 Saladi RN, Nektalova T, Fox JL. Induction of skin carcinogenicity by alcohol and ultraviolet light. *Clin Exp Dermatol* 2010; **35**: 7-11.

257 Mukamal KJ. Alcohol consumption and self-reported sunburn: a cross-sectional, population-based survey. *J Am Acad Dermatol* 2006; **55**: 584-9.

258 Warthan MM, Sewell DS, Marlow RA *et al.* The economic impact of acute sunburn. *Arch Dermatol* 2003; **139**: 1003-6.

259 Leonardi-Bee J, Ellison T, Bath-Hextall F. Smoking and the risk of nonmelanoma skin cancer: systematic review and meta-analysis. *Arch Dermatol* 2012; **148**: 939-46.

260 Rollison DE, Iannacone MR, Messina JL *et al.* Case-control study of smoking and non-melanoma skin cancer. *Cancer Causes Control* 2012; **23**: 245-54.

261 Song F, Qureshi AA, Gao X *et al.* Smoking and risk of skin cancer: a prospective analysis and a meta-analysis. *Int J Epidemiol* 2012; **41**: 1694-705.

262 Marehbian J, Colt JS, Baris D *et al.* Occupation and keratinocyte cancer risk: a population-based case-control study. *Cancer Causes Control* 2007; **18**: 895-908.

263 Rees JR, Stukel TA, Perry AE *et al.* Tea consumption and basal cell and squamous cell skin cancer: results of a case-control study. *J Am Acad Dermatol* 2007; **56**: 781-5.

264 Mills CM, Hill SA, Marks R. Altered inflammatory responses in smokers. *BMJ* 1993; **307**: 911.

265 Pothiawala S, Qureshi AA, Li Y *et al.* Obesity and the incidence of skin cancer in US Caucasians. *Cancer Causes Control* 2012; **23**: 717-26.

266 Gerstenblith MR, Rajaraman P, Khaykin E *et al.* Basal cell carcinoma and anthropometric factors in the U.S. radiologic technologists cohort study. *Int J Cancer* 2012; **131**: E149-55.

267 van Dam RM, Huang Z, Rimm EB *et al.* Risk factors for basal cell carcinoma of the skin in men: results from the health professionals follow-up study. *Am J Epidemiol* 1999; **150**: 459-68.

268 Gilbody JS, Aitken J, Green A. What causes basal cell carcinoma to be the commonest cancer? *Aust J Public Health* 1994; **18**: 218-21.

269 Krathen MS, Gottlieb AB, Mease PJ. Pharmacologic immunomodulation and cutaneous malignancy in rheumatoid arthritis, psoriasis, and psoriatic arthritis. *J Rheumatol* 2010; **37**: 2205-15.

270 Long MD, Kappelman MD, Pipkin CA. Nonmelanoma skin cancer in inflammatory bowel disease: a review. *Inflamm Bowel Dis* 2011; **17**: 1423-7.

271 Chuang TY, Lewis DA, Spandau DF. Decreased incidence of nonmelanoma skin cancer in patients with type 2 diabetes mellitus using insulin: a pilot study. *Br J Dermatol* 2005; **153**: 552-7.

272 Goldacre MJ, Kurina LM, Wotton CJ *et al.* Schizophrenia and cancer: an epidemiological study. *Br J Psychiatry* 2005; **187**: 334-8.

273 White RS, Lipton RB, Hall CB *et al.* Nonmelanoma skin cancer is associated with reduced Alzheimer disease risk. *Neurology* 2013; **80**: 1966-72.

274 Conaghan PG. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. *Rheumatol Int* 2012; **32**: 1491-502.

275 Fischer SM, Hawk ET, Lubet RA. Coxibs and other nonsteroidal anti-inflammatory drugs in animal models of cancer chemoprevention. *Cancer Prev Res (Phila)* 2011; **4**: 1728-35.

276 Cuzick J, Otto F, Baron JA *et al.* Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. *Lancet Oncol* 2009; **10**: 501-7.

277 Liebman TN, Stein JA, Polsky D. Cyclo-oxygenase-2 inhibitors for chemoprevention of nonmelanoma skin cancer: is there a role for these agents? *J Am Acad Dermatol* 2013; **68**: 173-6.

278 Asgari M, White E, Chren MM. Nonsteroidal anti-inflammatory drug use in the prevention and treatment of squamous cell carcinoma. *Dermatol Surg* 2004; **30**: 1335-42.

279 Muller-Decker K. Cyclooxygenase-dependent signaling is causally linked to non-melanoma skin carcinogenesis: pharmacological, genetic, and clinical evidence. *Cancer Metastasis Rev* 2011; **30**: 343-61.

280 Rundhaug JE, Fischer SM. Cyclo-oxygenase-2 plays a critical role in UV-induced skin carcinogenesis. *Photochem Photobiol* 2008; **84**: 322-9.

281 Fischer SM, Lo HH, Gordon GB *et al.* Chemopreventive activity of celecoxib, a specific cyclooxygenase-2 inhibitor, and indomethacin against ultraviolet light-induced skin carcinogenesis. *Mol Carcinog* 1999; **25**: 231-40.

