Basal cell carcinoma – Epidemiology, risk factors, and outcome after surgical excision

Kappelin, Johan

2024

Document Version:
Publisher's PDF, also known as Version of record

Basal Cell Carcinoma

Epidemiology, risk factors, and outcome after surgical excision

JOHAN KAPPELIN
DEPARTMENT OF CLINICAL SCIENCES | FACULTY OF MEDICINE | LUND UNIVERSITY

Basal cell carcinoma
– Epidemiology, risk factors, and outcome after surgical excision

Basal cell carcinoma

Epidemiology, risk factors, and outcome after surgical excision

Johan Kappelin

LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 3rd of May at 13.00 in Segerfalksalen, BMC, Lund

Faculty opponent
Dr Sam Polesie, Associate Professor, Department of Dermatology and Venereology, University of Gothenburg.

Organisation: LUND UNIVERSITY,
Department of Clinical Sciences
Document name: DOCTORAL THESIS
Author: JOHAN KAPPELIN
Date of issue: 2024-05-03
Sponsoring organisation: Regional research grant, Southern health care region, Sweden, and the S.R. Gorthon foundation.

Title and subtitle: BASAL CELL CARCINOMA – EPIDEMIOLOGY, RISK FACTORS, AND OUTCOME AFTER SURGICAL EXCISION.

Abstract: Basal cell carcinoma (BCC) is the most common skin cancer in fair skinned populations and its incidence is increasing. Studies have suggested hydrochlorothiazide as a possible risk factor. Several treatments exist for BCC and standard surgical excision is among the most common. Incomplete excision increases risk of recurrence. To optimise patient care and utilisation of health care resources, increased knowledge regarding incidence, risk factors, and treatment outcome is essential.

Using the Swedish BCC Registry, we studied the incidence and trends of BCC in Sweden during the years 2004 – 2017. We also studied cases from the Swedish BCC Registry and compared their use of commonly prescribed antihypertensive medications to the use among matched controls, using data from well established, national registries. Regarding surgical outcome, we studied the local tumour registry at the Department of Dermatology, Helsingborg hospital, Sweden. Primary excisions of BCC tumours, performed during the years 2008 – 2015, were studied and the risk of an incomplete excision was analysed.

The person-based incidence of BCC in Sweden was 405/100 000 person years (European age-standardised rate) in 2017, increasing by 1.8% annually since 2004. Incidence was higher among males and increased with age. There was a latitude gradient with a higher incidence in the south. Among registered individuals, 40% developed at least two tumours. The risk of developing multiple tumours was higher among males and among older individuals. The cumulative risk of developing a new tumour after first diagnosis was approximately 30% after five years. Use of thiazide-containing combinations, angiotensin II receptor blockers, calcium channel blockers, and beta-blockers was associated to a significantly increased BCC risk. Meanwhile, single-agent thiazide diuretics did not affect BCC risk. Overall, surgical outcome showed 4.6% of BCC tumours to be incompletely excised. Risk of incomplete excision was significantly affected by tumour subtype and localisation. BCC type III, located on the nose or ears, were incompletely excised in 61.5% and 50% of cases respectively.

In conclusion, BCC is a common skin cancer in Sweden, with high incidence rates compared to countries on similar latitudes. Incidence is increasing and the high cumulative risk of consecutive BCC tumours puts a growing strain on health care services in our country. Risk of incomplete excision among aggressive BCC subtypes is high on nose and ears. To optimise patient care and use of health care resources, these tumours could be prioritised to surgical excision with perioperative histological margin control. Meanwhile, BCC risk in relation to commonly prescribed antihypertensive medications was scrutinised and an increased BCC risk with use of thiazide-containing combination treatments motivates further research on adjunctive agents, used in combination with thiazides.

Key words: BASAL CELL CARCINOMA, SKIN CANCER, EPIDEMIOLOGY, INCIDENCE, SURGERY, EXCISION, PHOTOSENSITIVITY, ANTIHYPERTENSIVE MEDICATION, RISK FACTOR
Classification system and/or index terms (if any)
Supplementary bibliographical information

Language: English
ISSN and key title: 1652-8220, Lund University, Faculty of Medicine Doctoral Dissertation Series 2024:53

ISBN: 978-91-8021-546-6
Number of pages: 125
Recipient's notes
Security classification
Price

Basal cell carcinoma

Epidemiology, risk factors, and outcome after surgical excision

Johan Kappelin

LUND
UNIVERSITY

Faculty of Medicine, Lund University, Sweden
Department of Clinical Sciences

ISBN 978-91-8021-546-6
ISSN 1652-8220
Printed in Sweden by Media-Tryck, Lund University
Lund 2024

To Anna

My love, my support, my life

Table of Contents

Abstract

Basal cell carcinoma (BCC) is the most common skin cancer in fair skinned populations and its incidence is increasing. Studies have suggested hydrochlorothiazide as a possible risk factor. Several treatments exist for BCC and standard surgical excision is among the most common. Incomplete excision increases risk of recurrence. To optimise patient care and utilisation of health care resources, increased knowledge regarding incidence, risk factors, and treatment outcome is essential.

Using the Swedish BCC Registry, we studied the incidence and trends of BCC in Sweden during the years 2004 – 2017. We also studied cases from the Swedish BCC Registry and compared their use of commonly prescribed antihypertensive medications to the use among matched controls, using data from well established, national registries. Regarding surgical outcome, we studied the local tumour registry at the Department of Dermatology, Helsingborg hospital, Sweden. Primary excisions of BCC tumours, performed during the years 2008 – 2015, were studied and the risk of an incomplete excision was analysed.

The person-based incidence of BCC in Sweden was 405/100 000 person years (European age-standardised rate) in 2017, increasing by 1.8% annually since 2004. Incidence was higher among males and increased with age. There was a latitude gradient with a higher incidence in the south. Among registered individuals, 40% developed at least two tumours. The risk of developing multiple tumours was higher among males and among older individuals. The cumulative risk of developing a new tumour after first diagnosis was approximately 30% after five years. Use of thiazide-containing combinations, angiotensin II receptor blockers, calcium channel blockers, and beta-blockers was associated to a significantly increased BCC risk. Meanwhile, single-agent thiazide diuretics did not affect BCC risk. Overall, surgical outcome showed 4.6% of BCC tumours to be incompletely excised. Risk of incomplete excision was significantly affected by tumour subtype and localisation. BCC type III, located on the nose or ears, were incompletely excised in 61.5% and 50% of cases respectively.

In conclusion, BCC is a common skin cancer in Sweden, with high incidence rates compared to countries on similar latitudes. Incidence is increasing and the high cumulative risk of consecutive BCC tumours puts a growing strain on health care services in our country. Risk of incomplete excision among aggressive BCC subtypes is high on nose and ears. To optimise patient care and use of health care resources, these tumours could be prioritised to surgical excision with perioperative histological margin control. Meanwhile, BCC risk in relation to commonly prescribed antihypertensive medications was scrutinised and an increased BCC risk with use of thiazide-containing combination treatments motivates further research on adjunctive agents, used in combination with thiazides.

Populärvetenskaplig sammanfattning

Jag har i denna avhandling samlat fyra studier som behandlar basalcellscancer; den vanligaste hudcancerformen i Sverige och andra länder med en övervägande ljus hudtyp. Basalcellscancer är en hudcancerform som uppkommer ur celler i det yttersta hudlagret, epidermis. Den exakta orsaken till varje enskild tumörs uppkomst är oklar men involverar mutationer i arvsanlaget i de drabbade cellerna. Mutationerna kan uppkomma av flera olika skäl, men den mest kända riskfaktorn för utveckling av basalcellscancer, såväl som för annan hudcancer, är ultraviolett strålning. Den primära exponeringen för ultraviolett strålning sker ifrån solen, men även solariesolning ökar risken för hudcancer.

Basalcellscancer har god prognos i förhållande till andra cancerformer. Risken för spridning och dödlig utgång är mycket låg, men tumörerna kan växa aggressivt och invasivt på tumörens ursprungsplats. I dessa fall kan underliggande vävnad, såsom brosk och ben, påverkas och invaderas. Både tumörens växt och den kirurgi som behövs för att bota tumören kan i dessa fall göra stor åverkan på både utseende och funktion i området där tumören sitter.

Basalcellscancer uppkommer framför allt i huvud- och halsregionen men kan uppkomma varsomhelst på huden. Tumören kan ha olika utseende och ett varierande mikroskopiskt växtsätt där olika tumörtyp kan kräva olika typer av behandling. I Sverige delar vi in basalcellscancer i fyra grupper baserat på växtsätt: typ IA, IB, II och III. Ju högre siffra, desto högre aggressivitetsgrad. De lågaggressiva formerna kan ofta frysbehandlas eller skrapas bort, medan de mer aggressiva formerna behöver opereras bort i sin helhet.

Basalcellscancer är mycket vanligt förekommande, men eftersom denna tumör sällan registreras nationellt är den exakta förekomsten svårvärderad. I Sverige registrerar vi samtliga basalcellscancertumörer som verifieras med vävnadsprov, något som är ovanligt ur ett internationellt perspektiv. På det viset kan vi lättare få en uppfattning om dess förekomst i vårt samhälle och hur utvecklingen har varit över tid. Trots att inte heller denna metod ger en komplett bild kan vi få en god uppskattning av hur denna tumörform är fördelad i samhället, på ett sätt som sällan kan uppnås i andra populationer.

Då basalcellscancer är en så vanlig tumör lägger den en stor belastning på de ekonomiska och personella resurserna i svensk sjukvård. För att kunna bidra i värderingen kring den faktiska belastningen är det viktigt att ha god kännedom om förekomsten av denna hudcancer såväl som hur trenden ser ut över tid. Det är också viktigt att veta om det finns några riskfaktorer som går att förebygga och om

den behandling man ger är välanpassad till diagnosen som ställs. I detta syfte har denna avhandlings fyra studier genomförts.

I min första studie plockade vi ut data gällande alla registrerade fall i basalcellscancerregistret under åren 2004 – 2017 för att få en bild av mängden diagnoser som ställs årligen (incidens) samt hur denna har utvecklats över tid. Vi kunde se att 405 personer per 100 000 invånare diagnostiserades i Sverige år 2017, vilket är en hög incidens i förhållande till andra länder på en liknande geografisk lokalisation. Detta innebar en faktisk förekomst av nästan 55 000 tumörer hos 40 000 individer det året. Incidensen ökade årligen under studieperioden med i snitt 1,8%. Förekomsten var som högst i södra Sverige, möjligen relaterat till en högre exponering för ultraviolett strålning där.

I min andra studie ville jag undersöka i hur stor utsträckning de personer som utvecklar basalcellscancer fortsätter utveckla fler tumörer över tid. Vi vet sedan tidigare att detta är ganska vanligt, men i vilken utsträckning har varit svårt att värdera med tanke på bristen på nationell registrering. I vår studie såg vi att ungefär 40% av alla som hade blivit diagnostiserade med basalcellscancer hann utveckla mer än en tumör under studietiden 2004 – 2017. Risken att utveckla en ny tumör under loppet av fem år efter sin första diagnos var ca 30%. Motsvarande risk efter den tredje tumören var ca 50%. Risken att drabbas av fler basalcellscancertumörer över tid var alltså relativt hög. Vi kunde också se att risken ökar ju fler tidigare tumörer man haft. Med fynden i studien kan vi ytterligare poängtera vikten av att vara uppmärksam på sin hud och söka vård vid tillkomst av nya hudförändringar. Behovet av detta är ännu större om man blivit diagnostiserad med basalcellscancer flera gånger tidigare.

I delstudie tre undersökte vi om blodtrycksmediciner kan öka risken för basalcellscancer. Tidigare studier har fokuserat på läkemedel som ökar ljuskänsligheten. Bland dessa har en typ av blodtrycksmedicin, tiazider, visats kunna öka risken för framför allt skivepitelcancer. Huruvida den även ökar risken för basalcellscancer har varit svårt att dra några slutsatser om. Vi valde därför att undersöka detta i den svenska populationen och då även jämföra med andra blodtrycksmediciner. Vi kunde i vårt material inte se någon ökad risk för basalcellscancer efter användning av tiazider i singelbehandling. Däremot såg vi en ökad risk för basalcellscancer vid användning av tiazider i kombinationspreparat. Även behandling med angiotensin-receptorhämmare, calciumhämmare och beta-blockare visade sig öka risken för basalcellscancer i vårt material. Det är rimligt att personer som står på blodtrycksmedicin erhåller solskyddsråd. Eftersom högt blodtryck är en så viktig åkomma att behandla bör dock preparaten fortsätta att användas av dem som behöver detta och ytterligare forskning behövs för att kunna ge goda rekommendationer till denna patientgrupp i framtiden.

I min sista studie ville vi undersöka utgången efter vår vanligaste behandlingsform för basalcellscancer, vanlig kirurgi. Den så kallade vanliga kirurgin går ut på att man i lokalbedövning skär bort tumören tillsammans med en säkerhetsmarginal på 3 – 5 mm. Preparatet skickas sedan för analys för att säkerställa diagnos och växtsätt samt för att bedöma om tumören är fullständigt borttagen. I förekommande fall är den inte det utan måste opereras på nytt. Vi ville med vår studie undersöka hur vanligt detta var på vår hudklinik i Helsingborg och om det fanns några riskfaktorer för att en basalcellscancer blir ofullständigt borttagen. Denna kunskap är viktig när vi sedan planerar vilken behandling som är mest lämplig för varje enskild patient. I vår studie kunde vi se att 4,6% av de basalcellscancertumörer som bortopererades blev ofullständigt borttagna. Detta är en relativt låg siffra i jämförelse med andra studier. Vi kunde också se att risken för en ofullständig operation ökade när man opererade bort tumörer med aggressivt växtsätt på känsliga lokaler i huvud- och halsregionen. Den största risken för en ofullständig operation såg vi gällande högaggressiva basalcellscancertumörer på öron eller näsa där så mycket som drygt hälften av alla tumörer blev ofullständigt borttagna. I dessa fall bör man om möjligt överväga en annan kirurgisk metod med större förutsättningar att säkerställa fullständigt borttagande. Ett exempel på detta är så kallad Mohs kirurgi som i dagsläget genomförs i Lund, Göteborg och Stockholm. Vid denna kirurgiform tar man bort tumören med en snäv marginal. I stället för att patienten får gå hem i väntan på provsvar analyseras preparatet på plats medan patienten väntar. För att göra detta krävs speciella tekniker och metoden är därför resurskrävande. I de fall man i analysen ser att tumören inte är fullständigt borttagen genomförs ytterligare ett ingrepp med fokus på det område där tumören fortsatt växer. Målsättningen är att tumören skall vara borta och huddefekten rekonstruerad innan patienten går hem. Tekniken är effektiv, men bör endast användas på tumörer där risken är stor för en ofullständig operation. Detta för att säkerställa att sjukvårdens resurser används till rätt saker. Vår studie visade nämligen också att lågaggressiva tumörer på mindre känsliga lokaler på kroppen nästan alltid blev fullständigt borttagna. Den vanliga kirurgin är snabb och enkel för både sjukvård och patient och bör användas i första hand i de lägen när Mohs kirurgi inte bedöms som nödvändig.

Sammanfattningsvis är basalcellscancer en vanlig tumörform i vårt land och förekomsten fortsätter att öka. Vi behöver bli bättre på förebyggande åtgärder där solskydd synes vara den viktigaste åtgärden. Våra studier talar också för att personer som står på blodtrycksmedicin är i extra stort behov av goda solskyddsrutiner. De patienter som drabbats av flera basalcellscancertumörer bör vara extra uppmärksamma på uppkomst av nya tumörer då dessa personer har en förhöjd risk att drabbas igen. Vid val av behandling bör man ta hänsyn till såväl tumörens karaktärsdrag och växtsätt som var tumören sitter. Sitter tumören på näsa eller öra är det lämpligt att ta vävnadsprov för att bedöma hur tumören växer och om det skulle vara lämpligt med mer avancerad kirurgisk behandling, såsom Mohs kirurgi.

List of Papers

Paper I

Kappelin J, Green AC, Ingvar Å, Ahnlide I, Nielsen K. Incidence and trends of basal cell carcinoma in Sweden: a population-based registry study.

Br J Dermatol. 2022 Jun;186(6):963-969.

Paper II

Kappelin J, Ahnlide I, Ingvar Å, Nielsen K. The burden of multiple basal cell carcinomas – a population wide study.

Accepted for publication in Acta Dermato-Venereologica.

Paper III

Kappelin J, Ahnlide I, Christensen GB, Ingvar Å, Nielsen K. Antihypertensive medication as a risk factor for basal cell carcinoma – A nationwide registry-based case-control study.

In manuscript.

Paper IV

Kappelin J, Nielsen K, Nilsson F, Bjellerup M, Ahnlide I. Surgical treatment of basal cell carcinoma: a case series on factors influencing the risk of an incomplete primary excision.

J Eur Acad Dermatol Venereol. 2020 Nov;34(11):2518-2525.

Related papers not included in the thesis.

Nätterdahl C, **Kappelin J**, Persson B, Lundqvist K, Ahnlide I, Saleh K, Ingvar Å.

Risk factors for complicated Mohs surgery in the South Sweden Mohs Cohort.

J Eur Acad Dermatol Venereol. 2022 Jul;36(7):1113-1117.

Saleh K, Ingvar Å, **Kappelin J**, Persson C, Lundqvist K, Ahnlide I, Persson B.

Agreement between patients and surgeons on assessments of the cosmetic outcomes of Mohs micrographic surgery: Results of a single-center blinded prospective study.

JAAD Int. 2021 Aug 23;5:52-53.

Christensen G B, **Kappelin J**, Sandgren J, Nielsen K, Ingvar Å.

Photosensitizing drugs and risk of skin cancer in women – a prospective population-based study.

In manuscript.

Author's contribution to the papers

Paper I

Johan Kappelin (JK) took part in the scientific planning of the study and formulated the application for approvement of the study from the Regional Ethical Review Board, Lund University, in cooperation with supervisors. JK formulated the application for data withdrawal from and managed the main correspondence with the Swedish National Board of Health and Welfare. JK had the main correspondence with the statistician appointed for the project. Furthermore, JK was the first author of the published article and was the corresponding author in conjunction with the peer review process.

Paper II

JK took part in the scientific planning of the study and formulated the application for approvement of the study from the Regional Ethical Review Board, Lund University, in cooperation with supervisors. JK also formulated the application for data withdrawal from and managed the main correspondence with the Swedish National Board of Health and Welfare. JK had the main correspondence with the statistician appointed for the project. JK was the first author of the article and was the corresponding author in conjunction with the peer review process.

Paper III

JK took part in the scientific planning of the study. JK formulated the application for approvement of the study from the Swedish Ethical Review Authority in cooperation with supervisors. JK also formulated the application for data withdrawal from and managed the main correspondence with the Swedish National Board of Health and Welfare as well as Statistics Sweden. JK had the main correspondence with the statistician appointed for the project. Furthermore, JK was the first author of the article and was the corresponding author in conjunction with the peer review process.

Paper IV

JK took part in the scientific planning of the study. JK had the main communication with the statistician appointed for the project. JK also performed parts of the statistical calculations in the project. Furthermore, JK was the first author of the published article and was the corresponding author in conjunction with the peer review process.

Abbreviations

ACE	Angiotensin converting enzyme
ACEi	Angiotensin converting enzyme inhibitor
ALA	5-aminolevulinsyra
ARB	Angiotensin II receptor blocker
ASP	Australian standard population
ATC-code	Anatomic Therapeutic Chemical code.
BCC	Basal cell carcinoma
BFTZ	Bendroflumethiazide
CCB	Calcium channel blocker
CI	Confidence interval
CSR	Canadian standardised rate
DDD	Defined Daily Dose
DNA	Deoxyribonucleic acid
EASR	European age standardised rate
ENT	Ear nose throat
pDDD	Prescribed number of defined daily doses
FET	First ever tumour
GLI	Glioma-associated oncogene
HCTZ	Hydrochlorothiazide
HIV	Human immunodeficiency virus
HR	Hazard ratio
iBCC	Infiltrative basal cell carcinoma
IRR	Incidence rate ratio
KC	Keratinocyte carcinoma
LISA	Longitudinal integrated database for health insurance and labour market studies
MAL	Metyl-aminolevulinat
MM	Malignant melanoma

MMS	Mohs micrographic surgery
nBCC	Nodular basal cell carcinoma
NMSC	Non-melanoma skin cancer
NSAID	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PBR	Person-based incidence rate
PDT	Photo dynamic therapy
PTCH	Receptor from the patched gene family
PUVA	Psoralen treatment in combination with UVA
RAS	Renin angiotensin system
RTB	Register över totalbefolkningen (Total population registry)
sBCC	Superficial basal cell carcinoma
SCC	Squamous cell carcinoma
SHh	Sonic hedgehog pathway
SIR	Standardised incidence ratio
SMO	Smoothened, transmembrane receptor gene
SPF	Sun protective factor
TBR	Tumour-based incidence rate
USR	United States standardised rate
UV	Ultraviolet (radiation)
UVA	Ultraviolet A (radiation)
UVB	Ultraviolet B
UVC	Ultraviolet C
UVR	Ultraviolet radiation
WHO	World Health Organization
WASR	World age standardised rate

Introduction

Skin cancer is an increasingly common disease worldwide. Depending on skin cancer subtype, the prognosis is varying and regarding the more common forms, mortality is relatively low. However, the diagnosis is often stressful for the patient and treatment can result in considerable morbidity. The increasing incidence of skin cancer also puts a strain on health economy, and action is needed to alleviate its effect on society. To do this, further knowledge about the epidemiology of skin cancer is needed.

In this thesis, I have chosen to study two main areas regarding the most frequent skin cancer type, basal cell carcinoma (BCC). Firstly, I have studied the epidemiology of this common tumour form and secondly, I chose to evaluate one of the most common treatment forms of BCC, standard surgical excision.

In this introductory section of the thesis, a summarised information regarding what we know so far of BCC epidemiology and surgical outcome will be presented. At the end of the thesis, the included papers will be summarised and discussed. Initially, however, let us start at the beginning and look at the construction of human skin to easier grasp the biology of BCC.

The human skin

The human skin is the largest organ of the body and acts as a protective shield to the environment. Every moment of every day, our bodies are exposed to potentially harmful substances and forces. The skin protects us from UVR (Ultraviolet radiation), toxins, and pathogens, while simultaneously maintaining homeostasis in the body by minimising fluid loss and helping to control body temperature[1].

The skin is divided into different layers with different functions. The outermost part is called the epidermis. Deep to the epidermis, we find the dermis and the deepest part consists of the subcutaneous layer.

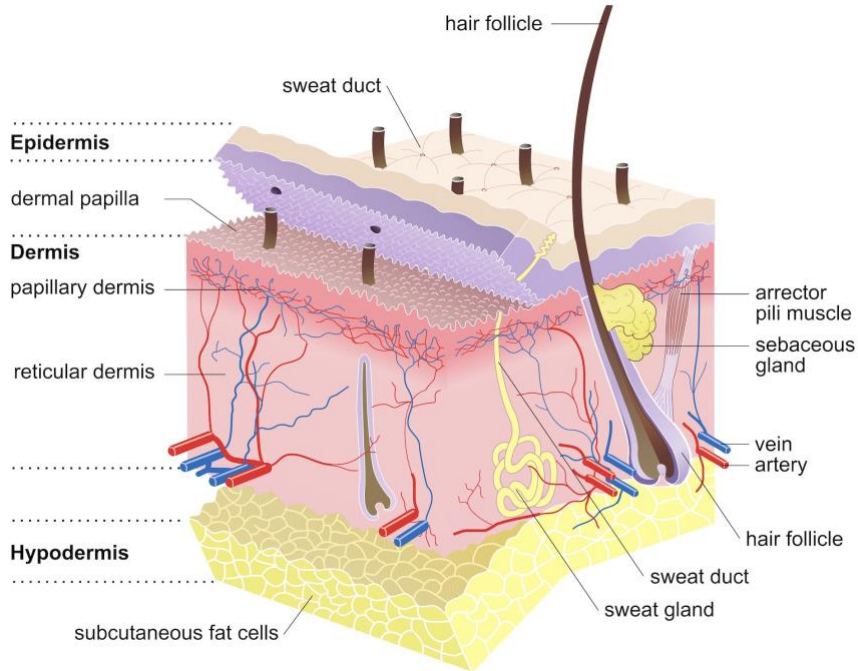

Figure 1. The basic layers and structures of the human skin. *Picture adapted from "Structure of mammalian skin and the layers typically present in parchment" by Sean P Doherty, licensed under CC BY-SA 4.0, https://creativecommons.org/licenses/by-sa/4.0/?ref=openverse.*

Epidermis

The epidermis is constructed primarily by keratinocytes, separated in several defined layers with different stages of maturity[1].

Stratum basale

This is the germinative centre of the keratinocytes, where new keratinocytes are produced. The stratum basale (the basal layer) is only one cell layer thick and is separated from the dermis by the so-called basement membrane, via which it anchors the epidermis to the dermis. In this layer, we also find melanocytes, responsible of producing and dispersing melanin (pigment granules), as well as Merkel cells (sensory cell). It is in the stratum basale that basal cell carcinomas arise.

Stratum spinosum

This layer is 8-10 cells thick and besides keratinocytes also contains Langerhans cells, responsible for antigen presentation, pivotal for the bodies primary defence against external pathogens.

Stratum granulosum

This layer is 3-5 cells thick. The keratinocytes of this layer contain cell granules of keratohyalin, important in the structural integrity and barrier function of the epidermis.

Stratum lucidum

Only a couple of cells thick, this layer only exists in hairless skin on the soles of the feet or the palms of the hands.

Stratum corneum

This is a 20-30 cells thick layer, consisting of denucleated keratinocytes. This layer is important as a physical barrier towards our surrounding environment and differs considerably in thickness depending on the location on the body surface.

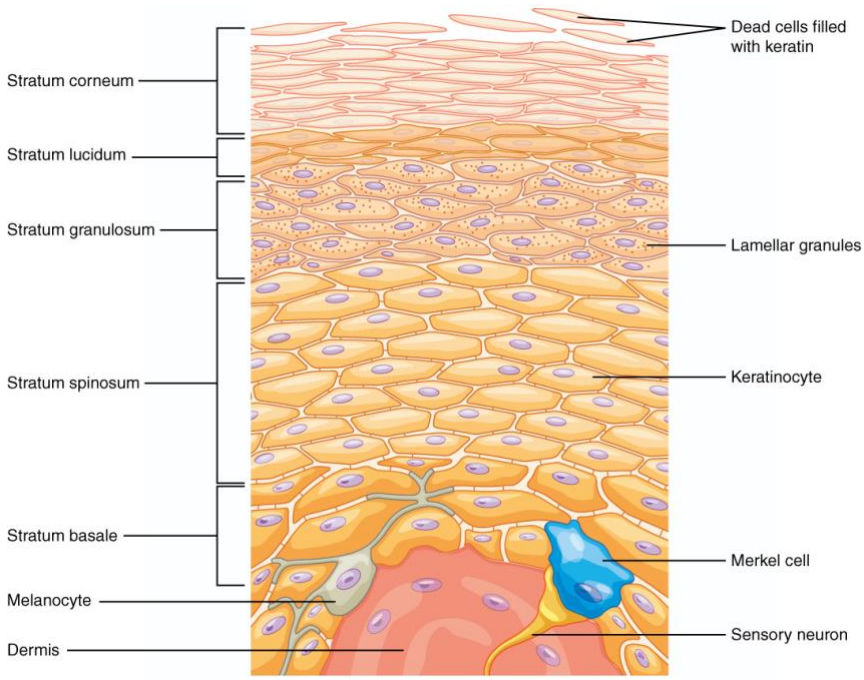

Figure 2. The epidermal layers. *Picture by J. Gordon Betts, Peter Desaix, Eddie Johnson, OpenStax College : Anatomy & Physiology, Jun 19, 2013, http://cnx.org/content/col11496/1.6/. CC BY 3.0, https://creativecommons.org/licenses/by/3.0/.*

Dermis

The dermis stands in contact with the epidermis via the basement membrane and is constructed by the upper papillary dermis and the lower, denser, reticular dermis. The dermis is constructed of collagen fibers, giving the skin its resilient nature. It also houses sebaceous glands, hair follicles, blood vessels, muscles, and sensory neurons[1].

Subcutaneous layer (hypodermis)

This layer consists primarily of fat cells, but also contains blood vessels, lymphatic vessels, and sensory neurons[1].

Pigmentation

Melanocytes are dispersed in stratum basale. These cells, equipped with dendrites, produce melanin granules needed to protect the skin from deleterious UVR, and are responsible for giving the skin its pigmentation. The number of melanocytes is relatively equal between individuals, no matter the level of skin pigmentation. The difference lies in the amount of melanin produced, where individuals with a dark skin type produce a lot more than individuals with a light skin type[2].

Skin type

Skin type, referring to level of pigmentation and the skins resilience to UVR, is often objectified according to Fitzpatrick. The Fitzpatrick skin types are divided into six levels, where skin type 1 is the lightest and skin type 6 is the darkest. Besides taking the actual skin colour under consideration when evaluating an individual's skin type, we also adapt their resilience towards sunburn. Thus, a person with skin type 1 has a light skin and reddish hair, while always burn when spending time in the sun and never tan. Conversely, a person with skin type 6 has very dark skin and hair, never gets burned in the sun and always gets tanned (Figure 3)[3].

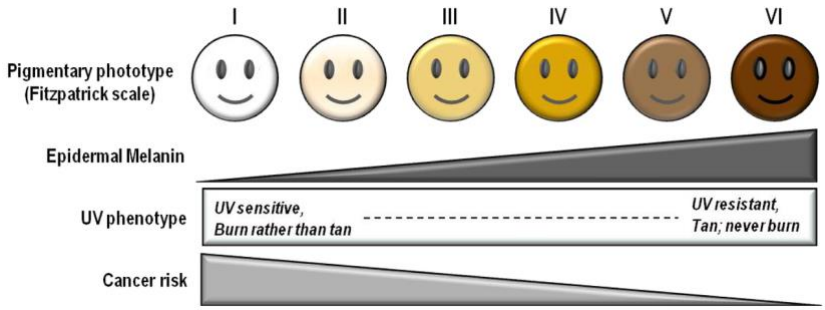

Figure 3. Skin type according to Fitzpatrick. I lighter skin tone and a tendency to burn in the sun indicates a lower skin type, while a darker skin tone and a low tendency to burn in the sun indicates a higher skin type. *Picture adapted from John D'Orazio, Stuart Jarrett, Alexandra Amaro-Ortiz and Timothy Scott, CC BY 3.0 <https://creativecommons.org/licenses/by/3.0>, via Wikimedia Commons*

Skin cancer

Skin cancer is primarily represented by three subtypes: malignant melanoma (MM), squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Together, they account for a large part of all diagnosed cancers in Sweden. In 2021, 5 038 persons were diagnosed with MM; 11 366 persons were diagnosed with SCC and 49 120 persons were diagnosed with BCC in Sweden[4]. Meanwhile, approximately 11 400 individuals were diagnosed with breast cancer and 10 200 individuals with prostate cancer the same year. SCC and BCC both derive from keratinocytes in the epidermis and are collectively called keratinocyte carcinoma (KC, formerly non-melanoma skin cancer, NMSC). This thesis will focus on BCC; however, we will start with a summary of the two other common skin cancer forms.

Malignant melanoma

Pathogenesis and risk factors

Malignant melanoma (MM) is a cancer derived from melanocytes in the basal layer of the epidermis. Melanocytes can also be found in hair follicles, in mucous membrane, in the eye and in the meninges[5]. MM develops after genetic alterations through mutations in melanocytes, based on factors including UV-exposure; phenotypic factors, such as light skin type or many nevi; and hereditary genetic modifiers[6]. There are several known mutations in the pathogenesis of melanoma, and which mutations that are present in each tumour can amongst others depend on level of UV-exposure and MM subtype.

MM develops through the non-invasive precursor MM in situ. This form has no metastasising capabilities[7], however after a varying amount of time, progression to an invasive MM can ensue.

MM is the skin cancer form that is most prone to metastasise. With tumour thickness and ulceration being the prime marker for risk of tumour spread[8], some of the most common sites of metastasis are the lung, liver and brain[9].

There are several known risk factors for MM, including number of melanocytic nevi (>100 nevi increase the risk 7-fold) and presence of atypical nevi (increases the risk of MM 10-fold) according to a review by Long et al[6]. Another important risk factor is previous MM diagnosis, increasing the risk 10-fold for a new primary tumour. Light skin colour, blue eyes, red hair, previous sunburn, and use of indoor tanning beds increase MM risk by a factor of 1.5 – 2.5[6]. Regarding UV-exposure, MM risk seems to be related primarily to intermittent sun exposure as opposed to chronic sun exposure, correlated to SCC[10].

Epidemiology

In 2021, just over 5 000 cases of MM in around 4 800 individuals were registered in the Swedish National Cancer Registry[4]. The same year, MM was the third most common invasive cancer in men and the fifth most common in women. The incidence of MM is increasing in Sweden. In 1970, the MM incidence was estimated at 7.1/100 000 in men and 8.4/100 000 in women, reaching 26.3 and 24.0/100 000 respectively in 2007[11]. During the following years, incidence has continued increasing, reaching an age-standardised incidence rate of 51/100 000 in males and 40/100 000 person years in females (Swedish standard population) in 2021[12].The same tendency of heavy increases in incidence has been seen in other countries, such as Denmark, USA, Germany and New Zealand[13]. For reference, Australia, a country known for its high skin cancer incidence, had an age-standardised incidence rate of 54/100 000 person years in 2018[14]. Incidence is generally higher in males, however it has been shown that incidence might be higher among women in younger age categories[8].

Due to its correlation to UV-exposure, MM incidence has been shown to correlate with geographical latitude. Thus, in populations of similar skin type, incidence is higher in areas closer to the equator (with a lower latitude) in comparison to areas further from the equator[15, 16].

As mentioned, MM is prone to metastasis and in 2021, over 500 individuals died from the disease in our country. The overall relative 10-year survival rate in Sweden has been estimated at 90% in men and 94% in women[4].

Diagnosis

The preliminary diagnosis of MM is made by clinical examination, including dermoscopy. The final diagnosis is made through histopathological examination.

Visually, MM is hyperpigmented in most cases. Typically, it is larger and with a differing colour and shape than the surrounding nevi. Dermoscopically, the features are often chaotic and may include atypical network, atypical vascular patterns and signs of regression (such as scar like areas)[17]. However, particularly in early lesions, both the macroscopical and the dermoscopical appearance of melanoma can be exceedingly difficult to separate from a benign lesion. In these cases, dermoscopic follow up with photography might be an alternative to visualise pathologic change over time.

Treatment

The primary treatment for MM is wide surgical excision. In cases where the tumour has a thickness over 1 mm, sentinel lymph node biopsy, in search for lymphatic spread, might be needed to assess prognosis. Metastasised disease is treated with chemotherapy, immunotherapy or radiotherapy[8].

Squamous cell carcinoma

Pathogenesis and risk factors

SCC develops in keratinocytes in the epidermis, primarily in chronically sun damaged skin. The process of SCC development starts with UV-induced mutations in the keratinocytes, resulting in a dysplastic lesion (actinic keratosis). Initially, the dysplasia is low grade and localised in the basal portion of the epidermis. In time, however, high grade dysplasia can develop and when the dysplasia involves the entire epidermis, the lesion is referred to as SCC in situ. This is a malignant, but non-invasive lesion which in turn can develop into an invasive SCC tumour[18].

SCC develops primarily in sun exposed regions of the skin, such as the head- and neck region as well as forearms and dorsal aspects of the hands.

Epidemiology

In 2021, around 11 400 cases were diagnosed in 10 100 persons in Sweden[4], with an age-adjusted person-based incidence rate of 124/100 000 person years in men and 77/100 000 in women (Swedish standard population, year 2000)[12]. The incidence rate has increased considerably from 18/100 000 in men and 9/100 000 in women in 1970 to 50/100 000 in men and 22/100 000 in women in year 2000.

SCC has potential for metastasis, and in 2021 almost 90 individuals died from the disease[4].

Diagnosis

The preliminary diagnosis of invasive SCC is made on a clinical bases, with the aid of dermoscopy. The final diagnosis is made with histopathology. The clinical

appearance of SCC includes an infiltrated, red to pink tumour. There is often hyperkeratosis present, and the tumour might be ulcerated. Dermoscopically, the main features are the vascular patterns. In SCC in situ, glomerular vessels are often present, while polymorphous vessels are a more common feature in invasive SCC[19]. Other features in SCC includes surface scales, white circles and white structureless zones[20].

Treatment

The primary treatment for invasive cutaneous SCC is surgical excision. Advanced disease, including metastasis, can be treated with cytostatic therapy or radiotherapy[18].

Non-invasive precursor lesions can be treated destructively with cryotherapy, with or without curettage; topically with imiquimod or 5-fluorouracil; or with photodynamic therapy (PDT)[21].

Basal cell carcinoma

Pathogenesis

BCC develops from the basal layer (stratum basale) of the epidermis (Figure 2). However, there is conflicting evidence as to its exact cellular origin. Studies demonstrate that BCC develops from either the interfollicular epidermis or from hair follicle stem cells[22]. On a molecular level, several mutations are known to be involved in BCC pathogenesis.

Sonic Hedgehog (SHh) pathway. This is the most well-known pathway for BCC pathogenesis and entails the PTCH transmembrane receptor, the SMO signal transducer and GLI transcription factors. The function of SMO is to induce production of GLI transcription factors, necessary for BCC development. SMO is normally inhibited by PTCH. However, when SHh binds to PTCH, this suppression is lifted, and SMO is free to activate GLI transcription (Figure 4). The increased activation of the SHh-pathway is the grounds for BCC development in most cases. It is also involved in Gorlin syndrome, where the affected individual, among other symptoms, develops a large amount of BCC tumours. The increased tumour burden is caused by a “loss of function”-mutation of the PTCH gene, giving rise to an uncontrolled activation of SMO. Similar, sporadic mutations have been shown to be caused by UV-radiation[23].

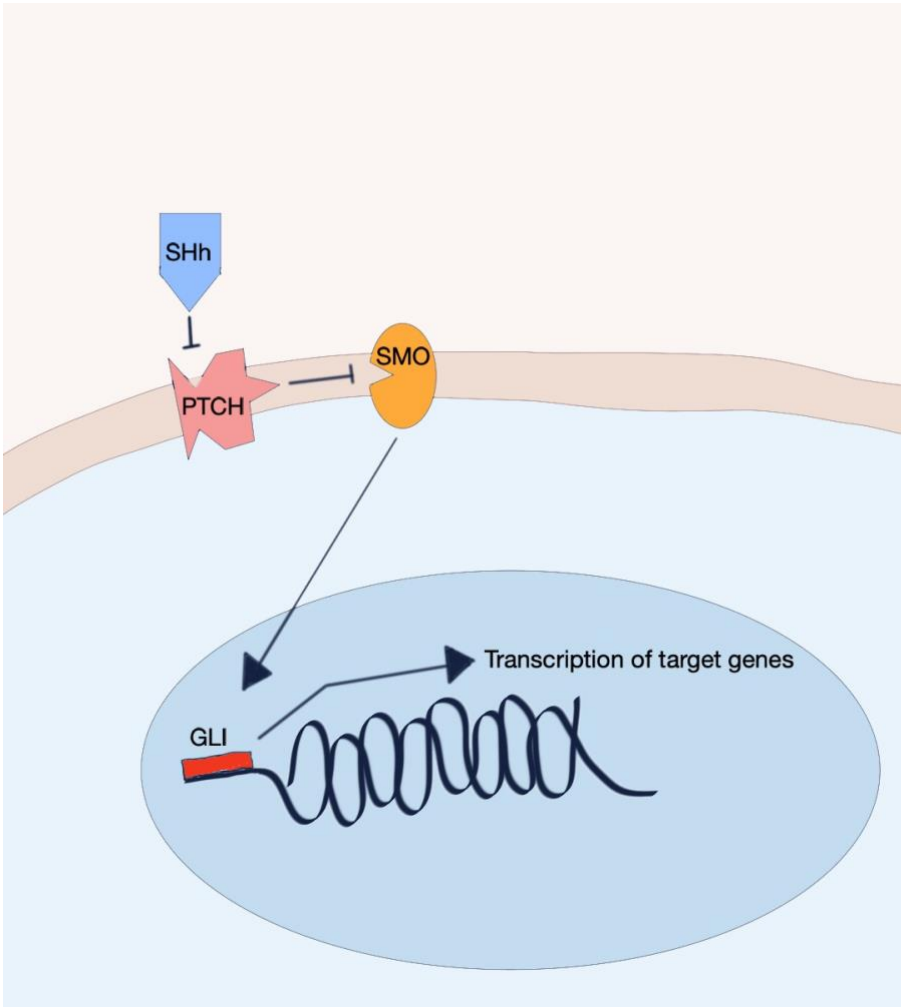

Figure 4. Signal transduction in the Sonic Hedgehog pathway. *Illustration by J. Kappelin*.

Mutations in p53 suppressor gene. Another common molecular pathway to BCC development is via the p53 suppressor gene. This tumour suppressor is vital for the maintenance and regulation of genomic material in the cells, inhibiting mutations to give way to tumour progression. Mutations in the p53-gene have been detected in 20-60% of sporadic BCC tumours[23].

Besides mutations in the SHh-pathway and p53, several other mutations have been implicated to be a part of sporadic BCC tumour progression[23].

Histopathological subtype

BCC is a skin cancer type with low mortality rates and the cure rate is generally excellent. However, the prognosis and available treatment modalities are dependent on the histopathological growth pattern. BCC is potentially complex to categorise according to growth pattern, and in the literature 66 different subtypes have been described[24]. This has necessitated the search for a categorisation that facilitates the histopathological diagnostic procedure. In a recent position paper, endorsed by the European Academy of Dermatology and Venereology, subtypes with an infiltrative growth pattern was proposed to be combined to a single group[25].

Meanwhile, in Sweden a specific categorisation of histopathological subtype has been constructed and used since the late 1980s. The categorisation, named the Sabbatsberg method, or the classification according to Glas, separates subtypes according to growth pattern into four different "Glas-types": BCC type IA (nodular BCC), type IB (superficial BCC), type II (superficially infiltrative BCC) and type III (infiltrative/morpheaform BCC)[26], see Table 1. A fully corresponding method is not found internationally, however the Sabbatsberg method is still used in pathology reports and in the Swedish BCC Registry[27]. According to the Sabbatsberg method, the following histopathological definitions of subtypes are described. However, BCC tumours may carry a mix of different growth patterns[28].

Table 1. Characteristics of the different histopathological subtypes of BCC.

Glas-type	Pathological behaviour	Growth pattern	Invasion
BCC IA	Low aggressive	Nodular	Dermis
BCC IB	Low aggressive	Superficial	Papillary dermis
BCC II	Medium aggressive	Micronodular/Infiltrative	Dermis
BCC III	Highly aggressive	Morpheiform	Dermis, hypodermis and deep structures

BCC type IA. The tumour grows in a nodular fashion with a rounded, well-defined border (Figure 5). Subcutaneous structures are not involved. The tumour subtype is defined as low aggressive.

BCC type IB. Superficial, potentially multifocal growth of well-defined tumour areas (Figure 6). The tumour subtype is defined as low aggressive.

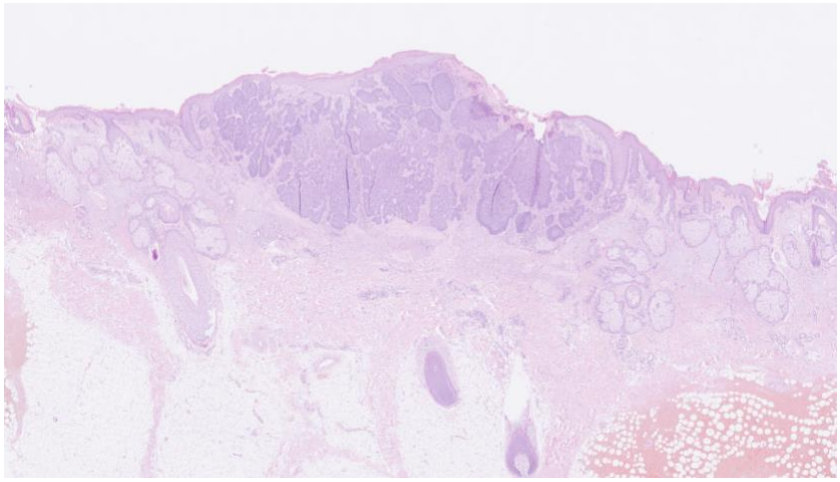

Figure 5. Nodular basal cell carcinoma (type IA). *Photo: J. Kappelin. Published after patient consent.*

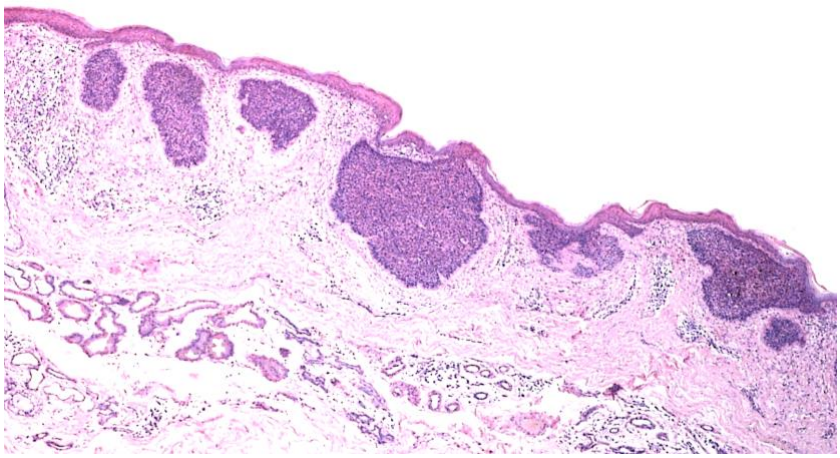

Figure 6. Superficial basal cell carcinoma (type IB). *Photo: L. Wozniak & K. W. Zielinski. Adapted by J. Kappelin. https://creativecommons.org/licenses/by-sa/3.0/.*

BCC type II. Described in the paper by Jernbeck et al as an intermediary form between type I and type III. This subtype, however, has a potentially varied growth pattern from superficially infiltrative to growth patterns bordering on highly aggressive (Figure 7).

BCC type III. Infiltrative tumour that may affect subcutaneous structures. The tumour growth is irregular and diffuse with smaller strands of tumour (Figure 8). The tumour subtype is defined as highly aggressive.

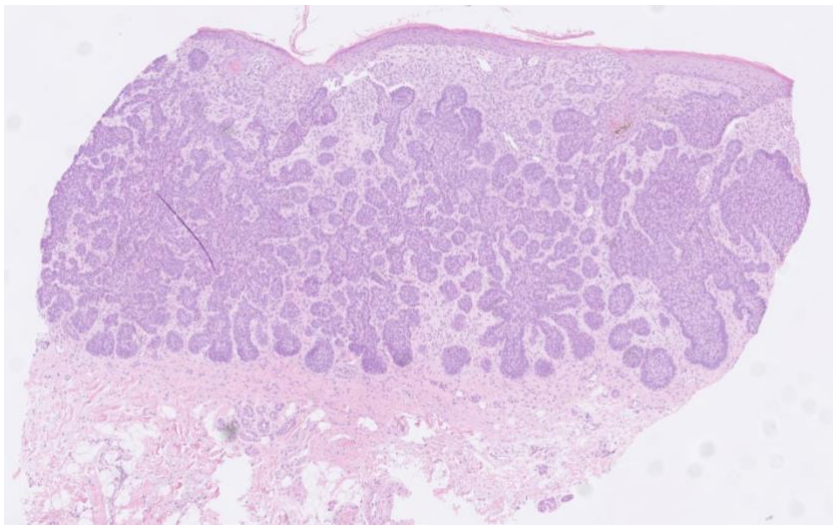

Figure 7. Infiltrating basal cell carcinoma (type II). *Photo: J. Kappelin. Published after patient consent.*

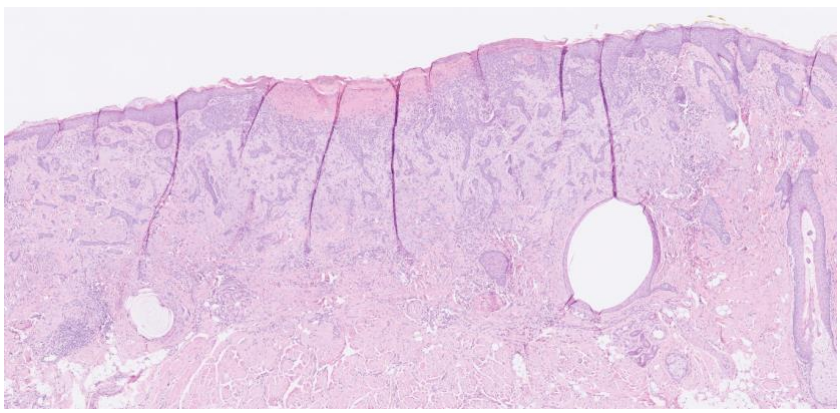

Figure 8. Infiltrating basal cell carcinoma (type III). *Photo: J. Kappelin. Published after patient consent.*

Epidemiology

BCC is known to be the most common skin cancer form in fair-skinned populations[29]. Still, not much is known about the true incidence of BCC. The reason for this is the near lack of national registration. Due to the very high incidence of BCC and SCC, collectively referred to as non-melanoma skin cancer (NMSC) or keratinocyte carcinoma (KC), in Europe there are no strict recommendations regarding national registration of these cancers[30]. It is essentially up to every country to decide whether to register all skin cancers, to exclude BCC or to exclude both BCC and SCC, dependant on the countries financial and logistical capabilities to hold a register of that magnitude. Furthermore, standard registration of KC is defined by solely registering the first ever diagnosed tumour of a specific histological subtype (BCC or SCC) in every individual. These recommendations are not exclusive for Europe. Indeed, Australia as well as America have the same registration routines and thus do not have national registration for KC[31, 32].

This, of course, means that there is an under-registration of these cancer types, and especially BCC.

International incidence

When comparing incidence rates of BCC between countries, there are several factors to take notice of. Firstly, incidence rates can be based on national data or on smaller cohorts. The cohorts, in turn, can be based on defined geographical regions or even patient populations seeking medical advice at a specific hospital. Secondly, incidence can be based on "first ever" BCC diagnosis (first ever tumour, FET), first annual BCC diagnosis (person-based incidence rate, PBR) or all diagnosed tumours annually (tumour-based incidence rate, TBR). Thirdly, incidence rates can be presented in crude numbers or as age-standardised rates. In turn, the age-standardised rate could be standardised to different standard populations, such as the World population, the European population, or the Swedish population. Lastly, of course, incidence studies can differ in time from one another. While incidence rates from one country is based on older numbers from the early 2000s, another study might base their incidence rates on numbers from 2020. It is safe to say that published incidence rates can differ quite substantially because of these disparities. For that reason, real incidence of BCC is difficult to compare between countries. Nonetheless, published incidence rates give us an idea of how BCC is distributed across countries and in the following section I will present incidence rates worldwide, as they can be read in the published reports. Swedish incidence will be discussed in the next section. Rates are summarised in detail in Table 2 and illustrated graphically in Figure 9.

Europe

In the Nordic countries, numbers are based on national registration. However, there are differences as to whether incidence rates are person-based, tumour-based or based on first ever tumour. Registered incidence rates are quite similar between the countries. In Finland in 2009, a PBR of 126/100 000 person years was reported (European age standardised rate, EASR)[33], while Denmark showed an FET of 91/100 000 in males and 97/100 000 in females in 2007 (World age standardised rate, WASR)[34]. Meanwhile, in Iceland in 2013 – 2017, mean incidence rates reached 60/100 000 in males and 83/100 000 in females (WASR)[35].

From the United Kingdom, all recovered published studies report annual PBR. In a study by Venables et al., covering England, Scotland, Wales, and Northern Ireland, an overall incidence of 352/100 000 person years among males and 219/100 000 among females was reported in 2013-2015 (EASR). In the same study, incidence rates were shown to be the greatest in the southwest of England, reaching 362/100 000, while the lowest incidence was encountered in Dumfries and Galloway in western Scotland (39/100 000)[36]. A further study of BCC incidence in England by Ascott et al. showed the highest incidence rates to be in the Southwest Peninsula region with an incidence of 426/100 000 in 2017-2019 (EASR)[37]. Garbe et al presented Scottish rates from 2017 of 178/100 000 in males and 123/100 000 in females (EASR)[13]. Somewhat older data from southern Wales in 1998 reported incidence rates for BCC of 114/100 000 (WASR)[38]. Meanwhile, in Ireland the incidence was shown to be 91/100 000 person years during the period 1994-2003 (WASR)[39]. Thus, the incidence seems to be highest in England and lower in the northern part of the United Kingdom, whereas rates from Ireland and Wales are too old to be justifiably compared.

Focusing on Central and Western Europe, a study by Rudolph et al presented FET incidence rates for BCC in Germany in 2010 of 82/100 000 person years (EASR)[40]. Regarding France, no studies on true national BCC incidence was recovered. However, in a study from 2008, an estimated annual person-based crude incidence of 239/100 000 person years was reported, based on diagnoses made by a sample of dermatologists in the country[41]. Incidence studies from the Netherlands are more numerous. The latest available incidence numbers from 2022, based on first ever BCC diagnosed, was reported at 304/100 000 person years in males and 274/100 000 in females (EASR)[42]. In the neighbouring country Belgium, all histopathologically verified tumours during the years 2004 – 2012 were counted. Annual person-based incidence in 2012 was reported to be 88/100 000 in males and 93/100 000 in females (WASR)[43].

In Eastern Europe, the Baltic country Lithuania had an FET rate of 46/100 000 in 2010 (EASR)[44]. Further south, in Croatia, incidence during the years 2003 – 2005 was reported to be 34/100 000 in males and 25/100 000 in females (WASR)[45]. On

a similar latitude in Belgrade (Serbia), an incidence of 28/100 000 was reported in 2011 (WASR)[46].

In Southern Europe, studies on incidence are primarily represented by Spain and by one study from Malta. Studies in Spain are based on defined geographical regions. Bielsa et al described BCC incidence in the Barcelona region in 2009, where the tumour-based incidence was estimated at 196/100 000 (EASR)[47]. In this study histologically verified as well as clinically diagnosed tumours were included, which likely increased the incidence numbers. Meanwhile, during the years 1998 – 2000 in Soria (north-eastern Spain), a person-based incidence rate of 58/100 000 person years was presented (WASR)[48]. The same standard population was used in a study in the Girona region in 2008 – 2012, where a FET rate of 96/100 000 person years was reported[49]. Regarding Malta, the country´s BCC incidence was presented in a study by de Vries et al. In the study, PBR rate in 2009 was estimated at 96/100 000 person years (EASR)[33].

North America

Incidence reports for BCC from three different regions in Canada have been published. In Alberta, an FET rate of 132/100 000 person years in 2006 was recorded (Canadian standardised rate, CSR)[50]. In New Brunswick, during 2002 – 2010, the corresponding rate was 126.5/100 000 among males and 98.9 among females (CSR)[51]. Meanwhile, the FET rate for BCC in Manitoba for the year 2000, adjusted to the World population, was estimated at 93.9/100 000 in males and 77.4/100 000 person years in females[52]. The difference in reported incidence rate between the first two studies and the last might be explained by the differing standard populations used.