282 Orengo IF, Gerguis J, Phillips R *et al.* Celecoxib, a cyclooxygenase 2 inhibitor as a potential chemopreventive to UV-induced skin cancer: a study in the hairless mouse model. *Arch Dermatol* 2002; **138**: 751-5.

283 Pentland AP, Schoggins JW, Scott GA *et al.* Reduction of UV-induced skin tumors in hairless mice by selective COX-2 inhibition. *Carcinogenesis* 1999; **20**: 1939-44.

284 Wilgus TA, Koki AT, Zweifel BS *et al.* Inhibition of cutaneous ultraviolet light B-mediated inflammation and tumor formation with topical celecoxib treatment. *Mol Carcinog* 2003; **38**: 49-58.

285 Mikulec CD, Rundhaug JE, Simper MS *et al.* The chemopreventive efficacies of nonsteroidal anti-inflammatory drugs: the relationship of short-term biomarkers to long-term skin tumor outcome. *Cancer Prev Res (Phila)* 2013; **6**: 675-85.

286 Gupta AK, Paquet M, Villanueva E *et al.* Interventions for actinic keratoses. *Cochrane Database Syst Rev* 2012; **12**: CD004415.

287 Elmets CA, Viner JL, Pentland AP *et al.* Chemoprevention of nonmelanoma skin cancer with celecoxib: a randomized, double-blind, placebo-controlled trial. *J Natl Cancer Inst* 2010; **102**: 1835-44.

288 Tang JY, Aszterbaum M, Athar M *et al.* Basal cell carcinoma chemoprevention with nonsteroidal anti-inflammatory drugs in genetically predisposed PTCH1+/- humans and mice. *Cancer Prev Res (Phila)* 2010; **3**: 25-34.

289 Parkinson J, Davis S, Van Staa T. The General Practice Research Database: Now and the Future. In: *Pharmacovigilance* (Mann RD, Andrews EB, eds), 2nd edn. Chichester: John Wiley & Sons, Ltd. 2007; 341-8.

290 Williams T, Van Staa T, Puri S *et al.* Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. *Ther Adv Drug Saf* 2012; **3**: 89-99.

291 Jick SS, Kaye JA, Vasilakis-Scaramozza C *et al.* Validity of the general practice research database. *Pharmacotherapy* 2003; **23**: 686-9.

292 Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract* 2010; **60**: e128-36.

293 Meal A, Leonardi-Bee J, Smith C *et al.* Validation of THIN data for non-melanoma skin cancer. *Qual Prim Care* 2008; **16**: 49-52.

294 Johannesdottir SA, Chang ET, Mehnert F *et al.* Nonsteroidal anti-inflammatory drugs and the risk of skin cancer: a population-based case-control study. *Cancer* 2012; **118**: 4768-76.

295 Butler GJ, Neale R, Green AC *et al.* Nonsteroidal anti-inflammatory drugs and the risk of actinic keratoses and squamous cell cancers of the skin. *J Am Acad Dermatol* 2005; **53**: 966-72.

296 Clouser MC, Roe DJ, Foote JA *et al.* Effect of non-steroidal anti-inflammatory drugs on non-melanoma skin cancer incidence in the SKICAP-AK trial. *Pharmacoepidemiol Drug Saf* 2009; **18**: 276-83.

297 de Vries E, Trakatelli M, Kalabalikis D *et al.* Known and potential new risk factors for skin cancer in European populations: a multicentre case-control study. *Br J Dermatol* 2012; **167 Suppl 2**: 1-13.

298 Grau MV, Baron JA, Langholz B *et al.* Effect of NSAIDs on the recurrence of nonmelanoma skin cancer. *Int J Cancer* 2006; **119**: 682-6.

299 Torti DC, Christensen BC, Storm CA *et al.* Analgesic and nonsteroidal anti-inflammatory use in relation to nonmelanoma skin cancer: a population-based case-control study. *J Am Acad Dermatol* 2011; **65**: 304-12.

300 Vogel U, Christensen J, Wallin H *et al.* Polymorphisms in COX-2, NSAID use and risk of basal cell carcinoma in a prospective study of Danes. *Mutat Res* 2007; **617**: 138-46.

301 An KP, Athar M, Tang X *et al.* Cyclooxygenase-2 expression in murine and human nonmelanoma skin cancers: implications for therapeutic approaches. *Photochem Photobiol* 2002; **76**: 73-80.

302 Elwood PC, Gallagher AM, Duthie GG *et al.* Aspirin, salicylates, and cancer. *Lancet* 2009; **373**: 1301-9.

303 Harris RE. Cyclooxygenase-2 (cox-2) blockade in the chemoprevention of cancers of the colon, breast, prostate, and lung. *Inflammopharmacology* 2009; **17**: 55-67.

304 Moore DE. Drug-induced cutaneous photosensitivity: incidence, mechanism, prevention and management. *Drug Saf* 2002; **25**: 345-72.