As in Canada, incidence studies in the United States have been performed in defined geographical regions. In New Hampshire, in the north east, annual person-based incidence rate was reported to be 310/100 000 person years among males and 166/100 000 among females during 1993 – 1994 (United states standardised rate, USR)[53]. In northern California, a crude annual person-based incidence of 535/100 000 was recorded in 2012[54]. In the southern part of the United States, incidence is higher, as shown by the PBR in New Mexico in 1999 and in Arizona in 1996 (930/100 000 for males and 486/100 000 for females in New Mexico, USR[55] and 936/100 000 for males and 497/100 000 for females in Arizona, USR[56]).

South America

In a regional study in Brazil in 2008, an incidence rate of 295/100 000 person years was reported[57]. Meanwhile, in Chile during the years 1994-2000, a mean crude incidence rate of only 4/100 000 was recorded[58].

Table 2. Published incidence rates for basal cell carcinoma, divided by country.

Country	Incidence rate /100 000 person years (M/F)[a]	Inclusion [b]	Standard population [c]	Year
Northern Europe				
Sweden	430/353	TBR	SSP	2004 – 2008
Finland	126	PBR	EASR	2009
Denmark	91/97	FET	WASR	2007
Iceland	60/83	TBR	WASR	2013 – 2017
United Kingdom	352/219	PBR	EASR	2013 – 2015
England	300	PBR	EASR	2013 – 2015
Scotland	178/123	N/A[d]	EASR	2017
Wales	114	PBR	WASR	1998
Ireland	91	PBR	WASR	1994 – 2003
Central Europe				
Germany	82	FET	EASR	2010
Netherlands	304/274	FET	EASR	2022
Belgium	88/93	PBR	WASR	2004 – 2012
France	239	PBR	CR	2008
Lithuania	46	FET	WASR	2010
Southern Europe				
Croatia	34/25	N/A[d]	WASR	2003 – 2005
Serbia	28	N/A[d]	WASR	2011
Spain				
Barcelona	196	TBR	EASR	2009
Girona	96	FET	WASR	2008 – 2012
Soria	58	PBR	WASR	1998 – 2000
Malta	96	PBR	EASR	2009
Asia				
Israel	188	FET	WASR	2011 – 2016
Jordan	29	PBR	WASR	2016
Qatar	10	FET	CR	1990 – 1994
Kazakhstan	38/33	N/A[d]	EASR	2012 – 2016
Japan	4	PBR	WASR	2016 – 2017
South Korea	2	TBR	WASR	2011 – 2017
Singapore	6	N/A[d]	WASR	1993 – 1997
North America				
Canada				
Alberta	132	FET	CSR	2006
New Brunswick	127/99	FET	CSR	2002 – 2010
Manitoba	94/77	FET	WASR	2000
USA				
New Hampshire	310/166	PBR	USR	1993 – 1994
California	535	PBR	CR	2012
New Mexico	930/486	PBR	USR	1999
Arizona	936/497	PBR	USR	1996
South America				
Brazil	295	N/A[d]	N/A[d]	2008

Chile	4	TBR	CR	1994 – 2000
Africa				
South Africa	51/25	TBR	N/A[d]	2000 – 2004
Oceania				
Australia	770	PBR	ASP	2011 – 2014
Queensland	1355	PBR	ASP	2011 – 2014
Northern Territory / South Australia	565	PBR	ASP	2011 – 2014
Western Australia	736	PBR	ASP	2011 – 2014
New South Wales	751	PBR	ASP	2011 – 2014
Victoria/Tasmania	482	PBR	ASP	2011 – 2014
New Zealand				
Auckland	1385	TBR	ASP	2008
Central part	299	PBR	WASR	1997 – 2007

[a] Published incidence rate /100 000 person years. Incidence is primarily presented as total incidence. However, when only incidence categorised by sex is published, this is presented in the table as Male/Female (M/F) incidence rate.
[b] Inclusion methodology. Person-based rate (PBR), Tumour-based rate (TBR) or first ever tumour (FET).
[c] Standard population used. World age standardised rate (WASR), European age standardised rate (EASR), Swedish standard population (SSP), United States standardised rate (USR), Canadian standardised rate (CSR), Australian standard population (ASP), Crude rate (CR).
[d] Data regarding the specific variable could not be extracted from the published article.

Oceania

Australia is known for its high skin cancer incidence, likely related to a light skin type on a geographical location with high UV-exposure. In a study by Pandeya et al of patients registered under Medicare, person-based BCC incidence during the years 2011 – 2014 was reported to be 770/100 000 person years, with numbers differing between 500 – 1400/100 000 person years in the different geographical regions (Australian standard population, ASP)[59]. The lowest incidence was found in the southern part of Australia, Victoria and Tasmania, where the average UV-index is the lowest[60]. Conversely, the highest incidence was found in Queensland, located in the north with a high UV-index. Likewise, a regional study in Nambour, Queensland, published a person-based incidence rate of 1541/100 000 person years for the years 1997 – 2006 (WASR)[61].

New Zealand has a more southern location than Australia. A person-based incidence of 299/100 000 years has been recorded for the years 1997 – 2007 in a study by Brougham et al (WASR)[62]. Meanwhile, a tumour-based incidence of 1385 /100 000 person years (ASP) was reported in a study by Pondicherry et al in 2008[62, 63]. The latter incidence was based on a study on all histopathologically verified tumours in the Auckland region (regardless of treatment modality) and the former on all individuals with surgically treated and histopathologically confirmed tumours in the central region of New Zealand. The differences in inclusions and age-standardisation are likely to be partly explanatory to the differing incidence

rates in the two studies. Likewise, due to methodological differences, none of the studies are truly comparable to the cited studies on Australian incidence rates.

Asia

Most studies on BCC in Asia report low incidence numbers, spanning between 2.3-9.9 / 100 000 person years regarding South Korea (tumour-based WASR, 2011 – 2014)[64], Japan (WASR, 2016 – 2017)[65], Singapore (WASR, 1993 – 1997)[66] and Qatar (first ever diagnose, crude rate, 1990 – 1994)[67]. In Jordan, incidence of 29/100 000 person years was reported in 2016 (WASR)[68], while in Astana region in Kazakhstan an incidence rate of 37.6/100 000 in males and 33.4/100 000 person years in females was presented between the years 2012 – 2016 (EASR)[69]. In Israel, however, incidence seems to be considerably higher, reaching 188/100 000 person years according to Sella et al in 2011 – 2016 (first ever tumour, WASR)[70].

Africa

During the years 2000 – 2004, tumour-based BCC incidence in South Africa was reported to be 51/100 000 person years in males and 25/100 000 in females[71]. These numbers included all different population groups in the country. The incidence was considerably lower among inhabitants with a darker skin type (3.0/100 000 among males and 1.7/100 000 among females). Regarding African countries with a primarily dark-skinned population, incidence of BCC is reported in number of diagnosed cases rather than incidence rate. In Madagascar, a total of 9 tumours were histopathologically verified at a single hospital during the years 2008 – 2015[72]. Likewise, a total of 5 histopathologically verified BCC tumours were reported from a single hospital in Nigeria during the years 2006 – 2010[73].

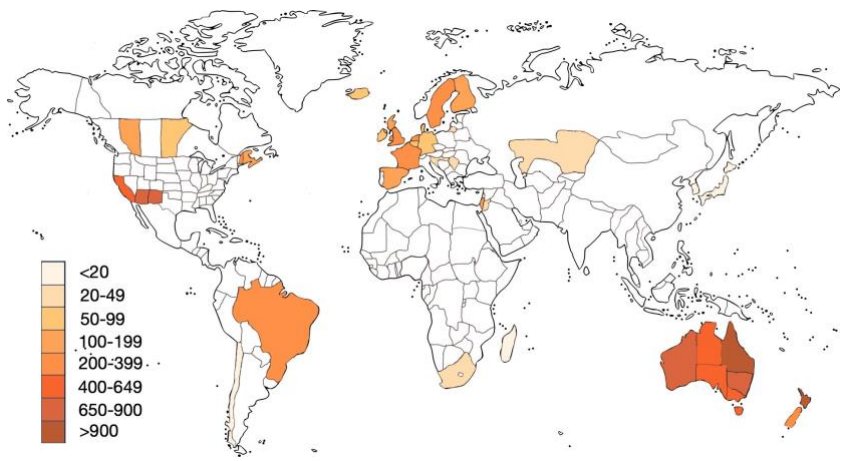

Figure 9. Selected incidence rates for BCC in countries worldwide. Based on data from individual studies, referred to in the text, made in different time periods. Incidence rate per 100 000 person years (differing standard populations). White colour indicates missing data. Illustration by J. Kappelin.

Swedish incidence

Swedish Basal Cell Carcinoma Registry

Since 2004, Sweden has registered all primary, histopathologically verified BCC tumours separately in the Swedish Basal Cell Carcinoma Registry, held by the Swedish National Board of Health and Welfare[27]. Thus, by using data from the registry, incidence based on multiple BCC diagnoses per individual is possible. In the registry, data regarding BCC subtype, patient sex and age, tumour localisation and diagnosing pathology laboratory is accounted for. Reported tumour subtype is based on the Swedish Sabbatsberg criteria[26]. Tumours are reported to the registry by the diagnosing pathologist.

Tumours that have been biopsied earlier are excluded to avoid double registration and only primary tumours are included. Thus, it is vital for the clinician to supply sufficient information to the pathologist regarding earlier biopsies or treatments of the tumour to avoid over registration.

Clinical vs histopathological diagnosis

In the Swedish BCC Registry, only histopathologically verified tumours are registered. Tumours diagnosed purely through clinical examination are not included. This means that there is a potential under registration of tumours in the BCC Registry, a problem common for all similar registries[74, 75]. The true number of diagnosed BCC tumours in Sweden is not possible to know without an unfeasibly large study of patient records across the country. However, a cohort study of treated patients in the Gothenburg area, specifically at the Department of Dermatology, Sahlgrenska hospital, was conducted retrospectively on patients diagnosed at the clinic in 2016. All diagnosed tumours were scrutinised regarding tumour subtype and whether the tumour was histopathologically verified or merely clinically diagnosed. In the study, as many as 85% of diagnosed superficial BCC tumours lacked histopathological confirmation. The corresponding number for nodular BCC was 42% and regarding infiltrative BCC, the number was 3%[76]. Whether the results presented in the study from Gothenburg can be extrapolated to the rest of the country is difficult to say. Most likely, there are cultural differences as to how large proportion of diagnosed BCC tumours are biopsied. Nevertheless, the study indicates that a substantial number of tumours might be overlooked in the national BCC Registry, a fact that must be considered when discussing the incidence of BCC in our country.

Earlier incidence studies

Previously, one larger report on BCC incidence based on the BCC Registry has been published by the Swedish National Board of Health and Welfare in 2009[27]. In this report, incidence from the first years of the registry, 2004 – 2008, was presented. In the report, a tumour-based BCC incidence of 430/100 000 person

years in males and 353/100 000 in females was presented (Swedish standard population, year 2000). Crude incidence rate was higher in the southern part of the country and lower in the north. The most registered tumour subtype was nodular BCC, and the most frequent tumour localisation was the head.

Overall, studies on BCC incidence in Sweden are scarce, but include a study by Wallberg et al. The study presents tumour-based incidence rate for BCC from a single centre in the Stockholm region during the years 1971 – 1980. An increasing incidence trend was shown and the incidence in 1980 was recorded to be 47/100 000[77]. More recent studies on incidence trends in Sweden are not available.

Geographical aspects, latitude, and skin type

Several studies, as well as comparisons between studies, indicate latitude to be a factor affecting BCC incidence. This seems to be the most relevant in areas with a population largely consisting of similar skin type. Illustrative examples include Australia, where incidence in the study by Pandeya et al was shown to be higher in Queensland, in the northern part of the country (closer to the equator) and lower in Tasmania in the southern part[59]. Similarly, in North America, when comparing epidemiological studies from different geographical regions, incidence is evident to be higher in the southern part (closer to the equator, with a higher solar UV-index, Figure 10)[50-56]. Meanwhile, in Europe as a whole, the same connection is not as obvious. Studies from this continent do not show the same gradient with a higher incidence in the south and a lower incidence in the north[33], except for when looking at a single country. When specifically studying United Kingdom and Sweden respectively, incidence was shown to be larger in the southern part of the country[27, 36]. The reason for this might well be differences in skin type, where a preponderance of slightly darker skin type is found in southern countries in Europe and a lighter skin type in the northern countries. Conversely, differences in skin type between Canada and Arizona as well as within the boundaries of Australia are not as obvious.

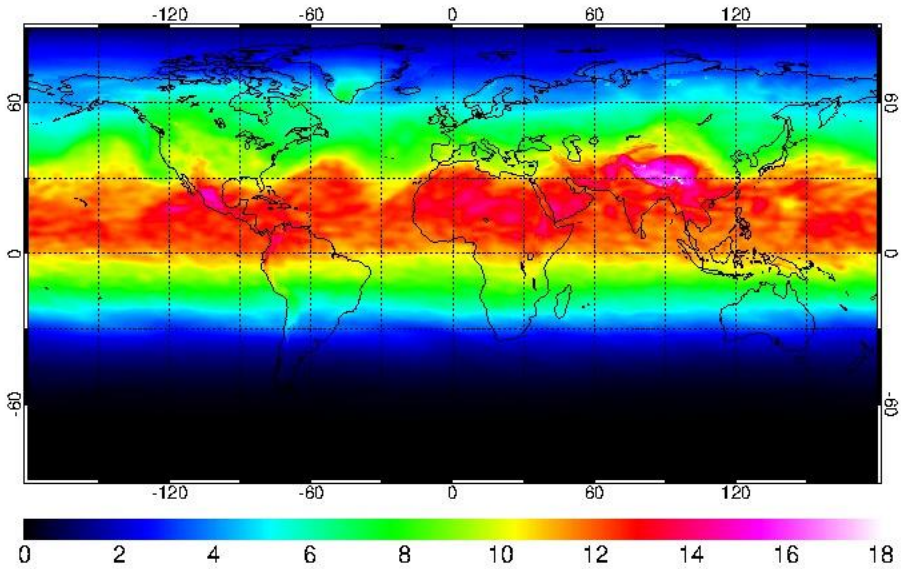

Figure 10. Solar UV-index June 10th, 2023. Summer on the northern hemisphere. *Based on spectrometer data from ESA (European Space Agency), originally published by KNMI (Royal Netherlands Meteorological Institute). https://www.temis.nl/uvradiation/UVdose.php. Reprinted with permission from KNMI.*

Incidence trends

Several studies on incidence trends regarding BCC in different countries have been conducted. Common to all of them is the increasing incidence of BCC, as well as for SCC and MM. In a review by Verkouteren et al. from 2017, studies regarding BCC incidence and trends in several countries across the globe was scrutinised. Incidence was shown to increase by 5% annually in Europe and by 2% annually in the USA. Likewise, incidence was shown to increase in Asian countries. Meanwhile, incidence in Australia showed trends indicating that they are about to reach a plateau[29].

Risk factors

BCC is a skin cancer with high and increasing incidence. Gathering information regarding risk factors for this tumour is pivotal to manage patient information and to optimise screening protocols. Furthermore, knowledge about risk factors enables the launch of prevention campaigns, necessary to flatten out the trend of an increasing skin cancer incidence.

There are several risk factors that have been studied in the literature regarding BCC, of which UV-exposure is the most well-known.

UV-exposure

Ultra-violet radiation (UVR) is the most studied risk factor for BCC and the human body is exposed primarily through natural or artificial sunlight (sunbeds). Overall, UV-exposure can be measured in two disparate patterns: chronic and intermittent.

Chronic UV-exposure is related to a relatively constant exposure throughout the year, dependent on UV-index. This mode of exposure is primarily related to outdoor work, where increased UVR exposure is present every day in various amounts.

Conversely, *intermittent* UV-exposure is primarily related to recreational sun exposure, such as sunbathing in Spain a couple of weeks annually. In between travels, the individual perhaps has an indoor work with low UV-exposure.

According to the published literature, risk of SCC increases primarily in relation to chronic sun exposure, while BCC and MM is more related to intermittent sun exposure[10, 22, 78, 79]. The distinct difference in exposure habits is more evident regarding SCC and MM, while BCC risk seems to increase somewhat in relation to chronic sun exposure as well[80].

UVR, naturally produced by the sun, is electromagnetic radiation spanning between a wide range of wavelengths. UVC (100 – 280 nm) is the most energetic form of UVR and is deleterious to any living organism. Virtually all UVC is absorbed by the ozone layer in the atmosphere and is therefore not a relevant, naturally existing, part of skin carcinogenesis on earth. However, artificial exposure, such in the case of welding, might contribute to skin cancer risk[81]. UVB (280 – 315 nm) is only partly absorbed and UVA (314 – 400 nm) passes through the ozone layer in its entirety[82]. Both UVA and UVB exposure has been shown to increase risk of skin cancer development[83], however probably in different ways. UVB, with a higher energy level, induces direct DNA damage, while UVA to a larger extent promotes carcinogenesis through oxidative stress. Thus, UVA and UVB are the present sun-related contributors to skin cancer development. Normally, damage to cellular DNA is controlled by the inherent protective mechanisms in the cell, for example by proteins inducing repair. Every now and again, a mutation develops even in these controller genes, diminishing the possibility to repair any damages. In these scenarios, a skin cancer may develop[84].

Another source of UVR is artificial, via sunbeds. In a meta-analysis by Wehner et al., the odds ratio (OR) of developing BCC in ever users of sunbeds, in comparison to never users, was 1.29 (CI 95% 1.08 – 1.53). The corresponding OR for individuals exposed to sunbeds at a younger age (<25 years) was 1.40 (CI 95%

1.29 – 1.52)[85]. Sunbed use also increases risk of SCC and MM. In a large cohort of women in the south of Sweden, a hazard ratio (HR) of 1.55 (CI 95% 1.24 – 1.95) for SCC risk was found among women who had used a sunbed in comparison to women who had never used a sunbed[86]. In the same cohort, an increased risk for MM was found among younger women who had used sunbeds frequently (HR 2.5, CI 95% 1.0 – 6.2)[87].

UV exposure for medicinal purposes, such as in the case of treatment for various dermatological disorders, has also been studied as a potential risk factor for skin cancer. The risk in relation to BCC is related to the type of UVR-treatment used. The highest risk is correlated to PUVA (psoralen in combination with UVA). This treatment is known to be related to increased skin cancer risk, and after >450 treatments, BCC risk has been described to increase 3 – 4 times[88]. Conversely, use of traditional UVB-treatment is considered a more benign risk factor[29, 88].

The skin has intrinsic protective mechanisms to minimise risk of cellular DNA damage related to UVR exposure. The most obvious protection is visible to the naked eye and entails the production of melanin. Melanocytes in stratum basale in the epidermis produce melanin granules that are dispersed via dendrites to keratinocytes in its vicinity. The granules are ingested by the keratinocytes and placed as a cap above the nucleus, protecting its DNA from UVR[2]. The darker the skin, the more resilient towards UVR and, as mentioned previously, a darker skin type results in a lower tendency to burn in the sun[3].

Immunosuppression

Immunosuppression after solid organ transplantation is well known to be a risk factor for skin cancer, especially SCC. However, studies have shown that BCC risk is increased as well. In a registry-based study from Ireland during the years 1994 – 2001, risk of cancer in renal transplant recipients was investigated. In this study, the risk of developing SCC increased 82-fold, whereas the risk for BCC increased 16 times[89]. Meanwhile, in a Swedish study by Krynitz et al. in 2016, organ transplant recipients who received their new organ during the years 2004 – 2011 were followed regarding registrations in the Swedish BCC Registry. In the study, BCC risk increased 6-fold in comparison to the general population[90]. A similar study conducted during the years 1977 – 2006 in Denmark also showed a 6-fold increase in BCC risk, while presenting an 82-fold increased risk of SCC[91].

Immunosuppression for other reasons may also affect BCC risk. In a study from California by Silverberg et al., BCC occurred twice as often in HIV-positive individuals in comparison to HIV-negative individuals. It did not, however, seem like the actual CD4-count affected BCC risk significantly[92]. Regarding blood malignancies affecting immunocompetence, such as lymphoma and leukaemia, skin cancer risk has also been studied. In a Danish study by Jensen et al. in 2010,

an increased BCC risk was seen in lymphoma patients, while an increased SCC risk was seen among patients with leukaemia[93].

Photosensitising medication

Several medications have for a long time been known to interact with UVR and produce dermatological side effects. These kinds of photosensitising medications can produce a skin reaction through mainly two pathways: a phototoxic reaction or a photoallergic reaction. The reaction is mainly related to exposure to UVA, however UVB and even visible light is also a possible mediator[94].

The most common reaction pattern is the *phototoxic* reaction. In this setting, molecules absorbed from the medication interact with UVR reaching the skin, producing free oxygen radicals through a non-immunological process, and thereby inducing cellular damage. The reaction is quick and commences within minutes to hours and thereby simulates a sunburn[94, 95]. Conversely, in the more uncommon *photoallergic* reaction, the molecule from the medication binds to a protein in the skin in the presence of UVR, producing a complete allergen. A sensitisation process ensues and at a later stage, through the renewed involvement of UVR, an inflammatory response follows, creating an eczematous rash[94-96].

The phototoxic reaction is comparable to a sunburn; hence, one could assume that the late effects of such a reaction could be similar to the late effects of a sunburn as well. The potentially increased risk of skin cancer when using photosensitising medication has therefore been discussed for some time. The main example of a phototoxic drug and its effect on skin cancer risk is PUVA, where photosensitising psoralen treatment is administered in conjunction with UVA-treatment. In a 30 year follow up-study by Stern et al., a cumulative dose of >450 PUVA-treatments increased the rate of diagnosed SCC 38-fold, while the rate of BCC increased 4-fold when looking at total tumour count[88]. Further studies have later been put forward, with the aim to investigate photosensitising medication where UV-therapy is not part of the treatment itself. In a survey-based study by Karagas et al. in the United States, a significantly increased risk of skin cancer among persons treated with photosensitising medication was presented (SCC: OR 1.8, CI 95% 1.1 – 3.2; BCC: OR 1.5, CI 95% 1.0 – 2.4)[97]. This study also found an increasing skin cancer risk after a longer treatment period. Interestingly, the opposite was suggested by Kaae et al. in a Danish registry-based study, where a wide variety of suggested photosensitising medications were evaluated. When looking at use of any of the long-term medications, no increased risk for BCC was found and only a minimally increased risk of SCC (OR 1.03, CI 95% 1.02 – 1.04). Conversely, use of any of the short-term medications increased the risk of both BCC (OR 1.3, CI 95% 1.3 – 1.4) and SCC (OR 1.5, CI 95% 1.4 – 1.5)[98]. Thus, studies have so far not been able to find conclusive evidence of an increased skin cancer risk after use of photosensitising medication.

Antihypertensive medication

Some specific drugs have, thus far, been treated with greater interest than others as to whether they are potential risk factors for skin cancer. In my thesis, I have focused on antihypertensive treatments and their relation to skin cancer risk. There are two primary reasons for this.

1) Hypertension is a common disorder with possible serious long-term complications. In 2021, 21% of Swedish inhabitants were prescribed some kind of antihypertensive medication[99]. For this reason, even a relatively small increase in skin cancer risk, induced by antihypertensive medication, could have a noticeable effect on skin cancer incidence as well as on health economics.

2) Lately, several studies on skin cancer risk in relation to antihypertensive treatment in general and thiazide diuretics in particular have been published. Still, the true relation between antihypertensive treatment and skin cancer is unclear, making this area prioritised for further investigation.

Thiazide diuretics

During the recent decade, several studies on antihypertensive medications and their effect on skin cancer risk have been presented. Primarily, thiazide diuretics have been studied. Thiazide diuretics are one of the recommended treatments for hypertension, and in Sweden they are one of the most prescribed antihypertensive medications, together with calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), and beta-blockers[99]. Thiazides inhibit sodium reabsorption in the kidney nephron and produce their antihypertensive effect partly by lowering the amount of extracellular fluid and decreasing cardiac output and partly by a vasodilatory effect on the blood vessels[100]. Thiazides are believed to act out their photosensitising effect via its sulphonamide component[101] and it is primarily hydrochlorothiazide (HCTZ) that has been pointed out as a potential risk factor for skin cancer. So much so, that HCTZ has been implicated as possibly carcinogenic to humans in a report by The international Agency for Research on Cancer (IARC)[102]. The effect on skin cancer risk has to date primarily been related to the risk for SCC. In a meta-analysis by Shin et al., a significantly increased risk of SCC (OR 1.9, CI 95% 1.2 – 2.8) was presented. There was a borderline significant result for BCC in the same study (OR 1.2, CI 95% 1.0 – 1.4). When investigating long term use, only a significantly increased risk for SCC was shown[103]. Several other studies on thiazide diuretics, not included in the mentioned meta-analysis, have shown an increased risk of SCC[104-109]. Meanwhile, the relation between thiazide diuretics and BCC risk seems to be more elusive. Some studies show a significantly increased risk, with odds ratio spanning from 1.06 – 1.14[104-107], while others fail to confirm a correlation[98, 108, 110, 111]. Thiazides are often used in combination with for

example amiloride. However, studies seldom separate risk estimates regarding single-agent thiazides from those of thiazide-containing combination treatments[104-106, 109, 112]. In a study by Jensen et al., however, a significant effect on SCC risk was seen with use of HCTZ in combination with amiloride. Meanwhile, no significant increase in risk was seen when using single-agent HCTZ[111].

ACE-inhibitors

ACE-inhibitors (ACEi) perform their effect on hypertension by inhibiting angiotensin converting enzyme (ACE). ACE in turn affects the balance between vasoconstriction/vasodilation as well as salt retention via the renin-angiotensin system (RAS) and the bradykinin system[113]. ACEi are reported to create photosensitising reactions in treated individuals, however this seems to be less common compared to thiazide diuretics[101, 114]. Studies on its effect on skin cancer risk have given contrasting results. Pre-clinical studies have shown ACEi to block activation of cytokines important for BCC carcinogenesis, theoretically inducing a preventive effect against this skin cancer[115, 116]. In fact, studies on selected high-risk individuals could show a decreased BCC risk in individuals treated with ACEi[117, 118]. Conversely, a registry-based population study in Denmark could not show any association between BCC risk and ACEi-treatment[119]. Thus, the true effect of ACEi on BCC risk is still to be decided.

Angiotensin II receptor blockers

Like ACEi, ARB acts on the renin-angiotensin system (RAS) in its effect against hypertension. However, in contrast to ACEi, which inhibits the formation of angiotensin II, ARB blocks angiotensin II from docking to one of its receptors (AT1R), thereby inhibiting vasoconstriction as well as sodium and water retention. Photosensitising reactions after use of ARB seems to be unusual but have been reported[114]. Regarding ARB and skin cancer risk, few studies have been performed. In a study by Schmidt et al., ARB was presented to increase BCC risk slightly (OR 1.09)[119].

Calcium channel blockers

Calcium channel blockers (CCB) decrease blood pressure by inhibiting cellular calcium intake. In the vessel wall, this leads to relaxation and vasodilation which in turn results in decreased blood pressure[120]. As with ACEi, CCB seems to be less common as a mediator for photosensitivity in comparison to HCTZ[101, 114]. Not many studies exist on the relation between CCB and skin cancer risk. Regarding BCC, a meta-analysis by Tang et al presented a significantly increased risk (OR 1.15, CI 95% 1.09 – 1.21). Meanwhile, in two studies on selected high-risk populations, no significant effect of CCB on BCC risk was found[117, 118].

Betablockers

Betablockers decrease blood pressure mainly by vasodilation[121]. There is very little evidence to a photosensitising effect in these medications[101, 114]. Similarly, betablockers have in some published studies not shown a significant effect on BCC risk[117-119]. However, in a meta-analysis by Tang et al, they presented a modestly increased risk for BCC (OR 1.09, CI 95% 1.04 – 1.15) but no increased risk for SCC[122].

In all, studies of antihypertensive treatments in relation to BCC risk have shown conflicting results. Antihypertensive treatment is fundamental in decreasing morbidity and death secondary to cardiovascular disease. On the other hand, skin cancer is a common disease with huge implications on quality of life and health economy. A careful study of these medications and their impact on skin cancer incidence is vital to make sound and reasonable recommendations on antihypertensive treatment.

Socioeconomic factors

Skin cancer risk has been shown to correlate with socioeconomic status. Evidence of this has been presented for both BCC, SCC, and MM. In an Irish study by Carsin et al., BCC was more common in areas with less deprivation and less common in areas where inhabitants had a lower educational level[39]. In another study, by Kiiski et al., a higher educational level increased the risk of being diagnosed with multiple BCC[123]. Meanwhile, in a Swedish survey study, individuals with a higher educational level described a higher tendency to use sunscreen. They also seemed to have a higher tendency to change their sun protective behaviour for the better[124]. Regarding MM, the differences depending on socioeconomic status seems to contrast with that of BCC. In a Swedish study, a lower educational level was related to a more advanced tumour stage at diagnosis and a worse prognosis[125]. In all, the findings might relate to differences in health care seeking behaviour. Individuals with a higher socioeconomic status might seek medical attention more frequently for abnormal skin lesions, while individuals with a lower socioeconomic status seek their physician later, with a more advanced tumour stage as a result. However, the increased incidence of BCC in individuals with higher socioeconomic status might also be related to differences in UV-exposure habits.

Diagnosis

The diagnosis of BCC is primarily based on clinical examination. The examination is in turn set on two pillars: visual- and dermoscopic inspection. Histopathologic diagnosis is used either postoperatively, to ensure diagnosis and free excision margins, or before treatment when diagnosis is unclear.

Clinical appearance

The clinical appearance of BCC is dependent on the subtype of tumour. In the following, we divide the different visual aspects of BCC in nodular, superficial, infiltrating, and morphoeiform BCC, in accordance with the Sabbatsberg criteria[26].

Nodular BCC (nBCC): This subtype corresponds to BCC type IA in the Sabbatsbergs method[26]. As the name implies, it is nodularly raised from the skin surface. It is well demarcated and pinkish to reddish in colour. Older tumours may ulcerate[22], see Figure 11.

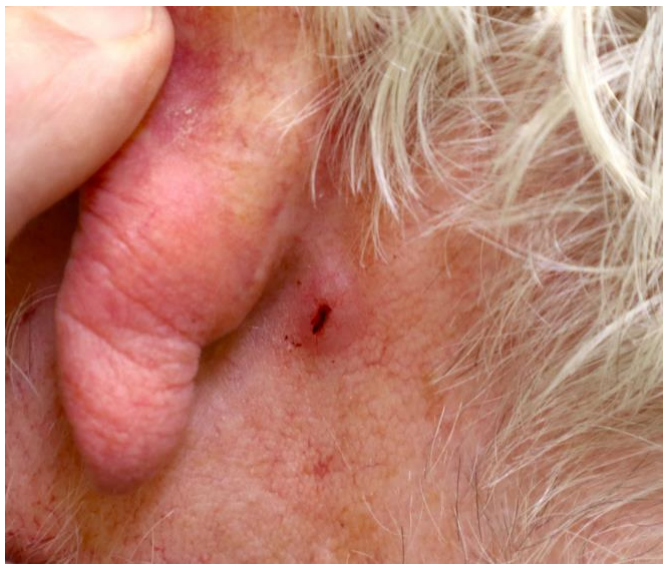

Figure 11. Nodular basal cell carcinoma (BCC type IA). *Photo: J. Kappelin. Published after patient consent.*

Superficial BCC (sBCC): This subtype corresponds to BCC type IB[26]. It is macular or slightly raised and without any obvious infiltration when palpated. It is reddish in colour and can be slightly scaly[22], see Figure 12.

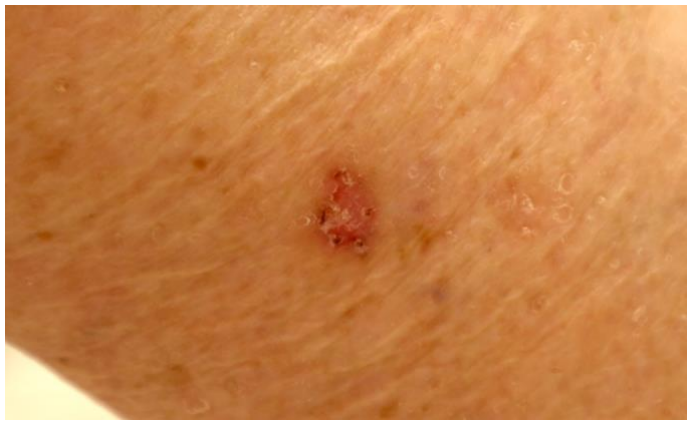

Figure 12. Superficial basal cell carcinoma (BCC type IB). *Photo: J. Kappelin*. *Published after patient consent.*

Infiltrating BCC: This subtype can have a quite varying clinical signature and corresponds, in the Sabbatsberg method, to BCC type II[26]. Its appearance can span from that of a nodular BCC to a more diffusely circumscribed tumour. Ulceration is more common, and the colour is often pink to red (Figure 13).

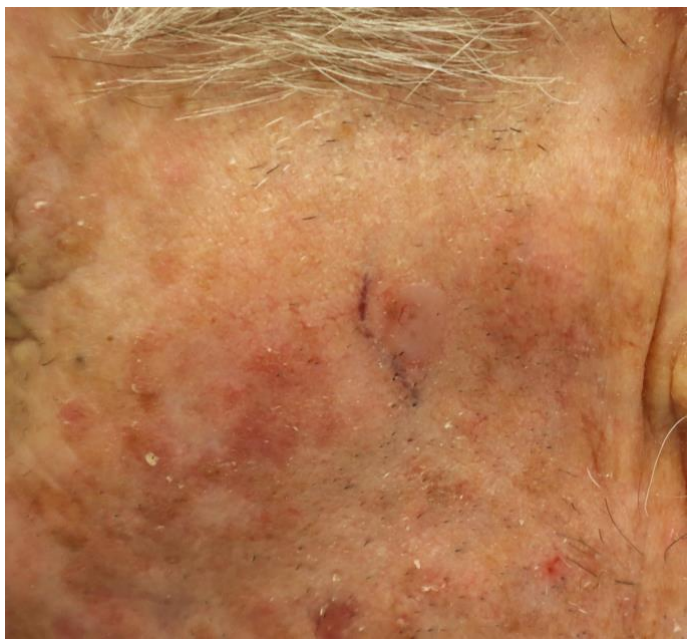

Figure 13. Infiltrating basal cell carcinoma (BCC type II). *Photo: J. Kappelin. Published after patient consent.*

Morphoeiform BCC: This tumour subtype corresponds to BCC type III[26]. The classic clinical feature involves a diffusely demarcated tumour. Its colour can span from white to pink. It can be ulcerated, alternatively it can develop as a discrete scar like lesion, avoiding detection (Figure 14). It is not uncommon for these tumours to become relatively large before the patient seeks medical attention.

Efforts have been made to simplify BCC classification and in a publication by Fernandez-Figueras et al, infiltrating and morphoeiform BCC was proposed to be collectively referred to as infiltrating BCC (iBCC)[25].

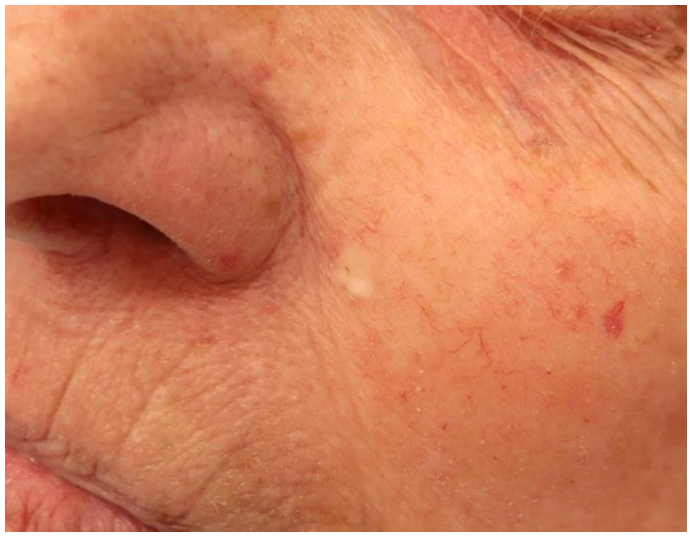

Figure 14. Infiltrating, morphoeiform basal cell carcinoma (BCC type III). *Photo: J. Kappelin. Published after patient consent.*

Pigmented BCC

BCC may demonstrate pigmentation, either visually obvious or by more discrete pigmented areas seen dermoscopically. In fact, heavily pigmented BCCs may at first glance mimic an atypic melanocytic lesion. Histopathologically, pigmentation occurs through the presence of benign melanocytes and phagocytosed melanin within the tumour[126]. Pigmented BCCs are more common in darker skin types[127, 128].

Dermoscopic features

Dermoscopy has grown to be a vital tool in the diagnosis of skin tumours, and BCC is not an exception. In a meta-analysis by Reiter et al., a pooled sensitivity of 91% and a specificity of 95% was presented. The same study showed that diagnostic accuracy increased with dermoscopy in comparison to purely visual,

non-dermoscopic evaluation[129]. Likewise, in a study on a Swedish cohort by Ahnlide et al., mandatory use of dermoscopy and specific training on dermoscopic features of BCC increased diagnostic accuracy for sBCC significantly[130].

The most common dermoscopic finding is known to be arborising vessels. This feature is primarily seen in nBCC and iBCC, while sBCC mostly displays short-fine telangiectasia. The second most common dermoscopic feature was in a review by Reiter et al. described to be shiny white lines. Furthermore, pigmentation can be presented as ovoid nests or globules (mainly in nBCC and iBCC) or leaf-like and spoke weel patterns (primarily in sBCC)[131]. Some of the dermoscopic findings seen in basal cell carcinomas are illustrated in Figure 15.

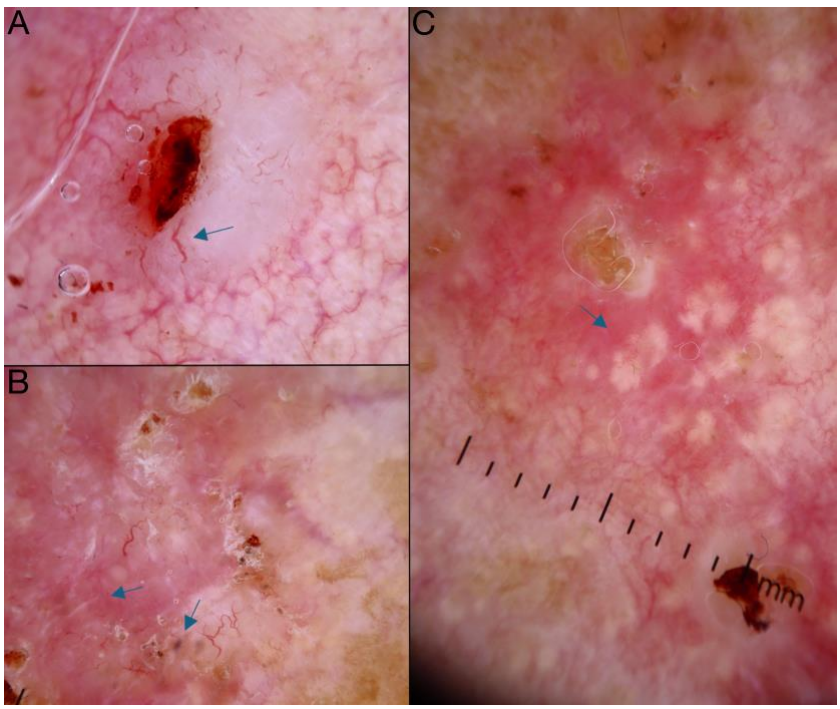

Figure 15. Dermoscopic findings in basal cell carcinomas. Picture A illustrates arborising vessels. In picture B, we see shiny white lines and globules. In picture C, fine telangiectatic vessels are seen. *Photo: J. Kappelin. Published after patient consent.*

Treatment

The choice of treatment for BCC is based on several factors. Small, low aggressive tumours might be treated with simple curettage, while large, highly aggressive tumours on high-risk areas in the face might need surgical excision with perioperative histological evaluation and margin control. In this chapter, I will

browse through the major treatment alternatives for localised (non-metastasised) tumours.

We will start by looking at different non-surgical alternatives. While the incidence of BCC is high and increasing, the need of cost-effective treatments with high cure rates are essential. Non-surgical treatments are often good alternatives in cases of low aggressive BCC.

Curettage alone

This treatment entails the removal of the tumour with a curette, scraping the tumour from the skin surface after local anaesthesia. The technique demands experience from the physician, while the recurrence risk is dependent on a thorough completion of the treatment. Curettage is used on low aggressive tumours and has been shown to achieve high cure rates of 90-96% after 5 years[132]. In a randomised single centre study from Sweden, results on sBCC after one year showed 96% cure rates in comparison to 100% after cryosurgery (no statistically significant difference). Meanwhile, they saw shorter wound healing times and good patient satisfaction[133]. However, despite showing promising results and good cosmetical outcome, this treatment modality seldom is recommended in treatment guidelines[78, 134].

Curettage and electrodesiccation (C & E)

This treatment combines the use of curettage with the subsequent use of electrodesiccation, burning the superficial part of the resulting ulceration and thereby adding in the destruction of potential BCC remnants. The treatment is usually repeated immediately after the first session, thus being performed in two cycles. C & E is used for low-risk tumours (low aggressive on low risk areas, such as on the torso) and has shown cure rates of 93 – 97% after 5 years[132]. It is mentioned as a recommended therapeutic option on low-risk tumours in European and American guidelines[78, 134]. However, the cosmetic outcome is described as inferior to that of surgical excision.

Cryotherapy

This treatment can be done either on its own, or after initial curettage and is included as recommended therapies of low-risk BCC tumours in European and American guidelines[78, 134]. The cryotherapy is achieved by freezing the tissue (the tumour or the ulcerated area after curettage) with liquid nitrogen (-196 °C). The freezing is continued until a predefined area around the tumour is frozen, the so-called lateral spread of freeze (or halo). This area is usually around 5 mm. During the freeze cycle, the tumour cells in the area are destroyed. Curettage and cryotherapy has cure rates of 97 – 99% after 5 years and cryotherapy without curettage also have shown good results[132]. Treatment below the knee is not recommended, due to the longer healing time in this area.

Photodynamic therapy (PDT)

In PDT, topical treatment with metyl-aminolevulinat (MAL) or 5-aminolevulinsyra (ALA) is administered to the tumour and to a few millimetres of healthy skin surrounding the tumour. A couple of hours after administration, the area is exposed to red light (ca 630 nm), which reacts with protoporphyrin IX in the skin, created because of an enzymatic process involving MAL or ALA. The amount of protoporphyrin is enriched in the tumour cells, while these cells to a lesser extent transform protoporphyrin IX to heme. In reaction with light, free oxygen radicals develop, destroying cell membranes. Because of the greater levels of protoporphyrins accumulated in the tumour cells, the destructive reaction is relatively selective for the tumour tissue[135]. The treatment is repeated after 1-2 weeks and an inflammatory response ensues, creating swelling and crusting before the area heals within 2-6 weeks[132].

PDT has been shown to be an effective treatment for sBCC. In a meta-analysis by Wang et al., a pooled estimate of complete clearence of 86% was presented. In the same study, no significant difference in complete clearance or recurrence rate between PDT, cryotherapy or topical treatment was found. However, PDT was significantly less effective in achieving total clearance in comparison to surgical excision[136]. PDT is a recommended treatment for sBCC and thin nBCC in international guidelines[78, 134].

Topical treatment

For sBCC, topical treatment with imiquimod is a potential treatment modality. Imiquimod acts through an immunomodulatory mechanism, stimulating inflammation at the tumour site. In a randomised controlled trial by Arits et al., imiquimod was shown to have a greater clearance rate for sBCC in comparison to PDT and after one year, 93% were tumour free in comparison to 87% among patients receiving PDT[137].

A possible alternative treatment of sBCC, however seldom used in Sweden, is 5-Fluorouracil (5-FU). This is a cytostatic medication used topically on the tumour. In the study by Arits et al., no significant difference in clearance rates was seen between 5-FU, imiquimod or PDT[137].

Simple surgical excision

Surgical excision has been considered the standard treatment, or gold standard, for BCC[138]. For low aggressive tumours on uncomplicated localisations, other treatment options are available and discussed above. However, surgical excision is still the mainstay of treatment regarding infiltrating tumours or when the tumour is in a sensitive area, where you wish to minimise risk of recurrence.

The objective of a simple surgical excision is the complete removal of the tumour with a safety margin to minimise the risk on an incomplete excision. Studies have

shown the risk of recurrence to be 26 – 38% after an incomplete excision[139-142]. Meanwhile, the recurrence risk has been estimated to 3 – 6% after a complete excision[139, 140]. The importance of a complete excision is further underlined by publications, stating that the risk of recurrence is increased after excision of already recurrent tumours[139, 143, 144]. Thus, surgical excision must be approached with care, considering possible factors that might increase risk of an incomplete excision.

Firstly, we must clarify what we mean with a complete surgical excision. The simple definition of this concept is the histopathological statement, made by the pathologist, that the margin of the surgical specimen is free from tumour cells. It does not consider whether the distance between the surgical margin and the lateral or deep edge of the tumour is narrow or wide. It is, merely, a yes/no – question.

To minimise risk of recurrence, you must bear in mind potential risk factors for an incomplete excision. These include histological subtype, where an aggressive growth pattern is related to an increased risk of positive surgical margins[145-147]. Furthermore, tumour localisation in the face-region as well as excision of recurrent tumours are related to incomplete excisions[139, 145-149]. The standard approach in minimising risk of an incomplete excision is by altering the safety margin with visually tumour free skin around the tumour at the time of surgery. International guidelines recommend a safety margin of 3 – 4 mm in low aggressive tumours and 5 – 15 mm in high aggressive tumours (depending on tumour size, localisation and so forth)[78].

An important factor to be aware of is the technique used in sectioning the specimen before histopathological evaluation. The standard technique, used in Sweden among others, is serial transverse cross-sectioning. In this technique, sections are made with a pre-planned interval (for example every 4 mm), Figure 16. Thereby, a large part of the surgical margin is never studied. In a study of 42 excised BCC tumours, serial transverse cross-sectioning only revealed a true positive surgical margin in 44% of cases, explaining why a tumour might recur even after a complete excision[150].

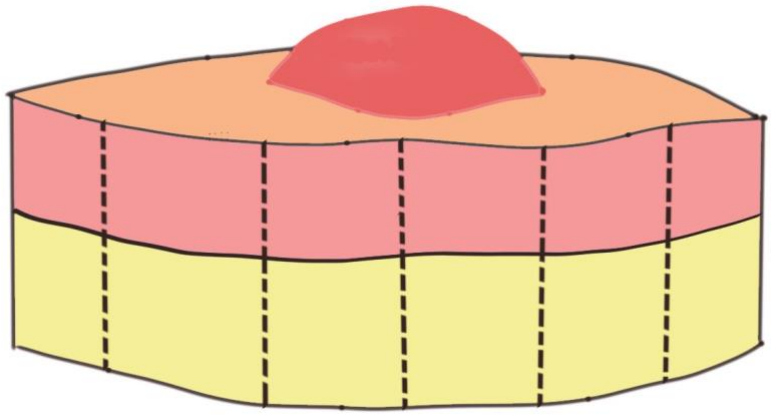

Figure 16. In transverse cross-sectioning, the surgical specimen is cut at specific intervals (the vertical, dashed lines). The tissue in between is not analysed. *Illustration by J. Kappelin.*

Mohs micrographic surgery (MMS)

The Mohs-technique was conceptualised by general surgeon Frederic Mohs during the 1930's[151]. Over time, the technique has been developed into what we use today. Today, MMS is the recommended surgical treatment for high-risk BCC tumours, including features such as aggressive growth pattern, large tumour size and critical tumour localisation (nose, periorbital region etc)[78, 134].

MMS differs somewhat in surgical approach, relative to simple surgical excision. In simple surgical excision, visually obvious tumour tissue is excised, together with a safety margin. The wound is closed directly after excision, generally making the procedure quite fast. The specimen is sent to the pathology office in a container with formalin, chemically fixating the tissue before preparing it for histopathological assessment. Information regarding diagnosis and tumour margins are obtained up to several weeks later. Conversely, in MMS, the visually obvious tumour is excised with a narrow margin, while carefully marking the edges of the specimen with a scalpel at pre-planned intervals (for example in every quarter of the circumference). The incision is made with a 45-degree angle to the skin surface. Afterwards, the wound is dressed. The specimen is fitted on a glass slide, while securing that the 45-degree edges are forced down on the slide, and frozen in a cryostat. Thin sections are taken parallel with the skin surface. These are stained with haematoxylin and eosin before being analysed in the microscope. The fact that the 45-degree edges of the specimen can be forced down on the glass slide and that sections are made parallel with the skin surface, enables the pathologist or surgeon to analyse the complete surgical margin (Figure 17). If

remaining tumour is found at, or close to, the surgical margin, a new surgical procedure is done, excising more tissue in the area where the tumour is deemed incompletely excised. This process is repeated until the tumour is completely cleared. At our clinic in Lund, the most common scenario is for the tumour to be cleared after two surgical stages, however occasionally as many as 4-6 stages may be necessary. In fact, like in simple surgical excision, earlier surgery increases the risk of complicated MMS, defined by the need of more surgical stages. In a single centre cohort study from our Mohs clinic at the Department of Dermatology, Skåne University Hospital, Lund, the risk for complicated MMS (≥3 stages) increased in tumours previously treated with >1 surgical excision[152]. This further emphasises the importance of choosing the appropriate treatment modality from the start.

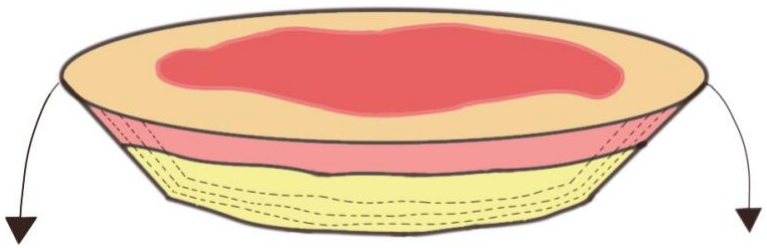

Figure 17. In Mohs surgery, the incision is made with a 45-degree angle, making it possible to fold down the edges to the glass slide and section the specimen horizontally (dashed lines). In this way, theoretically, 100% of the margins can be evaluated. *Illustration by J. Kappelin.*

There are a few benefits of MMS. Firstly, the possibility to analyse 100% of the surgical margin (at least in theory) gives an even more reassuring assessment of the tumour clearance. Secondly, by doing the histopathological evaluation perioperatively, the patient can be declared tumour free the same day. Thirdly, while the tumour can be judged as completely excised directly after completion of the excision, surgical reconstruction can be made without obvious limitations. This contrasts with simple surgical excision, where the wound must be closed without the benefit of a secured tumour free margin. In these cases, wound closure should be made with side-to-side closure, skin graft or secondary healing, to minimise orientational complications during a possible widened excision in the future. Conversely, after MMS, reconstruction can be done by the method opted to produce the best cosmetical and functional result, without regard to the previous tumour.

MMS has been shown to have low recurrence rates and a significantly lower risk of recurrence after excision of recurrent tumours, in comparison to simple surgical excision[138].

Meanwhile, MMS is also a labour intense and costly procedure. For this reason, in Sweden, the treatment is only used in highly aggressive, poorly demarcated, or recurrent tumours on sensitive locations in the head- and neck area. Furthermore, MMS is only used at three centres in our country: Lund, Gothenburg, and Stockholm. In order to optimise the surgical treatment of BCC, it is important to clarify which tumours would benefit from MMS and in which situations the less costly, simple surgical excision would suffice.

Prognosis

BCC has a very low risk of metastasis and death. Studies have shown the risk of metastasis to be 0.0028 – 0.55%[153]. Meanwhile, BCC tumours can grow invasively and destructively in the adjacent tissue, resulting in potentially high morbidity. Likewise, surgical treatment of large tumours, or of tumours with critical localisations can cause morbidity.

As mentioned earlier, tumour recurrence arises in 26 – 38% of cases after an incomplete excision[139-142]. The prognosis is considerably better after a complete excision, with only 3 – 6% of cases recurring[139, 140]. The main prognostic factor after first diagnosis of BCC is the risk of developing new primary tumours. It is well known that the risk of new tumours is increased in persons already diagnosed with BCC and in a study by Flohil et al, the cumulative risk of developing a new tumour within 5 years after first diagnosis was 29%[154]. A study by Ciazynska et al, where histopathological registries and medical records were investigated retrospectively, could show that there seem to be a continuity in the development of keratinocyte carcinoma in patients diagnosed with a first SCC or BCC. Patients first diagnosed with a SCC that developed a new primary KC was to a greater extent diagnosed with a new SCC, while persons diagnosed with a BCC primarily developed consecutive BCC tumours in case of a new primary tumour. In fact, they could also see that patients with a new BCC primarily developed the same histopathological subtype as in the first tumour[155]. However, as mentioned earlier, the true incidence of development of consecutive BCC tumours is difficult to appreciate, while multiple BCC tumours seldom are registered in national BCC registries.

Health economic aspects

This thesis focuses on the epidemiology of BCC and the surgical treatment of this common skin cancer. In 2021, almost 69 000 individuals were registered with an invasive cancer in the Swedish Cancer Registry[4]. During the same year, almost 70 000 new BCC tumours were registered in the Swedish BCC Registry. Thus, BCC is in terms of diagnostic volume corresponding to all other cancer forms combined in our country. Furthermore, studies have indicated the real incidence of

BCC in Sweden to be higher than we gather from the mere information of our national registry. It is safe to say that BCC is a serious and growing economic challenge for the Swedish health care. In a review by Gordon et al in 2015, Sweden and Denmark had the highest health care costs related to skin cancer after Australia and New Zealand, related to country size[156]. In a study by Tinghög et al in 2005, the total societal cost of skin cancer in Sweden was estimated at 142 million Euros, including health care costs and loss of production for MM, KC, nevi and actinic keratoses combined. KC stood for 25% of these, including costs related to SCC and BCC[157]. Some 20 years later, the incidence of MM, SCC and BCC have all increased and the added complex treatments of advanced or metastasised disease has produced an increase of health care costs and total societal costs that is likely to be vast.

Aims of the thesis

Basal cell carcinoma is the most common skin cancer and, even though the risk of metastasis and death is very low, the risk of morbidity in the affected patient as well as the health economic effects is substantial. The overall aim of this thesis was to *increase the knowledge of the incidence of BCC as well as potential and modifiable risk factors for the disease*, with the hope of contributing to the efforts of decreasing skin cancer incidence in the future. Furthermore, by increasing the knowledge about tumour- and patient specific factors that might affect outcome after surgical treatment, the aim was to contribute to a more cost- and treatment effective care. Ultimately, in the future, a decreasing BCC incidence and a more efficient use of healthcare resources would decrease societal costs and patient suffering.

Study I

How high is BCC incidence in Sweden today and how has it developed over time? How is the incidence distributed in different geographical regions in Sweden? How high is BCC incidence, related to patient (age and sex)- and tumour (subtype and localisation) specific factors?