305 Meier CR, Schmitz S, Jick H. Association between acetaminophen or nonsteroidal antiinflammatory drugs and risk of developing ovarian, breast, or colon cancer. *Pharmacotherapy* 2002; **22**: 303-9.

306 Freedman DM, Sigurdson A, Doody MM *et al.* Risk of melanoma in relation to smoking, alcohol intake, and other factors in a large occupational cohort. *Cancer Causes Control* 2003; **14**: 847-57.

307 Kubo JT, Henderson MT, Desai M *et al.* Alcohol consumption and risk of melanoma and non-melanoma skin cancer in the Women's Health Initiative. *Cancer Causes Control* 2014; **25**: 1-10.

308 Millen AE, Tucker MA, Hartge P *et al.* Diet and melanoma in a case-control study. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 1042-51.

309 Keeney S, McKenna H, Fleming P *et al.* Attitudes, knowledge and behaviours with regard to skin cancer: a literature review. *Eur J Oncol Nurs* 2009; **13**: 29-35.

310 Arthey S, Clarke VA. Suntanning and sun protection: a review of the psychological literature. *Soc Sci Med* 1995; **40**: 265-74.

311 Dixon HG, Warne CD, Scully ML *et al.* Does the portrayal of tanning in Australian women's magazines relate to real women's tanning beliefs and behavior? *Health Educ Behav* 2011; **38**: 132-42.

312 Lorenc T, Jamal F, Cooper C. Resource provision and environmental change for the prevention of skin cancer: systematic review of qualitative evidence from high-income countries. *Health Promot Int* 2013; **28**: 345-56.

313 Nolan BV, Taylor SL, Liguori A *et al.* Tanning as an addictive behavior: a literature review. *Photodermatol Photoimmunol Photomed* 2009; **25**: 12-9.

314 Schneider S, Kramer H. Who uses sunbeds? A systematic literature review of risk groups in developed countries. *J Eur Acad Dermatol Venereol* 2010; **24**: 639-48.

315 Goulart JM, Wang SQ. Knowledge, motivation, and behavior patterns of the general public towards sun protection. *Photochem Photobiol Sci* 2010; **9**: 432-8.

316 Koblenzer CS. The psychology of sun-exposure and tanning. *Clin Dermatol* 1998; **16**: 421-8.

317 Williams AL, Grogan S, Clark-Carter D *et al.* Appearance-based interventions to reduce ultraviolet exposure and/or increase sun protection intentions and behaviours: a systematic review and meta-analyses. *Br J Health Psychol* 2013; **18**: 182-217.

318 Tuong W, Armstrong AW. Effect of appearance-based education compared with health-based education on sunscreen use and knowledge: a randomized controlled trial. *J Am Acad Dermatol* 2014; **70**: 665-9.

319 Paul CL, Paras L, Harper A *et al.* Harm minimization in tan seekers: an exploration of tanning behaviour and the potential for substitutional use of sunless tanning products. *J Health Psychol* 2011; **16**: 929-37.

320 U.S. Departement of Health and Human Services. The Surgeon General's Call to Action to Prevent Skin Cancer. Washington, DC: U.S. Dept of Health and Human Services, Office of the Surgeon General; 2014.

321 Pawlak MT, Bui M, Amir M *et al.* Legislation restricting access to indoor tanning throughout the world. *Arch Dermatol* 2012; **148**: 1006-12.

322 Health Promotion Agency and Cancer Society of New Zealand. Sunbeds (available from http://sunsmart.org.nz/being-sunsmart/sunbeds [cited 2014 September 28]).

323 Osterwalder U, Sohn M, Herzog B. Global state of sunscreens. *Photodermatol Photoimmunol Photomed* 2014; **30**: 62-80.

324 Burnett ME, Wang SQ. Current sunscreen controversies: a critical review. *Photodermatol Photoimmunol Photomed* 2011; **27**: 58-67.

325 Nash JF. Systemic effects of topically applied sunscreen ingredients. In: *Clinical Guide to Sunscreens and Photoprotection* (Lim HW, Draelos ZD, eds). New York, NY, USA: Informa Healthcare. 2009; 139-54.

326 Witorsch RJ, Thomas JA. Personal care products and endocrine disruption: A critical review of the literature. *Crit Rev Toxicol* 2010; **40 Suppl 3**: 1-30.

327 Greenman J, Jones DA. Comparison of advertising strategies between the indoor tanning and tobacco industries. *J Am Acad Dermatol* 2010; **62**: 685 e1-18.

328 Bettoli V, Zauli S, Virgili A. Retinoids in the chemoprevention of non-melanoma skin cancers: why, when and how. *J Dermatolog Treat* 2013; **24**: 235-7.

329 Lehmann AR, McGibbon D, Stefanini M. Xeroderma pigmentosum. *Orphanet J Rare Dis* 2011; **6**: 70.

330 Guide to Community Preventive Services. What Works. Cancer Prevention and Control: Skin Cancer Prevention. July 2014 (available from http://www.thecommunityguide.org/about/What-Works-Skin-Cancer-factsheet-and-insert.pdf [cited 2014 October 10]).