Study II

How often does multiple BCC tumours develop in the same person? Is the risk for a new BCC affected by the number of earlier developed lesions? What is the cumulative risk for a new BCC tumour after the first lesion in men and women?

Study III

How is the risk of BCC affected by using antihypertensive medication?

Study IV

How often are BCC tumours incompletely excised after simple surgical excision? Is the risk of an incomplete surgical excision of BCC affected by tumour- or patient related factors?

Materials and methods

All four studies are based on data received from registries. The first three studies are based on national registry data and the fourth study on single centre-data from a local tumour registry. Below, I will start by introducing the different registries used in the thesis.

Registries

Studies I-III

The Swedish Basal Cell Carcinoma Registry

Sweden has, since 2004, a national registry of all histopathologically verified, primary BCC tumours, held by the National Board of Health and Welfare[27]. The registry includes multiple tumours in each affected person, regardless of subtype or tumour localisation. Recurrent tumours and previously biopsied tumours are not included.

The BCC tumours are registered by the diagnosing pathologist, aided by the information given by the treating clinician via the pathology referral. The clinician is thereby obliged to provide adequate information regarding tumour localisation, previous biopsies, or suspicions of tumour recurrence.

The registry contains information regarding personal identification number, diagnosing pathology laboratory, tumour site (including side of the body) and histological subtype according to the Sabbatsberg method[26] (BCC type IA, type IB, type II, type III and metatypical BCC). For tumours with a mixed growth pattern, the most aggressive growth pattern is registered. Information regarding city of residence is not available.

The National Prescribed Drug Register

The Prescription Registry, held by the National Board of Health and Welfare, was started in 2005 and contains information regarding all prescribed medications, retrieved by the patient from the pharmacy. The registry contains information regarding patient sex, age, and city of residence, as well as information regarding

the prescribed medication (ATC-code, name, strength, size of the prescribed medication package), information regarding the prescription (prescribed amount, including defined daily dose (DDD), date of prescription, and date of retrieval from the pharmacy), costs (for the patient and for the county) and information regarding prescribing department[158].

ATC-code

Every active substance of medications is assigned an ATC-code (Anatomical Therapeutic Chemical code). The codes are grouped in a specific classification system, maintained by the World Health Organization (WHO)[159], based on anatomical subgroup, therapeutic subgroup, pharmacological subgroup, chemical subgroup and chemical substance in five different levels of hierarchy.

DDD – Defined Daily Dose

The concept of DDD is defined by the WHO[159]. One DDD is the average maintenance dose per day for a specific medication, based on the main indication of that medication.

> *Example: If a specific drug is used to treat hypertension and the most commonly prescribed dose is 25 mg daily, then the DDD of that medication is 25 mg.*

Furthermore, the prescription registry contains information regarding pDDD (prescribed defined daily doses). This is defined as the number of DDDs that one prescription contains.

> *Example 1: If the earlier mentioned antihypertensive medication has been prescribed as a prescription for 100 pills with the strength of 25 mg, then the patient has been prescribed a total of 100 pDDD.*

> *Example 2: If the antihypertensive medication, mentioned above, has been prescribed as a prescription of 100 pills with the strength of 50 mg, then the patient has been prescribed a total of 200 pDDD.*

The National Patient Registry

The Patient Registry, held by the National Board of Health and Welfare, was originally established in 1964. This registry reached national coverage as of 1987, however at that time, the registry only consisted of data regarding inpatient care. In 2001, the registry was supplemented with information regarding specialised outpatient care. Information regarding visits in primary care is not included.

The registry includes information regarding the patient (age, sex, marital status, country of birth, city of residence), diagnosis, and the visit (time, place)[160].

The National Cancer Registry

The Swedish Cancer Registry, held by the National Board of Health and Welfare, was started in 1958 and contains all malignant tumours diagnosed in Sweden. Basal cell carcinoma, however, is not included in this registry but is registered separately (see above).

The registry contains information regarding personal identification number, sex, city of residence at diagnosis, diagnosing clinic, date of diagnosis, clinical and morphological diagnosis and localisation[161].

The National Cause of Death Registry

The Cause of Death Registry, held by the National Board of Health and Welfare, contains all deaths that has taken place in Sweden, regardless of whether the individual was a registered citizen in Sweden at the time of death. In this thesis, information regarding date of death was gathered from this registry[162].

The Longitudinal Integrated Database for Health Insurance- and Labour Market Studies (LISA)

This registry, kept by Statistics Sweden, holds information regarding demography, education, employment/unemployment, income, family, and workplace. The registry contains information regarding all citizens, 16 years and above. As of 2010, all 15-year-olds were included as well[163].

Swedish Total Population Registry

This registry, kept by Statistics Sweden, was started in 1968, containing information from the Swedish Tax Agency. The registry contains information regarding personal identification number, sex, age, address, residence, marital status, citizenship, country of birth, immigration, emigration etc[164].

Study IV

Local tumour registry, Helsingborg hospital

This registry was started in 2008 and contains information regarding all patients who have undergone surgical excision of a skin tumour (benign or malignant) at the Department of Dermatology, Helsingborg hospital. The registry contains information regarding patient age and sex as well as surgeon. It also contains information regarding the tumour (size, localisation, clinically suspected diagnosis, postoperative histopathological diagnosis) and postoperative information (complications, complete excision – yes/no).

The tumours are registered using a template for order of surgery, filled out by the diagnosing physician. This information is registered through the computerised

patients file system (Journalsystem Melior®, Siemens AB, Upplands Väsby, Sweden). Data is extracted, using the software program Qlik View® (QlikTech International AB, Lund, Sweden) and exported to Excel® (Microsoft corporation, Redmond WA, USA). By using the surgical notification system, virtually all patients undergone surgical excision at the department are included in the registry.

Study design, study populations, and methods

Study I

Design

The study was a nation-wide, registry-based, cohort study.

Population

All registered patients in the Swedish Basal Cell Carcinoma Registry during the years 2004 – 2017 were included in the study.

Methods

Data regarding patients (age, sex) and diagnosis (date and year, morphological subtype, localisation and diagnosing pathology department) was collected from the Swedish BCC Registry. While information regarding registered city of residence could not be collected from the registry, an approximation of residency was done by using the address of the diagnosing pathology laboratory. To minimise erroneous conclusions regarding residency, based on discrepancies between city of diagnosis and city of residence, the person was assigned residency to one of the six medical regions in Sweden, in which the diagnosing pathology department was located.

Incidence was presented, categorised by sex (male/female), age (<45 years, 45-64 years, 65-84 years and >84 years), subtype (BCC IA, IB, II, III, and metatypical cancer), tumour localisation (head and neck, trunk, upper limb, and lower limb), and region of residence (North, Middle, Stockholm, West, Southeast, and South).

Statistics

Incidence rates were calculated in relation to patient characteristics (age, sex, and region of residence) and tumour characteristics (morphological subtype and localisation) and were standardised to the European standard population of 2013 (EASR, 2013). EASR was calculated both as person-based incidence, based on number of registered persons each year, and tumour-based incidence, based on

number of new tumours registered each year. Standardised incidence ratios (SIR) were calculated when we wanted to compare incidence rates between groups.

Changes of incidence over time (trends) was calculated, using Poisson regression models, and was expressed as incidence rate ratios (IRR). IRR illustrated the annual relative incidence rate change as a positive decimal number, where a value over 1.0 equalled an annual increase in incidence rate.

> *Example: An IRR value of 1.2 equals an average, annual relative increase in incidence of 20% during the years 2004 - 2017.*

We used interaction models to analyse whether there was any difference in trends depending on sex, age, tumour site, or morphological subtype.

A 95% confidence interval (CI) was presented when relevant, and a p-value <0.05 indicated a significant difference between groups.

Cases with missing data were excluded from relevant analyses.

Statistical analyses were made in collaboration with a statistician at Clinical Studies Forum South and all analyses were performed in Stata SE14® (StataCorp LLC, College station, Texas, USA).

Incidence and standard population

Incidence is the number of events, such as diagnosed BCC tumours, that take place during a specific period (often for one year)[165]. Usually, incidence is presented as a proportion of events in a specific population, so that an incidence rate is described as:

$$incidence\ rate = \frac{number\ of\ events}{total\ population \times number\ of\ years}.$$

Normally, this rate is very small and is therefore reported as number of cases per 100 000 person-years to make it more presentable.

Incidence rates can be presented either as crude rates or adjusted rates. Crude rates are the number of people diagnosed with the disease for one year and divided by the number of inhabitants in the studied population (and multiplied with 100 000). This is an easy way to get a feel for the number of events in the population annually. It can be used if you just want to follow the incidence of a diagnosis in a specific population and you have no interest in comparing your numbers to another setting, such as another country or time period. However, if you want to compare the incidence rate of BCC in Sweden with the incidence rate in Australia, adjustment must be performed to account for the different population compositions in these countries. The main difference, and the most common to adjust for, is a difference in age distribution. If there is a greater proportion of

elderly people in one of the countries, the number of diagnosed cases of BCC might increase merely due to the age difference. The comparison would not be fair. For that reason, the incidence rate is adjusted to a standard population used for both countries. The age-adjusted incidence rate is calculated by first computing the crude incidence rate in each age category and multiplying it with a factor (age-specific weights) that is decided by the proportion of inhabitants in the standard population, belonging to that age category. After that you sum all these rates together and thereby get an age-adjusted incidence rate[166]. This rate is comparable between countries, without the risk of confounding by age, and thereby advisable to use in epidemiological studies, published in international journals.

Poisson regression

Poisson regression is a statistical method for analysing the number of events that takes place during a specific period, given that these events are independent of one another and that the time until the next event is not affected by the last. To use Poisson regression, the events that we are about to study (number of BCC diagnoses annually) must follow a Poisson distribution. This is a modified form of normal distribution that correlate the mean to a linear scale using the logarithm. By using Poisson regression analysis, we can calculate the event rate as an incidence rate and simultaneously calculate incidence rate ratios that help us analyse differences in incidence rate between different years.

Study II

Design

The study was a nation-wide, registry-based, cohort study.

Population

All registered patients in the Swedish Basal Cell Carcinoma Registry during the years 2004 – 2017 were included in the study.

Methods

Data regarding patients (age, sex) and diagnosis (date and year, morphological subtype, and localisation) was collected from the Swedish BCC Registry. Incidence was presented, categorised by sex (male/female), age (<45 years, 45-64 years, 65-84 years and >84 years), morphological subtype (BCC IA, IB, II, III, and metatypical cancer), and tumour localisation (head and neck, torso, upper limb, and lower limb).

Statistics

Number of affected persons with 1, 2, 3 or >3 BCC tumours was analysed and descriptively accounted for. Furthermore, distribution between different morphological subtypes and tumour localisations among individuals with a single or multiple registered BCC tumours was analysed and presented as numbers and percent. The proportion of registered tumours assigned to a specific subgroup or tumour localisation in BCC tumour no 2 was described in percent in relation to the corresponding characteristics in tumour no 1.

A univariate Cox-regression analysis was performed for three different scenarios: estimating Hazard Ratio (HR) for developing a new primary BCC tumour after the diagnosis of one, two or three previous tumours respectively. Participants were followed from diagnosis of the first, second or third tumour until the end of the study period on 31 December 2017. Censoring event was death. HR was presented together with a 95% confidence interval (CI). A p-value <0.05 was considered significant. Cumulative risk for development of a new primary BCC tumour was presented in Kaplan-Meier graphs.

Statistical analyses were made in collaboration with a statistician at Clinical Studies Forum South and all analyses were performed in R version 2.2.2 (R core team)[167].

Survival analysis

In this study, two forms of survival analyses have been used, the Kaplan-Meier method and the Cox-regression analysis. In both methods, the time to a specific event is measured, in this case the time to development of a new BCC tumour. To measure this, information regarding the study period is needed (i.e. the start date and the end date of the study period). Secondly, we also need information regarding whether any of the included cases have left the study during the study period (for example died), and the specific date that this happened. This is important for one specific reason. We do not want people who have left the cohort to continue contributing so called person-time and thereby altering the resulting risk estimates. These individuals are excluded (censored) from the cohort as of the date of death (for example).

Kaplan-Meier method

This method is used to depict survival over time in a specific population during a specific period. The method results in a graph, making it possible to illustrate how the events are distributed over time[168]. Are most of the new BCC diagnoses made in the beginning of the period or in the end? The method is however not capable to incorporate other variables to adjust the result, as in a multiple regression analysis. To do this, Cox-regression is used. Another drawback of this method is the

inability to compare two curves as to whether any differences between the two are statistically significant.

Cox-regression

Cox-regression analysis is a survival analysis, where possible predictors of the event at hand can be included to evaluate their effect on time to event. In study II, we study the outcome of a new BCC tumour in relation to predictors in the form of age and sex. As a result, we get a Hazard ratio (HR). The hazard rate is the likelihood that a given event will happen at a specific point in time, given that the event has not already happened. HR is the ratio between the Hazard rate in two different groups (for example between males and females). For the Cox-regression to be viable, the HR between the different groups must be proportionate through the entire study period. For example, HR between males and females should not be higher at the start of the study period in comparison to the end of the study period. This is referred to as the assumption of proportional Hazards[169].

Study III

Design

The study was a nation-wide, registry-based, case-control study.

Population

The study included all persons with a registered BCC tumour in the Swedish Basal Cell Carcinoma Registry during the years 2007 – 2017, assigned as cases. Furthermore, two controls per case, matched by age, sex and region of residence, were extracted from the Swedish Total Population Registry.

Methods

Data regarding patients (age, sex) and diagnosis (date and year, morphological subtype, and localisation) was collected from the Swedish BCC Registry. Using the Swedish personal identification number, data was linked to other relevant registries as follows. Data regarding prescribed medications in cases and controls (ATC-code, date of retrieval from the pharmacy, pDDD) was collected from the National Prescribed Drug Register. Information regarding the following medications was collected. *Exposure variables (antihypertensive medications):* single-agent thiazide diuretics and two variants (hydrochlorothiazide, HCTZ and bendroflumethiazide, BFTZ), thiazide-containing combination treatments and one variant (HCTZ + amiloride), ACEi and two variants (enalapril and ramipril), CCB and two variants (felodipine and amlodipine), ARB, and beta-blockers. *As confounding variables, the following were extracted:* metformin, statins, acetylsalicylic acid, loop-diuretics, amiodarone and selected immunosuppressive

medications. Additionally, data regarding co-morbidities (organ transplantation, MM, SCC, lymphoma, leukaemia, HIV, Gorlins syndrome, xeroderma pigmentosum, psoriasis, ischemic heart disease, heart failure, diabetes, and chronic renal failure) was extracted from the National Patient Registry and the National Cancer Registry. Data regarding socioeconomic factors (highest educational level and gross salary) was extracted from the LISA-registry.

Individuals who had undergone organ transplantation or who was diagnosed with HIV, Gorlins syndrome, xeroderma pigmentosum or psoriasis at any time before index date (first BCC diagnosis) were excluded. Individuals who had been diagnosed with MM, SCC, lymphoma, or leukaemia were also excluded, however only when last registered diagnosis was made within a time period of 10 years prior to the index date, since the risk of skin cancer in these groups is likely to decrease over time. Patients treated with any of a selection of systemic immunosuppressive medications (selective immunosuppressives, TNF-alfa-inhibitors, interleukin inhibitors, calcineurin inhibitors, and other immunosuppressives, such as azathioprine and methotrexate) for a duration of at least 100 pDDD prior to index date were also excluded (see Results section, Figure 21).

Prescriptions registered within a two-year lag-time prior to index date were excluded from the final analysis, to minimise potential surveillance bias and allow for potential biological impact of the medication to take effect. This was in line with the methodological approach in earlier studies[104, 105, 112].

BCC risk in relation to cumulative dose of the included antihypertensive medications was investigated, using the variable pDDD. Low use was defined as a cumulative dose of <2000 pDDD and high use as a dose of ≥2000 pDDD, corresponding to approximately 5.5 years of treatment on a standard dose. This approach has been used in earlier studies[104, 107].

Statistics

General data regarding exposure variables and confounding variables were presented with descriptive statistics. The odds of being diagnosed with BCC when treated with a specific antihypertensive medication were estimated, using conditional logistic regression analysis. When comparing ever-users with never-users, OR was presented with a 95% CI. Calculations were made with and without adjustments for co-medication (metformin, statins, acetylsalicylic acid, loop-diuretics, amiodarone), co-morbidity (ischemic heart disease, heart failure, diabetes, chronic kidney failure) and socioeconomic factors (highest educational level and gross salary). The association between cumulative dose and BCC risk was estimated, using conditional logistic regression analysis, presenting an OR in relation to the lowest dose interval as reference category.

Statistical analyses were made in collaboration with a statistician at Clinical Studies Forum South and all analyses were performed in R v 4.2.2[167].

Conditional logistic regression

In ordinary logistic regression analysis (see under Study IV below), the odds of developing a certain outcome, for example an incomplete excision, are compared between two groups in a binary variable, producing an odds ratio (OR). In that case, the groups are independent of one another. A person with a complete excision and a person with an incomplete excision do not have any known characteristics in common with each other. Conversely, in a matched case-control study, we would like to compare the odds of developing a certain outcome in cases relative to controls. In Study III, we look at the odds of being treated with a certain antihypertensive medication in BCC cases in comparison to controls without a BCC diagnosis. These two groups are matched by age, sex and region of residence and are thus not independent of one another. In these cases, conditional logistic regression should be used instead[170].

Odds ratio

Odds ratio is the ratio between the odds of a specific outcome in two different groups. The odds (O) of a specific outcome are defined as the likelihood (P) that a certain event (A) will occur divided by the likelihood that it will not occur.

$$O(A) = \frac{P(A)}{1 - P(A)}$$

To put it in another way, the odds of developing a BCC tumour equals the number of individuals with a BCC diagnosis divided by the number of individuals without a BCC diagnosis.

When the odds are "0", it means that the outcome cannot occur. When the odds are "1", it means that that the outcome has the same likelihood of happening as it has of not happening. The value of the odds can be infinitely high[165, 171].

Study IV

Design

The study was a registry-based, single centre, cohort study.

Population

All patients, undergone a simple surgical excision of a primary BCC at the Department of Dermatology, Helsingborg hospital, during the years 2008 – 2015.

Methods

At the Department of Dermatology at Helsingborg hospital, Sweden, all skin tumours (benign or malignant) are prospectively enrolled in a quality registry as part of the surgical notification, see separate paragraph. We retrospectively included all primary BCC tumours during the study period 2008 – 2015. All wide/secondary excisions as well as shave excisions were excluded. Tumours were included regardless of pre-operative histopathological examination.

Excisions were made according to current Swedish guidelines and recommendations, with a 3 – 4 mm surgical margin for small, low aggressive tumours (<2 cm) and high aggressive and large tumours with a margin of at least 5 mm. Most of the excisions were made by specialists and residents in dermatovenereology, while a proportion of tumours in the head- and neck area were excised by ENT-physicians (otorhinolaryngologists). In all instances, an experienced specialist in dermatovenereology was available to discuss tumour margins.

Histopathological examination was made with traditional serial cross-sectioning. A complete excision was defined as an excision with free margins at histopathological examination.

During the inclusion period, categorisation of morphological subtype was registered in two different ways. During 2008 – 2011, BCC tumours were registered as morphoeiform and non-morphoeiform respectively. During the years 2012 – 2015, the subtypes were registered according to Sabbatsberg method as BCC type IA (nodular BCC), BCC type IB (superficial BCC), BCC type II (infiltrating BCC) and BCC type III (morphoeiform BCC).

Statistics

Population characteristics were presented with descriptive statistics. The relation between a certain tumour characteristic and an incomplete excision was analysed, using Fisher's exact test, and presented as OR, with a 95% CI. Since multiple tests were performed, output of significance was adjusted according to the Bonferroni-Holm method. Multiple logistic regression analysis was made with subtype, localisation, and size of the tumour as well as sex and age of the patient as independent variables. A p-value <0.05 was considered significant. OR, together with a 95% CI was presented in relation to a fictional reference group, defined as a 70-year-old female with a 1 cm large nodular BCC localised on the face (not ear or nose).

Cases with missing data regarding tumour clearance or relevant predictors were excluded from analysis.

Statistical analyses were made partly by the author, Johan Kappelin, and partly by a statistician at Clinical Studies Forum South. All analyses were performed, using

R versions 3.6.0 and 3.6.1 (R Core Team[172]) and SPSS® (IBM®, Armonk, NY, USA).

Fishers exact test and Chi2-test

These tests are similar in their use, looking at independent categorical variables and its relation to one another. However, the Chi2-test are sensitive to a low number of cases. In situations with a low number of cases, such as when looking at the number of incompletely excised BCC type III on the nose, it is better to use Fishers exact test.

Regarding Chi2-test, values of categorical variables are compared between two independent groups, using a 2x2 cross table. To do this, the observed values in each group are required (for example the number of completely excised and the number of incompletely excised tumours among males and females), see Table 3.

Table 3. Observed values regarding complete and incomplete excisions in male and female individuals.

	Complete excision	Incomplete excision	Total
Male	a	b	$a+b$
Female	c	d	$c+d$
Total	$a+c$	$b+d$	$a+b+c+d$

You also need the expected values of the same variables (Table 4). These are calculated under the idea that each value should be proportionate to the ratio between the total in the group and the overall total in order for the null hypothesis to hold[171]. The observed values and the expected values are then used to calculate a p-value based on the Chi2-test.

Table 4. Expected values regarding complete and incomplete excisions in male and female individuals.

	Complete excision	Incomplete excision
Male	$\frac{(a+c)}{(a+b+c+d)} \times (a+b)$	$\frac{(b+d)}{(a+b+c+d)} \times (a+b)$
Female	$\frac{(a+c)}{(a+b+c+d)} \times (c+d)$	$\frac{(b+d)}{(a+b+c+d)} \times (c+d)$

Thus, while the expected values are based on approximations, they are imprecise in situations with low values (<5) in any of the cells with expected values. Conversely, the Fishers exact test use so called hypergeometric distributions to calculate the p-value. This is a more precise, but also a more complicated way to

perform the calculations and is therefore suitable when low values are present in any of the cells in the cross table[173].

Logistic regression

This is a regression model designed to be used for dichotomous variables, such as regarding complete excision (yes/no). This is to be compared to linear regression, where the dependent variable is continuous. By using a logarithmic transformation, an Odds ratio can be calculated. In a multiple logistic regression, multiple variables can be included in the analysis, in order to adjust for confounding variables[165].

Bonferroni correction

In every situation where you perform a statistical test, there is a risk for a type I-error (i.e. detecting a difference that does not exist). When many tests are performed, this risk increases. For example, in our study on incomplete excisions, the OR of an incomplete excision in relation to several different tumour subtypes and localisations is estimated. Since the significance level is set to 0.05 (below which an observed p-value is interpreted as statistically significant), it is expected that every 20th OR might be significant only by chance. Therefore, there is greater chance of a significant result, the more comparisons you do. To adjust for this, a so-called Bonferroni correction can be used. In the original Bonferroni method, the pre-defined significance level (often 0.05) is divided by the number of comparisons made, α/n. If you for example want to look at 10 different combinations of subtypes and tumour localisations, the new significance level should be 0.005 instead. In this way, we are more conservative in our interpretations of statistical significance and keep the total risk that we find a significant difference in any of the ten comparisons to 0.05.

In our study, we used the Bonferroni-Holm single step method instead. This method is somewhat less conservative but with a smaller risk of Type II-error (where a true difference exists, but we miss it). Instead of comparing all p-values to a new significance level of α/n, a stepwise correction is performed. All p-values are listed from the lowest to the highest in sequential order. The lowest p-value is compared to the original significance level divided by the number of comparisons made. The next p-value is compared to the significance level divided by the remaining number of comparisons and so forth. This can be depicted as follows:

$$\frac{\alpha}{n-i+1}$$

In this formula, i is the i^{th} smallest p-value. In a list of 10 different comparisons, the smallest p-value should be compared to a significance level of 0.005. The next p-value should be compared to a significance level of 0.0056 and so on[174].

Ethical approval

All four studies were approved by the Ethical Review Board, Lund (studies I-IV), and the National Ethical Review Authority, Sweden (study III). Ethical registration numbers are presented below. Further ethical considerations are discussed under the section *Methodological and ethical considerations* in the Discussion section for each of the included studies.

Study I

2017-378, and 2017-993.

Study II

2017-378, and 2017-993.

Study III

2017-378, 2017-993, 2021-01784, and 2022-02239-02.

Study IV

2011-195.

Results

Study I

During the years 2004 – 2017, 579 889 tumours in 447 070 individuals were registered in the Swedish BCC Registry. We chose to look closer at the year 2017, when 54 639 BCC tumours were diagnosed in 40 360 individuals. This year, the European age-standardised, person-based incidence rate (EASR, year 2013) was 387/100 000 in females and 423/100 000 person-years in males. The difference in incidence between the sexes was significant, with an SIR of 0.92 (CI 95%, 0.90 – 0.93). However, in the younger age-categories, crude incidence was higher among females, approximately up to an age of 64 years. The greatest difference between the sexes was recorded among the youngest (<45 years), where the incidence was almost twice as high among females, compared to males (SIR 1.93, CI 95% 1.72 – 2.17). Conversely, in the age group >84 years, incidence among females was just over half that of males (SIR 0.62, CI 95% 0.59 – 0.66). Overall, incidence was highest in the older age-categories, with the highest crude rates recorded in the age-group >84 years (2 887/100 000 in males and 1 796/100 000 in females).

Incidence was highest in the south of Sweden with person-based EASR of 742/100 000 person years and tumour-based rate of 1 040/100 000. Conversely, the lowest incidence was found in the north with a person-based EASR of 175/100 000 and a tumour-based rate of 230/100 000 (Figure 18).

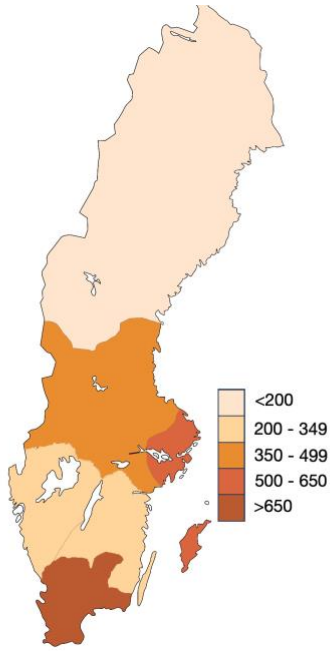

Figure 18. Regional differences in Sweden regarding occurrence of basal cell carcinoma in 2017. Person-based incidence. Age-standardised rate per 100 000 years, European standard population (2013).

Reference: Kappelin J, Green AC, Ingvar Å, Ahnlide I, Nielsen K. Incidence and trends of basal cell carcinoma in Sweden: a population-based registry study. Br J Dermatol. 2022 Jun;186(6):963-969. Adapted and republished after permission of Oxford University Press

Incidence trends

The incidence of BCC increased significantly, with an annual increase of 1.8% regarding person-based incidence (IRR 1.018) and 3.0% for tumour-based incidence (IRR 1.030) from a person-based incidence of 308/100 000 person-years in 2004 to 405/100 000 in 2017 and from a tumour-based incidence of 375/100 000 to 548/100 000. Incidence increased in both sexes, however more rapidly among women. Regarding tumour-based incidence, difference in annual increase was significant between the sexes (3.0% among females and 2.7% among males, $p<0.001$), Table 5. Incidence increased in all six geographical regions. The highest increase was found in the Middle, West, and South regions with over 4% annual increase of tumour-based incidence. The lowest was found in Stockholm and Southeast with an annual increase around 2%.

Table 5. Person-based and tumour-based incidence rate of basal cell carcinoma in relation to sex in Sweden, 2017, and annual relative change since 2004.

	FEMALE		MALE	
	Age-standardised rate (CI) [*]	**Annual relative incidence change (CI)** [**]	**Age-standardised rate (CI)** [*]	**Annual relative incidence change (CI)** [**]
Person-based rate	387.4 (382.0 – 392.7)	1.021 (1.020 – 1.022)	423.1 (417.2 – 429.1)	1.014 (1.013 – 1.015) [+]
Tumour-based rate	508.7 (502.6 – 514.8)	1.030 (1.029 – 1.031)	590.6 (583.6 – 597.7)	1.027 (1.026 – 1.027) [++]

[*] Age -standardised rate per 100 000 person years in 2017, European standard population (2013). Presented with a 95% CI.
[**] IRR, displaying annual relative change of person- and tumour-based incidence respectively for the years 2004-2017. IRR=1.030 corresponds to a 3% annual increase of incidence rate. Presented with a 95% CI.
[+] IRR differences between sexes p = 0.18.
[++] IRR differences between sexes p<0.001.
CI, confidence interval; IRR, incidence rate ratio.
Reference: Kappelin J, Green AC, Ingvar Å, Ahnlide I, Nielsen K. Incidence and trends of basal cell carcinoma in Sweden: a population-based registry study. Br J Dermatol. 2022 Jun;186(6):963-969. Adapted and republished with permission of Oxford University Press.

Tumour specific characteristics

The most common tumour localisation was the head/neck region (54%), followed by the trunk (31%), the lower limb (8%) and finally the upper limb (4%) being the least common in both sexes. Incidence increased in all tumour localisations. In females, the increase was steepest on the trunk and upper limb, while the increase was steepest on the limbs among males.

The most common morphological subtype was nodular BCC (type IA) and infiltrative BCC (type II) with an equal tumour-based incidence of around 150/100 000 among females and 190/100 000 among males. The least common subtype was morphoeiform BCC (type III) and metatypical BCC, the latter with a tumour-based incidence of 2.8/100 000 among females and 3.7/100 000 among males. All subtypes increased in incidence annually, however the increase was the steepest among aggressive subtypes. This difference in trend was significant.

Study II

In total, 579 890 tumours were registered in 306 551 individuals during 2004 – 2017 in the Swedish BCC Registry. Among male cases, 41% developed at least two primary tumours and in female cases, the corresponding proportion was 39%. In total, 40% of individuals in the registry developed more than one tumour. Among these, about half had two registered tumours and the rest had at least three tumours diagnosed. In individuals with one registered tumour, as well as in individuals with multiple diagnosed tumours, the most common tumour localisation was the head- and neck area and the most common morphological subtype was nodular BCC. However, the proportion of superficial BCC was somewhat bigger among individuals with multiple BCC in comparison to individuals with single BCC (21% vs 18%), while the opposite was true regarding nodular BCC (30% vs 38%). The second tumour diagnosed was more often of the same subtype and with the same localisation as the first tumour diagnosed in each individual (Table 6).

The median time to developing a new tumour was 1.4, 1.5 and 1.2 years for persons with one, two and three earlier BCC tumours respectively. Among persons with three earlier BCC, who developed a new tumour, 75% of new diagnoses were registered within 2.8 years (Table 7). The risk of developing a new primary BCC tumour increased significantly with age and was slightly higher in males in comparison to females as well as among people living the very south of Sweden (Table 8).

Table 6. Distribution of histological type of BCC 2004-2017 among second and third BCC based on histological type of first BCC. Illustrated with row percentages. Darker colours correspond to higher proportions.

Tumour 1	**Tumour 2**						
	Nodular BCC (%)	Superficial BCC (%)	Micronodular/Infiltrative BCC (%)	Morphoeiform BCC (%)	Metatypical BCC (%)	Information lacking (%)	Total, n
Nodular BCC	41.8	18.7	27.6	3.5	0.5	7.8	38 046
Superficial BCC	28.4	40.1	20.3	2.7	0.4	8.1	23 543
Micronodular/Infiltrative BCC	26.6	13.3	43.8	7.6	0.7	8.0	38 592
Morphoeiform BCC	15.9	8.6	36.0	29.2	0.8	9.5	7 431
Metatypical BCC	24.2	12.0	31.3	8.0	13.9	10.6	661
Information lacking	24.0	13.8	26.0	5.2	0.6	30.5	14 164

Tumour 1	**Tumour 2**					
	Head/Neck (%)	Trunk (%)	Upper limb (%)	Lower limb (%)	Information lacking (%)	Total, n
Head/Neck	79.0	12.3	1.8	3.0	4.0	67 713
Trunk	26.8	59.4	3.9	5.9	4.0	35 884
Upper limb	28.1	26.9	31.6	9.5	3.9	4 581
Lower limb	22.6	19.3	4.6	49.6	3.9	9 020
Information lacking	44.8	25.9	3.3	7.1	18.9	5 230

BCC, basal cell carcinoma.

Table 7. Baseline and follow-up characteristics divided by number of earlier diagnosed basal cell carcinoma (BCC) tumours.

	One earlier BCC		**Two earlier BCC**		**Three earlier BCC**	
	No new BCC	New BCC	No new BCC	New BCC	No new BCC	New BCC
Follow–up time, years (median [IQR]) *	4.5 [2.0, 7.9]	1.4 [0.3, 4.0]	3.7 [1.6, 6.6]	1.5 [0.4, 3.5]	2.9 [1.2, 5.3]	1.2 [0.4, 2.8]
Age at diagnosis (median [IQR])	71 [61, 80]	71 [62, 79]	74 [65, 82]	73 [65, 80]	76 [67, 83]	74 [66, 81]
Age categorised, n (%)						
<45	11 829 (5.4)	3 651 (4.1)	2 794 (3.4)	1 161 (2.9)	649 (1.9)	451 (2.2)
45–64	61 244 (28.0)	24 732 (28.1)	18 503 (22.5)	9 385 (23.4)	6 089 (17.7)	4 188 (20.0)
65–84	116 471 (53.3)	50 770 (57.7)	47 501 (57.7)	24 884 (62.1)	20 986 (61.1)	13 493 (64.4)
≥85	28 928 (13.2)	8 912 (10.1)	13 576 (16.5)	4 632 (11.6)	6 613 (19.3)	2 828 (13.5)
Sex, n (%)						
Male	102 414 (46.9)	43 366 (49.2)	39 861 (48.4)	20 370 (50.8)	17 341 (50.5)	11 016 (52.6)
Female	116 060 (53.1)	44 699 (50.8)	42 514 (51.6)	19 692 (49.2)	16 997 (49.5)	9 944 (47.4)
Region of residence ‡ (%)						
North	15 706 (7.2)	6 220 (7.1)	6 397 (7.8)	2 678 (6.7)	2 423 (7.1)	1 406 (6.7)
Middle Sweden	40 395 (18.5)	15 623 (17.7)	14 914 (18.1)	6 618 (16.5)	5 829 (17.0)	3 253 (15.5)
Stockholm-Gotland	48 848 (22.4)	20 038 (22.8)	18 123 (22.0)	9 320 (23.3)	7 824 (22.8)	4 973 (23.7)
West	36 763 (16.8)	13 680 (15.5)	13 165 (16.0)	5 978 (14.9)	5 280 (15.4)	3 050 (14.6)
Southeast	22 544 (10.3)	9 209 (10.5)	8 894 (10.8)	4 190 (10.5)	3 618 (10.5)	2 278 (10.9)
South	54 218 (24.8)	23 295 (26.5)	20 882 (25.3)	11 278 (28.2)	9 364 (27.3)	6 000 (28.6)
Total, n	218 474	88 065	82 375	40 062	34 338	20 960

* Median time of follow-up among individuals with and without diagnosis of new primary tumour depending on number of earlier BCC diagnoses, depicted together with interquartile range.
‡ Region of residence, defined by the medical region in which the diagnosing pathology laboratory was located, ordered from north to south.
BCC, basal cell carcinoma; IQR, interquartile range; n, number.

Table 8. Hazard ratio for developing a new primary basal cell carcinoma (BCC) tumour, depending on number of earlier diagnosed tumours, estimated using univariate Cox regression analysis.

Variable	One earlier BCC HR (95% CI) [§]	Two earlier BCC HR (95% CI) [§]	Three earlier BCC HR (95% CI) [§]
Age (years)			
<45	0.62 (0.60–0.64)	0.66 (0.62–0.70)	0.86 (0.78–0.94)
45–64	0.80 (0.79–0.81)	0.82 (0.80–0.84)	0.92 (0.89–0.95)
65–84	1.00 (Ref.) [*]	1.00 (Ref.) [*]	1.00 (Ref.) [*]
≥85	0.99 (0.97–1.01)	0.92 (0.89–0.95)	0.91 (0.87–0.95)
Sex			
Male	1.00 (Ref.) [*]	1.00 (Ref.) [*]	1.00 (Ref.) [*]
Female	0.89 (0.88–0.90)	0.87 (0.85–0.89)	0.90 (0.87–0.92)
Region of residence [‡]			
North	1.03 (1.00–1.06)	0.87 (0.84–0.91)	0.99 (0.93–1.05)
Middle Sweden	0.99 (0.98–1.02)	0.94 (0.91–0.97)	0.98 (0.94–1.03)
Stockholm–Gotland	1.00 (Ref.) [*]	1.00 (Ref.) [*]	1.00 (Ref.) [*]
West	0.97 (0.95–0.99)	0.95 (0.92–0.98)	1.00 (0.96–1.05)
Southeast	1.03 (1.00–1.06)	0.94 (0.91–0.97)	1.00 (0.95–1.05)
South	1.08 (1.06–1.10)	1.08 (1.05–1.11)	1.07 (1.03–1.11)

[§] Hazard ratio (HR) for developing a new primary tumour after diagnosis of one, two, or three earlier BCC tumours, in comparison to the reference category (ref). Numbers are presented with a 95% confidence interval (CI).
[*] Differences within the group was significant, with a p-value < 0.05.
[‡] Region of residence, defined by the medical region in which the diagnosing pathology laboratory was located, ordered from north to south.
BCC, basal cell carcinoma; HR, hazard ratio; CI, confidence interval; ref, reference category.

The cumulative risk of developing a new primary BCC within 5 years after first diagnosis was approximately 27% in females and 30% in males (Figure 19). After three previous BCCs, the cumulative risk increased to approximately 43% in females and 48% in males (Figure 20). The cumulative risk of developing a consecutive BCC was highest among individuals aged 65-84 years and lowest among the youngest.

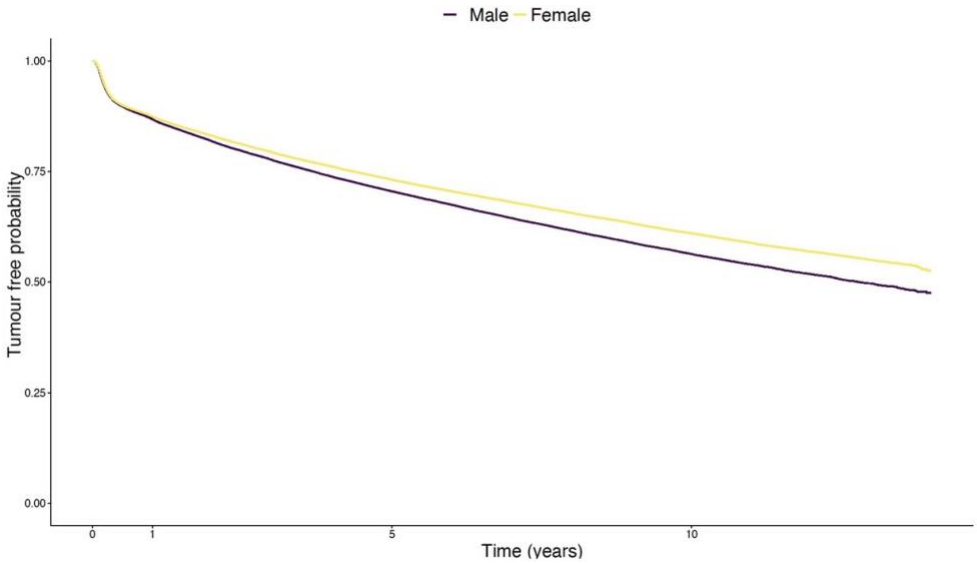

Figure 19. Cumulative risk of being diagnosed with a new primary BCC tumour after being diagnosed with one earlier tumour, divided by sex. Presented in a Kaplan-Meier graph.

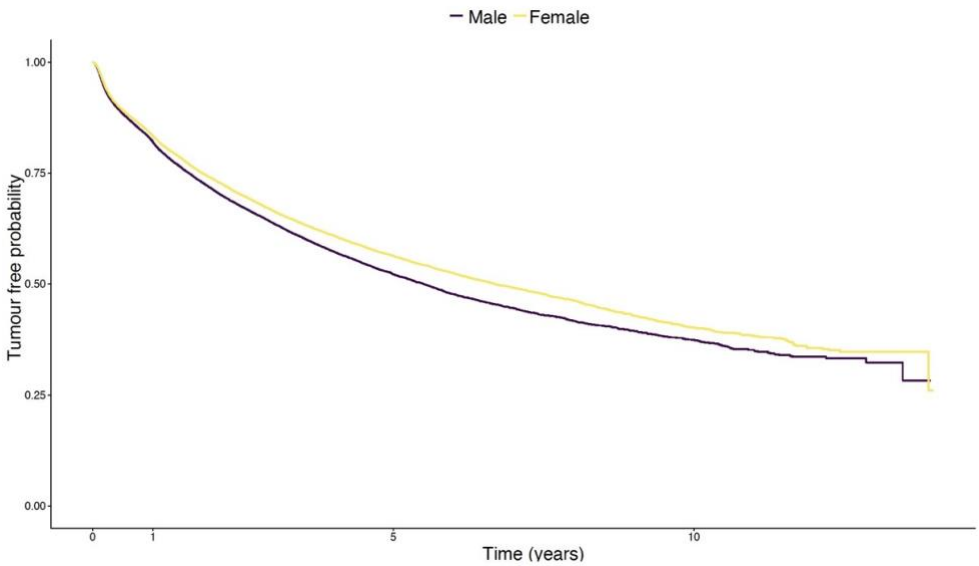

Figure 20. Cumulative risk of being diagnosed with a new primary BCC tumour after being diagnosed with three earlier tumours, divided by sex. Presented in a Kaplan-Meier graph.

Study III

After exclusions, 133 539 individuals with first diagnosis of primary BCC (cases) were included in the study (Figure 21). Additionally, 257 849 matched controls without registered diagnosis of BCC were included. The proportion of people with ischemic heart disease, heart failure and diabetes were slightly lower in cases than in controls. The proportion of people with a college/university degree or a post graduate degree was higher among cases than controls, while the opposite was true regarding proportion of people with a high school degree or pre-high school degree as highest educational level. Similarly, the proportion of people with a higher annual gross salary was higher among cases in comparison to controls.

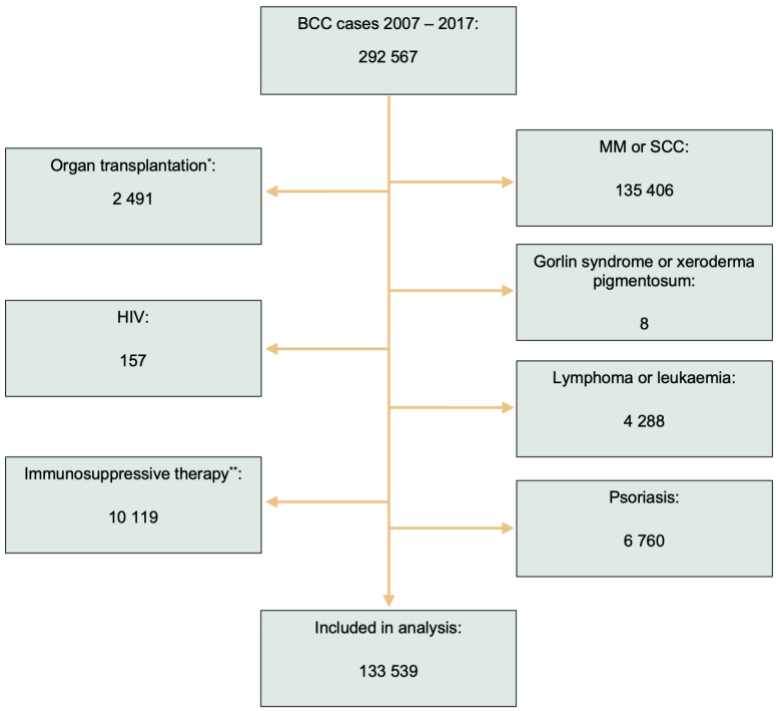

Figure 21. Number of exclusions among basal cell carcinoma cases in each exclusion category.

* Cases undergone solid organ transplantation.

** Including selective immunosuppressives, TNF-alfa inhibitors, interleukin inhibitors, calcineurin inhibitors and other immunosuppressives such as azathioprine and methotrexate.

BCC, basal cell carcinoma, HIV, human immunodeficiency virus; MM, malignant melanoma; SCC, squamous cell carcinoma.

In the adjusted conditional regression model, several of the included antihypertensive medications were associated with an increased BCC risk. These included ARB (OR 1.09, CI 95% 1.06 – 1.11), CCB (OR 1.09, CI 95% 1.07 – 1.11) and beta-blockers (OR 1.07, CI 95% 1.05 – 1.09). Thiazide-containing combinations were also associated with an increased BCC risk (OR 1.09, CI 95% 1.07 – 1.12), while single-agent thiazides were not. Individuals treated with HCTZ + amiloride combinations also had a significantly increased risk of BCC (OR 1.09, CI 95% 1.05 – 1.12). Regarding ACEi, a slight but significantly decreased BCC risk was detected (OR 0.98, CI 95% 0.96 – 1.00), Table 9.

Table 9. Effect of exposure variable (thiazide diuretics, ACEi, ARB, CCB and beta-blockers) on the development of basal cell carcinoma, calculated by conditional logistic regression.

	OR (95% CI)‡	p-value	Adjusted OR§ (95% CI)‡	p-value
Thiazide diuretics (single-agent)	1.00 (0.97-1.03)	0.954	1.02 (1.00-1.05)	0.094
HCTZ	0.99 (0.94-1.04)	0.647	1.02 (0.97-1.07)	0.447
BFTZ	1.01 (0.98-1.04)	0.648	1.03 (1.00-1.06)	0.079
Thiazide-containing combinations	1.06 (1.03-1.08)	<0.001*	1.09 (1.07-1.12)	<0.001*
HCTZ + Amiloride	1.07 (1.03-1.10)	<0.001*	1.09 (1.05-1.12)	<0.001*
ACEi	0.91 (0.89-0.92)	<0.001*	0.98 (0.96-1.00)	0.038*
Enalapril	0.92 (0.90-0.94)	<0.001*	0.98 (0.96-1.00)	0.130
Ramipril	0.88 (0.85-0.92)	<0.001*	0.97 (0.93-1.01)	0.094
ARB	1.05 (1.02-1.07)	<0.001*	1.09 (1.06-1.11)	<0.001*
CCB	1.03 (1.01–1.05)	0.003*	1.09 (1.07–1.11)	<0.001*
Amlodipine	1.01 (0.99–1.04)	0.272	1.07 (1.04–1.10)	<0.001*
Felodipine	1.03 (1.01–1.06)	0.013*	1.08 (1.05–1.11)	<0.001*
Beta-blockers	1.00 (0.98–1.02)	0.981	1.07 (1.05–1.09)	<0.001*

‡Odds ratio (OR) for the development of basal cell carcinoma in relation to use of antihypertensive medication. Presented with a 95% confidence interval (CI).
§Adjusted for co-medication (loop-diuretics, amiodaron, acetyl salicylic acid, statins, metformin), co-morbidity (ischemic heart disease, heart failure, diabetes, chronic kidney failure) and socioeconomic status (gross salary, and highest educational level).
*p-value <0.05 indicates a significant effect of the exposure variable on the odds of developing a basal cell carcinoma, given the matching strata.
OR, odds ratio; CI, confidence interval; HCTZ, hydrochlorothiazide; BFTZ, bendroflumethiazide; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers.

Regarding cumulative dose, the BCC risk was significantly increased after high use (≥2000 pDDD) with thiazide-containing combinations (OR 1.32, CI 95% 1.18 – 1.48) or the CCB variant amlodipine (OR 1.17, CI 95% 1.03 – 1.33), Table 10.

Table 10: Association between antihypertensive medication and the development of basal cell carcinoma, comparing low use (<2000 daily doses) with high use (≥2000 daily doses), calculated with conditional logistic regression with low use as reference.

	Cumulative dose (pDDD)[+]	OR (95% CI) [‡]	p-value	Adjusted OR[§] (95% CI) [‡]	p-value
Thiazide diuretics (single-agent)	<2000	-	-	-	-
	≥2000	1.00 (0.87-1.16)	0.990	1.01 (0.87-1.17)	0.940
HCTZ	<2000	-	-	-	-
	≥2000	0.78 (0.43-1.42)	0.421	0.76 (0.39-1.48)	0.415
BFTZ	<2000	-	-	-	-
	≥2000	0.91 (0.76-1.10)	0.327	0.93 (0.77-1.12)	0.427
Thiazide-containing combinations	<2000	-	-	-	-
	≥2000	1.31 (1.18-1.47)	<0.001[*]	1.32 (1.18-1.48)	<0.001[*]
HCTZ + Amiloride	<2000	-	-	-	-
	≥2000	1.13 (0.89-1.44)	0.302	1.13 (0.88-1.46)	0.326
ACEi	<2000	-	-	-	-
	≥2000	0.98 (0.92-1.04)	0.549	1.01 (0.95-1.08)	0.713
Enalapril	<2000	-	-	-	-
	≥2000	0.98 (0.90-1.07)	0.677	1.01 (0.92-1.10)	0.855
Ramipril	<2000	-	-	-	-
	≥2000	0.86 (0.67-1.11)	0.258	0.85 (0.65-1.11)	0.243
ARB	<2000	-	-	-	-
	≥2000	1.04 (0.94-1.15)	0.474	1.07 (0.96-1.19)	0.209
CCB	<2000	-	-	-	-
	≥2000	1.04 (0.97-1.11)	0.238	1.07 (1.00-1.14)	0.068
Amlodipine	<2000	-	-	-	-
	≥2000	1.15 (1.01-1.30)	0.032[*]	1.17 (1.03-1.33)	0.019[*]
Felodipine	<2000	-	-	-	-
	≥2000	0.96 (0.84-1.10)	0.565	0.97 (0.84-1.12)	0.663
Beta-blockers	<2000	-	-	-	-
	≥2000	1.00 (0.93-1.06)	0.874	1.05 (0.98-1.12)	0.199

[+]Cumulative dose, depicted as number of prescribed defined daily doses (pDDD).
[‡]Odds ratio (OR) for developing basal cell carcinoma in individuals treated with ≥2000 pDDD in comparison to individuals treated with <2000 pDDD, defined as reference. Presented together with 95% confidence intervals (CI).
[§]Odds ratio (OR) for developing basal cell carcinoma in individuals treated with ≥2000 pDDD in comparison to individuals treated with <2000 pDDD, adjusted for co-medication (loop-diuretics, amiodaron, acetyl salicylic acid, statins, metformin), co-morbidity (ischemic heart disease, heart failure, diabetes, chronic kidney failure) and socioeconomic status (gross salary, and highest educational level).
[*]p-value <0.05 indicates a significant effect of the exposure variable on the odds of developing a basal cell carcinoma, given the matching strata.
pDDD, Prescribed defined daily dose; OR, Odds ratio; CI, Confidence interval; HCTZ, hydrochlorothiazide; BFTZ, bendroflumethiazide; ACEi: Angiotensin-converting enzyme inhibitor; ARB, Angiotensin II receptor blocker; CCB, Calcium channel blocker.

After further categorising cumulative dose, a dose-dependent relationship was detected for thiazide-containing combinations, with the highest risk occurring among users of >4000 pDDD (OR 2.15, CI 95% 1.28 – 3.63). ARB had an increased risk after use of >6000 pDDD (OR 1.32, CI 95% 1.01 – 1.72), however a clear dose-dependent relationship among the other dose categories was otherwise not detected in this medication.

Study IV

During 2008 – 2015, 11 151 surgical excisions were performed at the Department of Dermatology, Helsingborg hospital, Sweden. After exclusions of tumours other than BCC, widened excisions and cases with missing relevant data, 3 911 excisions were included in the study. Of these, 579 excisions were made by ENT-physicians and the remainder by dermatovenereologists. Among included cases, 51% of tumours were treated in females and 49% in males. Overall, 4.6% of excisions made during the study period were incomplete.

Tumour localisation

On the torso and the extremities, the proportion of incomplete excisions was very low (1.2 – 1.8%). Meanwhile, the highest proportion of incomplete excisions was found on the surgically more sensitive areas nose and ear (20.3 and 23.7% respectively) when all morphological subtypes were included.

Tumour subtype

When looking at the entire study period, separating non-morphoeiform BCC from morphoeiform BCC, the proportion of incomplete excisions was 3.8 and 30.6% respectively. The odds of an incomplete excision were 11 times higher for morphoeiform BCC in comparison to non-morphoeiform BCC and the difference was statistically significant (OR 11.2, CI 95% 7.1-17.4).

In the subgroup analysis of the four different morphologic subtypes according to the Sabbatsberg method, during the period 2012 – 2015, the proportion of incomplete excisions in low aggressive BCC, nodular and superficial, was 1.1 and 2.1% respectively. Meanwhile, the proportion of infiltrating and morphoeiform BCC was 7.5 and 26.5% respectively. The odds of an incomplete excision were significantly higher in infiltrative and morphoeiform BCC in comparison to nodular BCC (OR 7.1, CI 95% 3.7-13.8 and OR 31.6, CI 95% 14.7-68.2 respectively).

Subtype and localisation

When further comparing the different morphological subtypes on different anatomical localisations, the lowest proportion of incomplete excisions was found

in non-morphoeiform BCC on the torso (0.5%). Meanwhile, the proportion of incomplete excisions regarding morphoeiform BCC on the nose and ear was 61.5% and 50% respectively (Table 11).

Table 11. Rates of incomplete excisions during the whole study period, 2008-2015, divided by tumour localisation and histopathological diagnosis.

Tumour localisation	***Histological diagnosis***	***Excisions, n***	***Incomplete excisions, % (CI)*** [§]	***OR (CI)*** [‡]
Face (ear and nose excluded) p<0.001 [**]	Non morphoeiform BCC	1369	5.6 (4.4–6.8)	1.0 (ref)
	Morphoeiform BCC	55	29.1 (18.2–41.9)	7.0 (3.7-13.1) [*]
Nose p=0.001 [**]	Non morphoeiform BCC	145	16.6 (11.1–23.2)	3.4 (2.1-5.5) [*]
	Morphoeiform BCC	13	61.5 (34.8–84.1)	27.2 (8.7-85.2) [*]
Ear p=0.14	Non morphoeiform BCC	53	20.8 (11.4–32.9)	4.5 (2.2-9.0) [*]
	Morphoeiform BCC	6	50 (15.6–84.4)	17.0 (3.4-85.7) [*]
Scalp p>0.99	Non morphoeiform BCC	156	5.1 (2.4–9.3)	0.9 (0.4-1.9)
	Morphoeiform BCC	2	0 (NA)	0
Neck p=0.27	Non morphoeiform BCC	176	4.0 (1.7–7.5)	0.7 (0.3-1.6)
	Morphoeiform BCC	7	14.3 (0.9–49.4)	2.8 (0.3-23.9)
Torso p<0.001 [**]	Non morphoeiform BCC	1147	0.5 (0.2–1.1)	0.1 (0.04-0.2) [*]
	Morphoeiform BCC	26	30.8 (15.4–49.7)	7.6 (3.2-17.9) [*]
Extremities p=0.18	Non morphoeiform BCC	706	1.6 (0.8–2.8)	0.3 (0.1-0.5) [*]
	Morphoeiform BCC	12	8.3 (0.2–38.5)	1.5 (0.2-12.1)
Missing data		38		
BCC (total)		3911	4.6 (4.0–5.4)	

[§] Proportion of incomplete excisions, presented with a 95% confidence interval (CI).
[‡] Odds Ratio (OR) for an incomplete excision in relation to tumour subtype and localisation is presented, together with a 95% CI. OR is related to the rate of incomplete excisions among non morphoeiform BCC located on the face (ear and nose excluded), which was defined as reference group.
[*] Significant result. This signifies a significant difference in rate of incomplete excisions in comparison to the reference group, p<0.05, adjusted according to Bonferroni-Holm.
[**] There was a significant overall difference in rate of incomplete excision dependent on tumour subtype on this localisation.
BCC, basal cell carcinoma; n, number; CI, confidence interval; OR, odds ratio.
Reference: Kappelin J, Nielsen K, Nilsson F, Bjellerup M, Ahnlide I. Surgical treatment of basal cell carcinoma: a case series on factors influencing the risk of an incomplete primary excision. J Eur Acad Dermatol Venereol. 2020 Nov;34(11):2518-2525. Adapted and reprinted with permission of Journal of the European Academy of Dermatology and Venereology.

When performing a multiple logistic regression analysis on patient- and tumour specific factors; superficial, infiltrating and morphoeiform BCC was related to a significantly increased risk of an incomplete excision in comparison to the

reference group (70-year-old female with a 1 cm large nodular BCC on the face, ear, and nose exluded). Furthermore, tumour localisation on the nose and ear had a significantly increased risk of an incomplete excision, while localisation on the torso and extremities had a significantly lower risk. The odds for an incomplete excision increased by 3% for every extra year of patient age. Furthermore, the odds increased significantly by increase in tumour size (Table 12).

Table 12. Multiple logistic regression analysis of patient and tumour specific variables for excisions performed during the years 2012-2015.

	Odds (CI)	**OR (CI)** [§]	**p-value** [‡]
Reference group [a]	0.02 (0.01-0.04)		<0.001 [*]
Male sex		0.5 (0.9-1.4)	0.56
Age		1.03 (1.0-1.1) [b]	0.02 [*]
Tumour subtype			
Superficial BCC		2.9 (1.0-7.8)	0.04 *
Infiltrating BCC		4.2 (2.1-8.3)	<0.001 [*]
Morphoeiform BCC		18.2 (8.0-41.6)	<0.001 [*]
Tumour localisation			
Extremities		0.4 (0.2-0.9)	0.02 [*]
Torso		0.1 (0.0-0.2)	<0.001 [*]
Neck		1.1 (0.4-2.5)	0.90
Scalp		1.5 (0.6-3.9)	0.42
Nose		4.9 (2.4-10.1)	<0.001 [*]
Ear		4.0 (1.4-11.1)	0.01 [*]
Ln (Tumour size in cm) [c]		2.4 (1.5-4.1) [d]	0.001 [*]

[§] Odds Ratio (OR) for an incomplete excision in relation to the reference group (intercept) is presented, together with a 95% confidence interval (CI).
[‡] Significance is presented as p-values. Significance level: p<0.05.
[a] Reference group includes female sex, age 70 years, tumour size 1 cm, nodular tumour subtype and facial localisation (ear and nose excluded).
[b] OR for incomplete excision related to age showed an increased odds for an incomplete excision for every year of increased age.
[c] This correspond to the $\log_e$ of the tumour size in cm.
[d] OR for incomplete excision related to tumour size showed an increased likelihood for an incomplete excision for every log-cm of increased size.
[*] Significant p-value.
CI, confidence interval; OR, odds ratio; BCC, basal cell carcinoma; Ln, natural logarithm; cm, centimetre.
Reference: Kappelin J, Nielsen K, Nilsson F, Bjellerup M, Ahnlide I. Surgical treatment of basal cell carcinoma: a case series on factors influencing the risk of an incomplete primary excision. J Eur Acad Dermatol Venereol. 2020 Nov;34(11):2518-2525. Adapted and reprinted with permission of Journal of the European Academy of Dermatology and Venereology.

Discussion

That basal cell carcinoma is a common skin cancer in fair-skinned people is not a secret. Exactly how common, however, has been difficult to elucidate. To maintain a good, manageable, and plannable national health economy, a good knowledge of the present health care challenges is essential. How should the limited resources be dispersed to identify disease as efficiently as possible, to treat as many as possible and to prevent as much disease as possible? Due to the inherent flaws in the registration system of BCC historically, a pivotal part of health care planning has been lacking. Before the start of the Swedish BCC Registry, sound knowledge of the presence of this tumour form was difficult, if not impossible, to obtain without time consuming cohort studies.

This thesis is based on three pillars: *incidence of BCC in Sweden, possible risk factors for BCC in Sweden and outcome of our most common treatment form, simple surgical excision*. In this triad of scientific questions, I scrutinise a sample of the ground blocks that are pivotal to understand when prioritising national health care: current incidence and trends, possible risk factors essential for prevention and the planning of efficient management and treatment of the diagnosed patient.

Study I

Methodological and ethical considerations

The use of the Swedish BCC Registry enabled us to study all histologically verified, primary BCC tumours in Sweden during our study period of 14 years. This is a rare opportunity, acknowledging the fact that national registration of BCC is a rarity world-wide. By using this source of data, we were able to estimate an incidence of BCC that is likely to be closer to the truth than many similar studies from other countries. With this said, it is important to discuss the source of the data, what it includes and its possible deficiencies. Only then, we can appreciate what the resulting incidence numbers tell us about the true BCC incidence in Sweden.

As mentioned, the BCC Registry entails all histologically verified, primary BCC tumours in Sweden. Since the diagnosing pathologist is responsible for reporting the tumour to the registry, it is important for the clinician to inform the pathologist on whether the tumour is primary or a recurrence and whether the tumour has been biopsied earlier. In cases where this information is not offered, inaccurate registration may follow (for example double registration). This is a likely but probably infrequent error in the registry that is difficult to further quantify. Whether this is a potential source of bias is less obvious. For such a double registration to be a cause of bias, there should be a difference in the frequency of double registration related to patient- or tumour factors. For example, the clinician might omit information regarding earlier biopsies more often in a certain subtype or in individuals of a certain age. This is not likely. The tendency to exclude information regarding earlier biopsies or surgeries is probably related to the diagnosing clinician rather than to the tumour or patient at hand. However, we could argue that recurrences are more common among morphoeiform BCC tumours and that this subtype thus are more prone to double registration, simply related to the higher proportion of recurrences in relation to low aggressive BCC. If we have more recurrences, there is a risk of more missed information regarding earlier treatment. The risk of selection bias is therefore not possible to disregard but is not likely to be a significant problem.

BCC tumours that are diagnosed clinically and treated without histological confirmation are not included in the Swedish BCC Registry. This is a potentially big source of error in this registry, albeit a difficult one to fully quantify. As clinicians in dermatology, dealing with skin tumours, we know that diagnosis and treatment of BCC without biopsy is a common entity. Low aggressive tumours can be treated with cryo-therapy, curettage, imiquimod or PDT and in a proportion of patients treated with these modalities, a biopsy is never taken. In situations where the clinical and dermoscopical appearance of the tumour is typical, the diagnostic accuracy is good enough to render the use of histopathological diagnosis unnecessary. Meanwhile, in infiltrative tumours with aggressive growth pattern, surgical excision is the treatment of choice and histological evaluation of diagnosis and surgical margins is mainstay. Thus, missing data on account of tumours not being histopathologically verified, is likely to be almost exclusively related to morphological subtypes with low aggressive growth pattern (BCC type IA and type IB). To verify the actual number of tumours that are missing in the registry due to this anomaly, a study of all patient records related to the diagnosis of BCC in Sweden would be necessary. An enormous task that is unfeasible to do on a national scale. It is, however, reasonable to assume that a proportion of low aggressive BCC tumours, diagnosed in Sweden, are left out of the national registry.

Another factor that makes comparison between epidemiological studies world-wide difficult, is the use of different standard populations in different studies. The

standard population is used to standardise an incidence estimate, to be comparable between different populations. The mere use of the crude incidence rate (number of people diagnosed during a year/100 000 inhabitants) is an insufficient way to compare incidence between populations and over time. This is because the age structure can be significantly different in each population and even differ in the same population over time. While cancer is inherently correlated to old age, a differing age structure would give us an insecure measurement of incidence if these differences were not accounted for. Hence the use of a standard population. A commonly used standard population is the world standard population, defined by WHO[175]. In a standard population, the proportion of the population represented by any given age-category is used to weigh the incidence rate in the new population of interest[166]. In this way, we can compare the incidence in Sweden today with the incidence in the year 1980 by using the same standard population both times and thereby achieve a true trend over time, undisturbed by changes in age structure. However, when reviewing epidemiologic studies of BCC from different parts of the world, many different standard populations have been used. This makes it impossible to truly compare BCC incidence in each country. In our study, we used the European age-standardised rate of the year 2013. This standard population has been used in several earlier studies and was thereby a reasonable choice for us. The alternative of using the Swedish standard population of year 2000, often used by the National Board of Health and Welfare in Sweden, would increase our possibility to compare to earlier incidence reports in Sweden (and to other cancer diagnoses in this country), but would make our study less interesting from an international perspective. To facilitate future international comparisons of incidence, the use of a standard population common to all publications would be valuable.

Ethical discussion

National data regarding all histopathologically verified BCC tumours during the years 2004 – 2017 was extracted. Data regarding medical history is considered of sensitive nature and studies based on this need ethical approval. The BCC Registry contains information about diagnosis, date of diagnosis and diagnosing pathology department. It also contains age, sex, and personal identification number. The most important ethical aspect of this study is the retrieval of potentially privacy breaching information in the form of medical history that could be linked to a specific person. The most obvious danger here would be the extraction of the personal identification number from each of the included cases. To decrease the risk of a privacy breach, the personal identification number was excluded from the data file and replaced with an encrypted code. The code could be paired with the correct personal identification number by using a key, kept by the National Board of Health and Welfare, and saved for a period of three years. This was important if we wanted to link information with other registries at a later stage. The data handled by the research group was thus pseudonymised and could not be coupled

to specific individuals. However, another way of breaching privacy would be to extract health data that in itself could be traced to a specific person. This could for example be a problem in the case of rare diseases. If we extract data regarding a rare genetic disease that could be traced to a specific family, then data regarding age and sex could be enough to breach privacy. In our case, we studied a very common tumour form, diagnosed in 50 000 individuals each year. The sheer volume of cases decreases the risk of being able to trace data to specific individuals and together with the lack of personal identification number in the data file, the ethical risks is most likely small. In order to further increase integrity, general information regarding the study was published on the clinic's website. We published contact information to the research group for members of the society to be able to opt out from the study if desired. Furthermore, all retrieved data was stored on an encrypted disc in a locked cabinet.

General discussion

In this study, we found a high incidence of BCC in Sweden, in relation to countries on similar latitudes. We also saw a steady increase in incidence during the study period.

Our high incidence numbers could be explained, partly, by the ability of the Swedish BCC Registry to account for multiple tumours per person. A feature not common to other registries. Some registries only register the first tumour in each person, others the first tumour on each anatomical localisation. Both these versions of registration are bound to produce lower incidence numbers in comparison to ours, due to the known tendency for a person diagnosed with BCC to produce more tumours over time. One of the studies most comparable to ours, as to the methodological procedure and likeness in population structure, is the epidemiological study from England by Ascott et al[37]. In this study, they investigated the incidence of BCC, SCC, and MM during the years 2017 – 2019, reporting first tumour per year and person (what we in our study call person-based incidence). Furthermore, like us, they used EASR 2013 as standard population. Northern England has a similar latitude as the southernmost part of Sweden and, lastly, the population in England has a similar skin type as in Scandinavia.

In the study by Ascott et al, the northern part of England had an estimated person-based incidence of around 300/100 000 person years[37]. Meanwhile, the southern part, with the highest incidence, had an age-standardised incidence rate of 426/100 000 person years. The latitude-gradient with a higher incidence in the south is consistent with our finding. However, the person-based incidence-rate in southern Sweden was estimated at 599/100 000 person years, which is considerably higher than any registered incidence rates in England. The reason for this could be several. Firstly, differences in the proportion of registered tumours could be a factor. Both countries study histopathologically verified tumours. However, the

custom of diagnosing and treating BCC without a biopsy might differ between us, rendering differing incidence estimates. Nonetheless, the difference in incidence could also partly or wholly be a true difference owing to varying UV-exposure or sun protection habits. Though, regulations regarding sunbed use are similar between the countries (banned for people under the age of 18 years) and inhabitants of both countries are known to appreciate travels to the south.

In our study, incidence was higher in men compared to women. This is in line with studies from other populations. We could, however, also see that the sex difference changed depending on age. In younger age groups, incidence was higher in women than men, while the opposite was true in older age categories. This has also been shown in earlier studies regarding BCC[38, 176-178] as well as for melanoma[8]. The exact reason for this is difficult to ascertain, while our study did not report any phenotypic or lifestyle related variables. However, one could speculate that differences in clothing and sun exposure between the sexes could be part of the explanation. Studies have also shown use of tanning beds to be more common among young women than men in Sweden[124, 179], which also could explain the higher female incidence among the younger.

We are yet to discuss the true incidence of BCC in Sweden. As mentioned, the true incidence is likely to be even higher than the level presented in our study, due to lack of tumours that have not been biopsied. A recent paper by Backman et al presented a single centre study from Sahlgrenska hospital in Gothenburg (Western Sweden). In this study they concluded that as much as 80% of superficial BCC tumours were clinically diagnosed, without histopathological confirmation[76]. Furthermore, they estimated that 70% of all diagnosed BCC tumours in Sweden might be missed in the national registry if all regions in Sweden had the same frequency of clinical, non-histological diagnosis of BCC at their dermatology clinic. If that were the case, it would mean that the true incidence of BCC in Sweden might be more than double the numbers reported in our study. However, it is of course possible that the amount of BCC tumours diagnosed and treated without biopsy is driven by local culture at the dermatology clinic at hand. While dermatologists in Gothenburg use clinical diagnosis to a high extent, another clinic might not. Thus, the extrapolation of the presented findings to a national basis is tricky and probably not fully valid. One finding in our study that might point to a relatively high degree of clinical diagnosis without biopsy in Gothenburg, is the relatively low incidence of BCC in Western Sweden in comparison to Middle Sweden and South Sweden. If we speculate that the true incidence of BCC in the West is somewhere between that of Middle Sweden and South Sweden, the lower rate here might indicate a proportionately high degree of diagnosis without biopsy.

Study II

Methodological and ethical considerations

The study of multiple BCC has been hampered internationally, due to the lack of national registration of this tumour form in many countries. In countries that do have national registration, it is often limited to the first diagnosis annually, or even just the first tumour ever in each person. It is uncommon for a national registry to contain multiple consecutive BCC tumours in each individual[33, 154]. The Swedish BCC Registry, as one of few, contains all histopathologically verified BCC tumours in the Swedish population since 2004[27], including multiple consecutive tumours in each person. This enables us to estimate how big the entity of multiple BCC in our population is, while many other countries have to settle on smaller cohort studies in order to estimate the volume of multiple BCC.

There is, however, one major drawback pertaining to this registry. This weakness of the registry was discussed previously and is related to the fact that it only contains histopathologically verified tumours. This construct is most likely a necessity to keep this registry functional, given the vast number of tumours diagnosed each year. However, since a significant proportion of tumours have been shown to be diagnosed clinically, without histopathology[76], not all tumours are included in the registry. Primarily low aggressive tumours, including nodular and superficial BCC, are diagnosed without a biopsy in the clinical everyday life. These tumours are treated with cryotherapy, curettage, PDT or topically and not always with the confirmation of histology. Thus, the lack of registration due to clinical diagnosis is a problem foremost related to low aggressive tumours. Furthermore, according to my own clinical experience, we are more likely to treat a tumour without histopathology in patients with a large number of tumours in their history. Thus, the more BCC tumours a person has been diagnosed with, the larger the proportion of clinically diagnosed tumours is likely to be. Given that this study focuses on multiple BCC, this construct of the Swedish BCC Registry is of course likely to affect the proportion of subtypes, tumour localisations and cumulative risk to some extent. To what degree is, most likely, not possible to ascertain, without a nationwide study of patient records, retrieving information on clinically diagnosed BCC tumours. However, this lack in the registry is not an isolated Swedish problem. To my knowledge, no national registry contains all histopathologically and clinically diagnosed BCC tumours. Thus, our registry has, from an international perspective, a good coverage on diagnosed BCC tumours. The main lesson is to be aware of the construction of the registry when interpreting the estimates presented in our studies.

Ethical discussion

The extraction of data in this study was similar to that of study I, with the exception of the added data from the National Cause of Death Registry, used to implement a survival analysis. This data was also pseudonymised and the ethical discussion is thereby analogous to that of study I.

General discussion

In the Swedish Basal Cell Carcinoma Registry, we found 40% of individuals to be registered with multiple BCC. This is to be compared to a pooled proportion of 29% according to a previous meta-analysis[180]. Meanwhile, an Australian study, based on the Nambour study, presented a proportion of 58% multiple BCC[181].

Our study showed the proportion of superficial BCC to be slightly higher among persons with multiple BCC in comparison to persons with single BCC. This is a phenomenon that has been shown before[123, 154, 180] and emphasises what practising dermatologists often see in their everyday surgery. This could possibly be related to lifestyle factors or phenotypic factors that affect the risk not only for superficial BCC, but for the development of multiple BCC tumours. Conversely, the proportion of nodular BCC was somewhat smaller among people with multiple BCC. This is possibly explained by the lack of registration regarding low aggressive tumours as described above.

The tumour subtypes were affected by the subtype in the previous tumour, such that the growth pattern in the second tumour to a large extent was the same as in the first tumour. The same was true regarding tumour localisation. These findings are in line with earlier findings[155] and might further imply a correlation between phenotypic or lifestyle-related factors on the development on different BCC subtypes, affecting the likelihood of development of a specific tumour form, on a specific site in a specific person. However, though our finding showed the correlation of subtype with the first BCC tumour diagnosed to affect the subtype in the third tumour as well, this correlation was not as strong. This suggests the association to dilute over time. Further in-depth studies of this phenomenon are warranted in the search for an explanation.

We could see that the risk of a new primary BCC tumour increased with age. The risk was also slightly affected by gender since males had a somewhat higher risk than females. Furthermore, the risk of multiple BCCs was significantly higher in the south of Sweden, a part of the country where our previous study indicated a high BCC incidence[182]. Meanwhile, the latitude gradient was not as evident for the remainder of the country, where the north of Sweden only hade a significantly lower risk than Stockholm-Gotland in case of two previous BCC tumours. Thus, it is difficult to draw any definitive conclusions regarding the effect of latitude on the risk of multiple BCC in the population.

The cumulative risk for a new BCC within five years after first BCC diagnosis was 27% among females and 30% among males. This is in line with the 5-year risk of 11 – 50%, presented in an earlier meta-analysis[180]. The cumulative risk increased to 43% among females and 48% among males after three previous BCC diagnoses, indicating an increasing risk of further tumours after multiple previous BCCs. Previous data on this pattern is scarce. However, in a study by van Iersel at al., similar results were presented[183].

In our population, 75% of persons with three earlier BCC tumours who developed a new primary tumour, was diagnosed with a new BCC within less than 3 years. The corresponding number among persons with one earlier BCC was 4 years. Our findings indicate that the increased risk of a new tumour after an earlier diagnosis seems to be primarily limited to the first 3 years. This implies the need of clinical surveillance to be biggest in the first couple of years after diagnosis of the latest tumour.

Study III

Methodological and ethical considerations

Sweden has a longstanding reputation of good and near complete registries. By using the Swedish personal identification number, we were able to collect information regarding BCC cases and controls from a variety of registries to analyse pharmacological risk factors for BCC.

Exclusions and confounding variables

In our study, we chose to gather information regarding confounding variables from the National Prescribed Drug Register, the National Patient Registry, the National Cancer Registry, and the LISA-Registry.

From the Patient Registry and the Cancer Registry, we collected data regarding co-morbidities. We wished to make exclusions and to adjust the results of the regression analysis based on specific diagnoses. These are accounted for in Table 13. Our choices regarding exclusion factors are based on diagnoses known to be potent risk factors for skin cancer, or that may be associated with factors that can influence the outcome of our study result significantly. Furthermore, decisions were also based on methodologies in previous studies[104, 105, 119]. Regarding organ transplantation, it is well known that the heavy immunosuppressive therapy given after this treatment substantially increases skin cancer risk[89-91]. This has been shown primarily for SCC; however, BCC risk is known to increase as well. Earlier skin cancer diagnosis would imply the person at hand to be at risk for a new skin cancer, including BCC. We chose only to exclude these persons if they had been

diagnosed with a previous skin cancer within 10 years before index date, since the greater risk increase is likely to be focused to the first years after diagnosis. Lymphoma and leukaemia can, either by itself or secondary to treatment, induce an immunosuppressive state that might be a risk factor for skin cancer[93]. HIV can result in immunosuppression and has been shown to be related to increased skin cancer risk[92]. Regarding lymphoma and leukaemia, only cases with a diagnosis within 10 years before index date were excluded. Psoriasis was chosen as an exclusion factor due to its relation to UVB- and PUVA-therapy and because of potential use of immunosuppressive treatments in this group. Finally, patients with Gorlins syndrome and Xeroderma pigmentosum were excluded because of their very high risk of BCC and skin cancer respectively[184, 185].

Table 13. Diagnoses used for exclusion criteria and as confounding variables in regression analysis.

Exclusion factors	Duration before index date	Adjustment factors	Duration before index date
Organ transplantation	Ever	Ischemic heart disease	10 years
Malignant melanoma	10 years	Heart failure	10 years
Squamous cell carcinoma	10 years	Diabetes	10 years
Lymphoma	10 years	Chronic kidney failure	10 years
Leukaemia	10 years		
HIV	Ever		
Gorlins syndrome	Ever		
Xeroderma pigmentosum	Ever		
Psoriasis	Ever		

HIV, Human immunodeficiency virus.

Ischemic heart disease was chosen as a possible confounder, since antihypertensive treatment to a greater extent is used in this group and while studies have shown indications of a lower skin cancer risk in these patients[186]. Heart failure was chosen due to its close relation to ischemic heart disease. Diabetes was chosen as a confounder while these persons are expected to be treated with antihypertensive treatment to a higher degree and while a study has shown a greater risk of MM and NMSC in diabetes patients[187]. Chronic renal failure was chosen as a confounder, while studies have shown these patients to be at an increased risk of skin cancer even before transplantation[188]. All these diagnoses were used as confounders, only if the diagnosis had been registered during the last 10 years before index date, to decrease the risk of over confounding of patients with for example short disease duration. When retrospectively analysing this design, I find it questionable to use the 10-year interval for chronic renal failure, heart failure and ischemic heart disease, since these patients are unlikely to be free of their disease. Furthermore, these patients might be followed in primary care and therefore not registered in the Patient Registry after their first contact with specialist care.

From the National Prescribed Drug Register, data regarding co-medication was extracted and used for exclusion- and confounding criteria. Medications are accounted for in Table 14.

Table 14. Medications used for exclusion criteria and as confounding variables in regression analysis.

Exclusion factors	Adjustment factors
Selective immunosuppressors *(for example Mycophenolate mofetil)*	Metformin
TNF-inhibitors *(for example Adalimumab)*	Statins
Interleukin inhibitors *(for example Sekukinumab)*	Acetyl salicylic acid
Calcineurin inhibitors *(for example Ciclosporin)*	Loop-diuretics
Other immunosuppressives *(for example Azathioprine)*	Amiodarone

TNF, Tumour necrosis factor

Regarding exclusion factors, the most common culprits in skin cancer risk are mycophenolate mofetil, ciclosporin and azathioprine. These were used as exclusion criteria. Further immunosuppressive treatments have been chosen as exclusion criteria, of which the interleukin inhibitors can be argued as unnecessary. These are today not acknowledged as strong carcinogens and should therefore perhaps not have been used as exclusion criteria in this study.

Regarding confounding criteria, metformin was used as a marker for diabetes in order not to miss patients treated in primary care and therefore not included in the Patient Registry. Statins, acetylsalicylic acid, and amiodarone are all used as confounders in earlier studies[104, 112, 117, 119, 189, 190]. Loop-diuretics are likely to be used to a higher extent among people with hypertension and is also correlated to BCC risk[189].

Data regarding socioeconomic factors was collected from the LISA-Registry. These are accounted for in Table 15.

Table 15. Socioeconomic factors used as confounding variables in regression analysis.

Highest level of education	Pre-High school
	High school
	College/University
	Post-graduate
Annual gross salary (thousand SEK)	<2000
	2000 – 2999
	3000 - 3999
	4000 – 4999
	5000 – 5999
	6000 – 7000
	>7000

SEK, Swedish krona

Socioeconomic factors have earlier been shown to correlate with skin cancer risk[39, 123]. Skin cancer risk tends to be higher in people with higher educational level or in populations in less deprived areas[39, 123]. It is also correlated to hypertension by an increased risk for hypertension in people with low socioeconomic status, particularly regarding women[191, 192]. To adjust for socioeconomic status as completely as possible, both salary and educational level was treated as confounders.

Collection of controls

We extracted data regarding controls from the Total Population Registry in Sweden. These were matched to the cases regarding age, sex, and region of residence (according to the six different health care regions used in Study I). Two controls per case were collected. Other studies have chosen to collect 10 controls per case. The reason why we chose just to collect two controls was mainly related to the size of the study population. BCC is a common tumour diagnosis with a high incidence rate. Therefore, the use of more than two controls per case was not deemed necessary to get good power in our analyses.

Weaknesses

The main weakness of this study was the lack of phenotypical data and data regarding lifestyle factors. The prime phenotypical variable of interest would be skin type. By adjusting for skin type, or even matching the controls by skin type, differences pertaining to ability to tan could have been taken into account. We considered using information regarding country of birth as a proxy. However, birth country would probably not align well enough with skin type, and we therefore chose not to use this variable.

Lifestyle factors, including smoking and UV-exposure would be of interest as well. Smoking is a possible confounding variable by being correlated to hypertension and by a possible connection to carcinogenicity overall. UV-exposure is of course correlated to skin cancer risk. Furthermore, use of potentially photosensitising medications may result in a reactively lowered UV-exposure. Thereby, both these parameters might be potential confounders that could be of interest as adjustment factors in the regression analysis.

The risk of mistakes in choosing confounding variables and exclusion criteria is never eliminated. The fact that the choice of confounding variables differ between studies further emphasises the difficulties of adequately adjusting for comorbidities and co-medications in this scenario[104, 111, 112, 117, 119]. Even though I spent a lot of time studying articles to inform me in choosing relevant parameters as potential confounders and even though we consulted an epidemiologist before starting up the project, I am still not convinced that the choice of variables is fully correct. I believe, however, that my choices are as close to the correct ones that I can come.

The variable pDDD was chosen to study cumulative dose in relation to BCC risk. This variable can be interpreted both as a variable of dose and a variable of time. Primarily, we are informed of the number of defined daily doses (DDD) that have been prescribed, i.e. the cumulative dose. Indirectly, by assuming that 1 DDD is used daily, we could extrapolate the amount of pDDD prescribed to a duration of treatment. For example, 100 pDDD could be interpreted as a treatment duration of 100 days. In reality, however, we cannot be sure about the treatment duration, while time is not a known factor in the variable. An individual can use a higher dose and thereby consume a given amount of pDDD in a shorter time span. With that said, pDDD is likely to be a valid measure of cumulative dose, as long as we keep in mind that the time aspect of the variable is dependent on the prerequisite that the "standard dose" of the medication (1 DDD per day) has been used. Similar strategies have been used in previous studies[104, 107].

Ethical discussion

Apart from data regarding BCC diagnosis, data regarding medication and co-morbidities as well as socioeconomic factors, such as educational level and gross salary was extracted. Data regarding these factors were also gathered from matched controls. Thus, the volume of sensitive information was considerably larger in this study in comparison to studies I and II. The personal identification number was used to link data between the different national registries. Meanwhile, the personal identification number in itself was not included in the data file collected by the research group. While the number of individuals in the study was very high, the risk of being able to link data to a specific person was small.

There is another potential ethical aspect to be discussed, related to this study. The purpose of the study was to investigate BCC risk in relation to use of the most common antihypertensive medications. Hypertension is a common disease that could result in atherosclerosis, ending in cardiac infarction or a stroke in extreme cases. The use of antihypertensive medication lowers the risk of these catastrophic consequences. If we were to find information regarding an increased BCC risk in relation to a specific antihypertensive medication, this could result in a decreased use of that medication. The important comment here is that decreased BCC risk, won by the stopped usage of a specific medication, has to be weighed against the potentially increased mortality risk, related to the altered recommendations of antihypertensive treatment. With that said, potential side effects and risks of every medication is important to clarify if we as clinicians are to make sound and relevant treatment decisions based on risk-benefit analysis.

General discussion

Our study could present an increased BCC risk with use of ARB, CCB and beta-blockers. Regarding thiazides, BCC risk increased after use of combination

treatments. The risk was increased in individuals with ever-use of thiazide-containing combinations as well as in relation to cumulative dose, indicating there might be a real association between this treatment and BCC risk. Meanwhile, single-agent thiazides did not affect risk in our material. This poses the question of whether the increased risk in conjunction with combination treatments is related to the thiazide agent itself or the adjunctive agent. Earlier studies on thiazide treatment and skin cancer risk seldom discriminate risk in relation to single-agent use from that of combination treatments[104-106, 109, 112]. In a study by Jensen et al., combination treatment with HCTZ + amiloride increased risk of SCC while no significant risk increase was shown after single-agent treatment with HCTZ[111]. Indeed, when we explored the association between HCTZ + amiloride and BCC in our data, we could see a significantly increased BCC risk among the consumers of this medication that could not be found when studying individuals with single-agent HCTZ. Future studies should focus on skin cancer risk in correlation to single-agent thiazide treatment to make a valid risk assessment in relation to these medications. Additionally, further knowledge regarding amiloride and skin cancer risk should be sought, for BCC as well as for SCC and MM.

We presented a 9% increased BCC risk in individuals treated with ARB. This association has rarely been studied. However, in a report by Schmidt et al., a similar risk increase was presented[119]. A further study by Nardone et al. also showed a significantly increased risk in individuals treated with ARB[193]. Meanwhile, Tang et al. performed a pooled analysis of these two studies in a meta-analysis, whereby no significant association with BCC risk or SCC risk was found[122].

Users of ACEi had a very slightly decreased risk of BCC in our cohort. This finding was corroborated by two earlier studies of high-risk populations, where use of ACEi or ARB showed a decreased BCC risk[117, 118]. In the study by Schmidt et al., however, ACEi did not affect BCC risk[119]. Studies have shown ACE to be an important part of BCC initiation[115, 116], indicating that ACEi in theory could have a preventive role regarding this skin cancer form. Regardless, however, the slight preventive effect found in our material is not likely to be of clinical relevance.

Calcium channel blockers were associated with an increased BCC risk in our material. This medication has only rarely been studied in relation to skin cancer risk. In a meta-analysis by Tang et al., however, an increased risk for BCC development was found, with risk estimates just above our own (OR 1.15)[122]. Additionally, we found an increased BCC risk when studying the two most commonly prescribed variants of CCB, amlodipine and felodipine. On top of this, high use of amlodipine was associated to an even higher tendency of developing basal cell carcinomas. Altogether, CCB could be seen as a potential risk factor for BCC, though the risk increase was only slight to moderate in our material. Further

studies, including risk for SCC and MM are warranted in order to further elucidate the role of CCB in skin cancer risk.

Beta-blockers were associated with a 7% increase in BCC risk. The risk did not seem to be dose dependent. As for several of the other antihypertensive medications, the association between beta-blockers and BCC risk has seldom been studied. In the meta-analysis by Tang, however, a similar risk increase of 9% was presented[122].

In conclusion, several of the commonly prescribed antihypertensive medications were associated with increased BCC risk in our study. The risk increase, however, was only slight to moderate and should not by itself affect recommendations regarding antihypertensive therapy. Meanwhile, instructions regarding sun-protective habits should be offered to all patients on these medications.

Study IV

Methodological and ethical considerations

In this study, we explored a registry of all excised skin tumours in a single dermatological centre in southern Sweden. The main strength of this study is the construction of the registry.

Firstly, in this part of southern Sweden, there is an agreement to primarily refer patients with a skin cancer to a dermatological department. During the years this study was performed, the absolute majority of specialised dermatologic appointments in the area were done at the hospital clinic where this study was performed. Furthermore, only a small minority of patients were referred to other clinics from the dermatology department for surgical treatment. Thus, a representative cohort of patients and tumours are present in this registry.

The registry is based on information from the internal referral for surgery. This referral is used for all planned surgery at the department and is needed to book an appointment. Tumours, treated by other means than simple surgical excision (such as shave, curettage, or cryotherapy) are not included. Thus, it is likely that close to 100% of all tumours, removed by simple surgical excision at the dermatology department, are included in the registry.

We chose to study the effect of tumour localisation and tumour subtype together with a number of other patient- and tumour specific variables on the risk of an incomplete excision of BCC. This study is one of few that actually studies the combined effect of a certain tumour subtype on a certain tumour localisation. This gives us very specific information regarding which tumours are at the highest risk

of being incompletely excised. Meanwhile, it also means that the number of excised lesions among uncommon tumours at more uncommon tumour localisations are rather few. To study statistics on groups with a small number of people or tumours always means a potential for less trustworthy results. For example, only seven morphoeiform BCC tumours on the nose were included. However, the proportion of incomplete excisions, measured in percent, is also presented. Because of the big difference in proportion of incomplete excision between the groups, descriptive statistics tells us a lot about the outcome in different scenarios and gives this study a credible conclusion. Furthermore, when analysing the data, Fisher´s exact test was used instead of Chi2-test. This method was chosen due to the small number of lesions in some of the studied categories.

Ethical discussion

In this study, we extracted data regarding diagnosis, tumour localisation and surgical outcome as well as age and sex of all individuals treated with surgical excision for BCC at the Department of Dermatology, Helsingborg hospital, Sweden, during the years 2008 – 2015. In essence, the same ethical aspects are at play in this study as in studies I-III. The main difference is the size of the study. In this study, only around 4000 excisions were evaluated. Furthermore, they were all made in an area with approximately 150 000 inhabitants. One could argue that the lower number of cases and the smaller geographical area could increase risk of linking extracted information to a specific person, thereby breaching privacy. Still, the number of included individuals was quite large, and the risk should be relatively small.

Another aspect is related to surgical treatment of the included individuals. An important part of medical research is that of evaluation of different treatments and therapies. This kind of research often entails the use of randomised trials, where some people are randomly selected for treatment A and others for treatment B. In these cases, the most important ethical aspect would be that one treatment might give much better (or worse) results than the other. In the end, some of the included individuals may take harm indirectly, by not being treated with the better alternative. In our case, however, the evaluation of surgical excision was done purely as a retrospective evaluation of a cohort, treated in accordance with national recommendations. No alternative treatments were offered. Thereby none of the included individuals gained or loosed anything by the study. In a wider sense, the results presented in the study have been used as reference in the production of the upcoming national guidelines for the management of BCC in Sweden, thereby contributing to a better care of future patients.

The data from the registry would allow for us to further analyse differences in rates of incomplete excisions between groups of surgeons. However, we opted not to study this further to decrease the risk of identifying individual doctors in our relatively small department.

General discussion

In this study, we found a very high proportion of incomplete excisions regarding morphoeiform and infiltrative BCC located on the nose and ear. A subsequently published article from western Sweden showed similar results[147], as did several previous studies[139, 145, 194]. To make an informed decision regarding choice of treatment modality, it is important to be aware of the likely outcome in different scenarios. This is important for two main reasons. Firstly, because we want to achieve as good an effect as possible with low risk of recurrence. Secondly, repeated surgery after incomplete excisions is costly. From a patient perspective, as well as from a cost efficiency perspective, we want to achieve full treatment effect as quick as possible.

So, how should we deal with highly aggressive BCC tumours on sensitive anatomical areas, such as the ear or nose? The recommended treatment modality for these tumours is surgery with perioperative histopathological assessment and margin control. One example of this is Mohs surgery, a surgical technique that is arguably the most common variety of this entity. The use of Mohs surgery is in some countries a lot more common than in Sweden. Sweden has, due to its health economy system, thus far, been restrictive in its use of Mohs surgery. Most likely, while this modality is quite resource heavy. In Sweden, Mohs surgery is only used in Lund, Gothenburg, and Stockholm. The relatively restrictive use of this surgical modality makes the indication narrow and historically only the more difficult tumours have been treated this way. However, our finding motivates the use of Mohs in a more liberal way.

As a Mohs-surgeon under training, I know that Mohs surgery of recurrent lesions or tumours that have not been completely excised after several tries, are more difficult than that of primary lesions. This has also been shown in a study from our Mohs-clinic[152]. Even though Mohs surgery is labour intensive and costly, it is most likely more so with several consecutive episodes with simple surgical excision before the tumour is fully excised. Not to mention the mental stress in the patient when having to go through several surgical treatments every 3-6 months before he/she is finally cured.

Since I first wrote this article, the indication for Mohs has broadened somewhat and the number of tumours treated annually in Lund is steadily increasing, today reaching around 200 tumours. The proportion of tumours that have gone through 4-6 earlier excisions is lower, indicating that patients in more recent years to a greater extent receives the “correct” treatment earlier. Meanwhile, it would be erroneous to assume that Mohs surgery is the correct therapy for every surgical quest regarding BCC. In our study, we also could see that nodular, low aggressive BCC located on the face (nose and ear excluded) only was incompletely excised in 1.7 % of cases. With that said, simple surgical excision is a fantastic treatment option for most tumours. Conserving Mohs surgery (or its equivalent) for patients

with high-risk tumours on high-risk localisations enables us to use health care resources as wisely and cost efficiently as possible, while giving our patients the best care we can achieve.

Conclusions

Study I

The study showed a high incidence of BCC in Sweden, in comparison to countries on similar latitudes. Furthermore, we presented a rising incidence trend. The numbers indicate a high and increasing load on the health services in Sweden.

Study II

The study showed that a relatively large proportion of individuals diagnosed with BCC develop multiple primary tumours. The risk of a new primary tumour increased with age and with the number of earlier tumours diagnosed, highlighting the need of patient education as well as clinical surveillance in persons with a history of multiple BCC, at least during the first couple of years after diagnosis. Furthermore, the high risk of developing multiple BCC tumours, together with our earlier findings of a high and increasing BCC incidence, further reveals the need for our country to increase our primary prevention efforts in order to decrease the burden of this tumour form on the Swedish health care system.

Study III

We presented associations between use of several of the commonly prescribed antihypertensive medications and an increased BCC risk, indicating that individuals treated with these medications should be given instructions on sun-protection habits. Meanwhile, thiazides only increased risk when given as combination treatments. Further studies on amiloride as well as on single-agent thiazides and skin cancer risk should be performed.

Study IV

Our study showed a low overall risk of an incomplete excision regarding BCC. However, regarding aggressive BCC tumours, and especially those located on the nose and ear, the risk of an incomplete excision was shown to be high. The study indicates that BCC tumours on the ear, nose, or other surgically and cosmetically sensitive areas, should be biopsied before treatment decision to correctly appreciate histopathological growth pattern. In cases of aggressive tumours on these localisations, surgical excision with perioperative margin control, such as Mohs micrographic surgery, should be considered. Meanwhile, the low proportion of incompletely excised low-aggressive tumours on other sites indicates that simple surgical excision is sufficient in these scenarios.

Future prospects

This thesis has focused on the incidence of BCC in Sweden, potential risk factors for BCC and outcome after simple surgical excision. We have been able to show that BCC-incidence in Sweden is high and increasing, putting considerable strain on health care services. In fact, given that the BCC Registry only contains histopathologically verified tumours, the incidence in Sweden is likely to be noticeably higher than the numbers presented in our study. Our findings motivate further efforts to improve primary prevention to flatten out the increasing incidence curve and ultimately decrease BCC incidence in Sweden.

The increasing BCC incidence entails several problematic consequences. Firstly, every case of BCC results in physical and mental stress for the diagnosed patient. Small tumours can often be treated quickly. However, even among these tumours, the risk of post therapeutic scarring is present. Surgery of larger BCCs located on cosmetically sensitive areas in the face result in obvious scarring and might also result in functional deficits. Thus, even though BCC has a very low mortality risk, the risk of cosmetical or functional complications are not insignificant. Secondly, the management of BCC puts a heavy financial strain on society. Surgical treatments are expensive and given that the number of affected persons in Sweden increases over time and that every affected person is at an increased risk of developing multiple tumours, the costs will increase as well. Healthcare is already spread thin, and the present global financial situation further emphasises the importance of finding means of decreasing costs without putting quality of care in jeopardy. Lastly, healthcare resources, in the form of personnel availability has also been an issue during the last years. Difficulties recruiting healthcare professionals have made our efforts of giving adequate care in good time difficult. An increasing amount of BCC tumours in our population would further increase this challenge. The primary solution for this part of healthcare economy would be to halt the increase of BCC incidence. This is a challenge that will take many years before obvious results are achieved. Nevertheless, action on a national level is essential in order for us to turn the trend of increasing skin cancer incidence around. Sun exposure is known to be the main risk factor for skin cancer, including BCC. Over decades, increased exposure through sunbathing and travels to warmer climates have been culturally infused in the Swedish soul. Fortunately, knowledge of the benefits of sun protection has increased. However, education in sun protective behaviour should be an even bigger part of our lives from an early

age. Parents should be offered counselling on sun protection at the childcare centre. Children should get further education at school and access to plenty of shade, when playing outdoors. Further campaigns with information regarding the importance of UV-protection should be launched intermittently for the general population to take part of. UV-protection should be a more natural part of our lives. When this happens, we would hopefully see the effects of a flattening curve, or even a decreasing BCC incidence, within decades. With this said, further research on BCC prevention strategies would be valuable, using a prospective approach in a randomised controlled trial. To what extent does sun protection decrease the risk of further BCCs, after first BCC diagnosis? What sun protective factor (SPF) should be used in order to decrease risk for further tumours? Should the same SPF be recommended for all? Most likely, guidance on sun protective habits in patients at risk of skin cancer can be individualised, and further research on this would be valuable.

Furthermore, in our study we presented an increased BCC risk with use of thiazide-containing combination treatments, angiotensin II receptor blockers, calcium channel blockers and beta-blockers. Our findings are based on a large amount of registry data. However, lack of phenotypic data and lifestyle factors are limitations in the study. To further evaluate antihypertensive medications as risk factors for BCC, future studies should entail the use of a prospective approach, following patients with and without antihypertensive treatment over time. In such a study, adjustment of the results for skin type, hair colour, history of sunburns, as well as recreational and professional UV-exposure is important. Furthermore, when studying skin cancer risk in relation to hydrochlorothiazide, the role of adjunctive agents, given in combination with these medications, should be evaluated. The use of antihypertensive treatment is pivotal in the risk management regarding ischemic heart disease and cerebral vascular disease. Possible future recommendations regarding the use of these medications in relation to skin cancer risk must be based on solid data in order not to exclude a vital medication prematurely. Preferably, larger pharmacoepidemiologic studies concerning the risk of other skin cancers in relation to antihypertensive treatment should be used in these assessments as well.

In our last study, we found a high ratio of incomplete excisions regarding aggressive BCC tumours, located on the nose and ear. Future studies on the risk of incomplete excisions on other sub-localisations, such as the periorbital region, would be of interest to further elucidate which tumours should be considered for surgery with perioperative margin control. Meanwhile, our findings indicate that non-nodular BCC tumours on the nose or ear should be biopsied before treatment decision. In cases with morphoeiform BCC on these localisations, surgical excision with perioperative histopathological evaluation and margin control should be considered. In fact, since our study was published, the use of Mohs surgery at the Department of Dermatology in Lund in southern Sweden has increased.

Furthermore, the latest published indications for Mohs surgery in Sweden included facial infiltrative and morphoeiform BCC, referring to the high level of incomplete excisions among these tumours published in our study. Most likely, Mohs surgery is still underutilised in our country. Since this surgical method is only practised at three centres in Sweden, individuals living in areas remote from the nearest Mohs clinic are at an increased risk of receiving a different primary treatment than people living in the vicinity of Lund, Gothenburg, or Stockholm. Further investments in the use of surgical treatments with perioperative margin control would most likely be beneficial for patients with facial BCCs. Furthermore, it is quite possible that Mohs actually would be of financial benefit as well, even though this surgical treatment is significantly more expensive than simple surgical excision. Our studies have shown aggressive BCCs on cosmetically sensitive locations, treated with simple surgical excision, to be at a high risk of incomplete excision. When this happens, widened excisions in order to completely remove the tumour is mainstay. At times, multiple excisions are needed, adding up to a higher cost than would be the case if we had used Mohs surgery as primary treatment. However, the financial benefit of Mohs surgery in the Swedish population should be studied further. In the purpose of increasing the incitement to invest in Mohs surgery at a national level, sound knowledge of the financial basis for BCC surgery is essential. By comparing the costs of simple surgical excision with that of Mohs surgery and investigate the likely financial result of these two treatment modalities, depending on tumour subtype and localisation, we would have a clearer picture regarding financially valid treatment decisions in a Swedish healthcare setting.

Thank you!

To my colleagues at the Department of Dermatology at Helsingborg hospital and Landskrona hospital and to the Mohs-team at Skåne University Hospital Lund, for giving me valuable insights on my work and for clearing my schedule to the extent that even I could pull this off.

To Kari, my supervisor and dear colleague. The amount of time you have put on my research education is most likely impossible to count and the value of your insights and your kind but constructive feedback impossible to measure.

To Ingela, my co-supervisor, colleague, and boss, who pulled me into research in the first place. You have been a source of inspiration both in the world of dermatology and in the world of academics.

To Åsa, my co-supervisor and Mohs-colleague, for your sharp intellect and honest thoughts that have guided me through many a hurdle during the past science projects.

To Mats, my colleague and former boss. I have informally titled you my mentor from the start of my career in dermatology. You were the reason that this career started in the first place, and you are still a huge inspiration.

To Fredrik, my statistics consultant and colleague. Thank you for all your hard work on our paper on incomplete excisions. Your help with my own feeble tries was invaluable. A special thanks for holding my back at the "Halvtidskontroll" (a true knight in shining armour), and for checking the facts in the statistics part of this thesis.

To Anna, our statistician on studies 1 – 3. Thank you for your thoughts, ideas, and work on our studies. Without your willingness to go that extra mile in helping me when I just wanted to change one extra thing, this would not have been possible.

To Alma, who at record pace created the cover art for my thesis. I am very grateful.

To my father (Örjan), my late mother (Kerstin), and my siblings (Hanna, Simon, and Sara) with families for all the support and boost of confidence. You have been with me through medical school and onward, through thick and thin. You are wonderful!

To Birgitta, Olle, and Kristian with family. For caring and listening. For cooking me supper when the night was too late for me to do it myself. For pep-talks. For everything.

To my friends (you know who you are). For giving me other things to think about and for boosting me when I needed it.

To my wonderful wife Anna, who has listened to my thoughts and contemplations through all these years and who has given me the support and the strength to carry on. You are my everything. I love you.

Lastly, to Milton. My dog and everlasting companion through the writing of this thesis.

References

1. Yousef H, Alhajj M, Sharma S. Anatomy, Skin (Integument), Epidermis. StatPearls: StatPearls Publishing; 2022 [cited 2023 November 14th]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470464/.
2. James D. J, Berger T. G, Elston D. M. Skin: Basic structure and function. Andrews' diseases of the skin: Clinical dermatology, Twelth edition2016.
3. D'Orazio J, Jarrett S, Amaro-Ortiz A, et al. UV radiation and the skin. *Int J Mol Sci*. 2013;**14(6)**:12222-48.
4. National Board of Health and Welfare. Cancer i siffror 2023. 2023. [cited 2023 October 17th]. Available from: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/dokument-webb/statistik/cancer-i-siffror-2023.pdf.
5. Leonardi GC, Falzone L, Salemi R, et al. Cutaneous melanoma: From pathogenesis to therapy (Review). *Int J Oncol*. 2018;**52(4)**:1071-1080.
6. Long GV, Swetter SM, Menzies AM, et al. Cutaneous melanoma. *Lancet*. 2023;**402(10400)**:485-502.
7. Naeser Y, Mikiver R, Ingvar C, et al. Survival in patients diagnosed with melanoma in situ compared to the general population. A Swedish population-based matched cohort study. *EClinicalMedicine*. 2023;**65**:102284.
8. Regional cancer centres. Malignt melanom, Nationellt vårdprogram 2019 [cited 2020 Oct 3]. Available from: https://kunskapsbanken.cancercentrum.se/globalassets/cancerdiagnoser/hud/vardprogram/nationellt-vardprogram-malignt-melanom.pdf.
9. Sundararajan S, Thida AM, Yadlapati S, et al. Metastatic Melanoma. StatPearls. Treasure Island (FL): StatPearls Publishing. Copyright © 2023, StatPearls Publishing LLC.; 2023.
10. Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. *J Photochem Photobiol B*. 2001;**63(1-3)**:8-18.
11. Claeson M, Andersson EM, Wallin M, et al. Incidence of cutaneous melanoma in Western Sweden, 1970-2007. *Melanoma Res*. 2012;**22(5)**:392-8.

12. National Board of Health and Welfare. Statistikdatabas för cancer 2022 [cited 2023 October 27th]. Available from: https://sdb.socialstyrelsen.se/if_can/val.aspx.
13. Garbe C, Keim U, Gandini S, et al. Epidemiology of cutaneous melanoma and keratinocyte cancer in white populations 1943-2036. *Eur J Cancer*. 2021;**152**:18-25.
14. Cancer counsil Australia. Melanoma of the skin statistics. 2022 [cited 2023 October 27th]. Available from: https://www.canceraustralia.gov.au/cancer-types/melanoma/statistics.
15. Cicarma E, Juzeniene A, Porojnicu AC, et al. Latitude gradient for melanoma incidence by anatomic site and gender in Norway 1966-2007. *J Photochem Photobiol B*. 2010;**101(2)**:174-8.
16. Eklund G, Malec E. Sunlight and incidence of cutaneous malignant melanoma. Effect of latitude and domicile in Sweden. *Scand J Plast Reconstr Surg*. 1978;**12(3)**:231-41.
17. Marghoob NG, Liopyris K, Jaimes N. Dermoscopy: A Review of the Structures That Facilitate Melanoma Detection. *J Am Osteopath Assoc*. 2019;**119(6)**:380-390.
18. Regional cancer centres. Nationellt vårdprogram skivepitelcancer i huden. 2021. [cited 2023 October 30th]. Available from: https://kunskapsbanken.cancercentrum.se/diagnoser/skivepitelcancer-i-huden/vardprogram/.
19. Zalaudek I, Kreusch J, Giacomel J, et al. How to diagnose nonpigmented skin tumors: a review of vascular structures seen with dermoscopy: part II. Nonmelanocytic skin tumors. *Journal of the American Academy of Dermatology*. 2010;**63(3)**:377-86; quiz 387-8.
20. Rosendahl C, Cameron A, Argenziano G, et al. Dermoscopy of squamous cell carcinoma and keratoacanthoma. *Archives of dermatology*. 2012;**148(12)**:1386-92.
21. Stewart JR, Lang ME, Brewer JD. Efficacy of nonexcisional treatment modalities for superficially invasive and in situ squamous cell carcinoma: A systematic review and meta-analysis. *Journal of the American Academy of Dermatology*. 2022;**87(1)**:131-137.
22. Marzuka AG, Book SE. Basal cell carcinoma: pathogenesis, epidemiology, clinical features, diagnosis, histopathology, and management. *Yale J Biol Med*. 2015;**88(2)**:167-79.
23. Hernandez LE, Mohsin N, Levin N, et al. Basal cell carcinoma: An updated review of pathogenesis and treatment options. *Dermatol Ther*. 2022;**35(6)**:e15501.

24. Nedved D, Tonkovic-Capin V, Hunt E, et al. Diagnostic concordance rates in the subtyping of basal cell carcinoma by different dermatopathologists. *J Cutan Pathol*. 2014;**41(1)**:9-13.
25. Fernandez-Figueras MT, Malvehi J, Tschandl P, et al. Position paper on a simplified histopathological classification of basal cell carcinoma: results of the European Consensus Project. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2022;**36(3)**:351-359.
26. Jernbeck J, Glaumann B, Glas JE. [Basal cell carcinoma. Clinical evaluation of the histological grading of aggressive types of cancer]. *Lakartidningen*. 1988;**85(42)**:3467-70.
27. National Board of Health and Welfare. Basal Cell Carcinoma in Sweden 2004-2008. 2009. [cited 2023 May 23rd]. Available from: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/statistik/2009-12-12.pdf.
28. Betti R, Radaelli G, Crosti C, et al. Margin involvement and clinical pattern of basal cell carcinoma with mixed histology. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2012;**26(4)**:483-7.
29. Verkouteren JA, Ramdas KH, Wakkee M, et al. Epidemiology of basal cell carcinoma: scholarly review. *The British journal of dermatology*. 2017.
30. European network of cancer registries. ENCR recommendations, Non-Melanoma Skin Cancers. 2000. [cited 2023 October 13th]. Available from: https://www.encr.eu/sites/default/files/pdf/skinrecs.pdf.
31. Olsen CM, Pandeya N, Green AC, et al. Keratinocyte cancer incidence in Australia: a review of population-based incidence trends and estimates of lifetime risk. *Public Health Res Pract*. 2022;**32(1)**.
32. Tang E, Fung K, Chan AW. Incidence and mortality rates of keratinocyte carcinoma from 1998-2017: a population-based study of sex differences in Ontario, Canada. *Cmaj*. 2021;**193(39)**:E1516-e1524.
33. de Vries E, Micallef R, Brewster DH, et al. Population-based estimates of the occurrence of multiple vs first primary basal cell carcinomas in 4 European regions. *Archives of dermatology*. 2012;**148(3)**:347-54.
34. Birch-Johansen F, Jensen A, Mortensen L, et al. Trends in the incidence of nonmelanoma skin cancer in Denmark 1978-2007: Rapid incidence increase among young Danish women. *Int J Cancer*. 2010;**127(9)**:2190-8.
35. Adalsteinsson JA, Ratner D, Olafsdottir E, et al. Basal cell carcinoma: an emerging epidemic in women in Iceland. *The British journal of dermatology*. 2020.
36. Venables ZC, Nijsten T, Wong KF, et al. Epidemiology of basal and cutaneous squamous cell carcinoma in the U.K. 2013-15: a cohort study. *The British journal of dermatology*. 2019;**181(3)**:474-482.

37. Ascott A, van Bodegraven B, Vernon S, et al. The geographical variation of melanoma, basal and squamous cell carcinoma in England. *The British journal of dermatology*. 2023;**189(1)**:142-144.
38. Holme SA, Malinovszky K, Roberts DL. Changing trends in non-melanoma skin cancer in South Wales, 1988-98. *The British journal of dermatology*. 2000;**143(6)**:1224-9.
39. Carsin AE, Sharp L, Comber H. Geographical, urban/rural and socioeconomic variations in nonmelanoma skin cancer incidence: a population-based study in Ireland. *The British journal of dermatology*. 2011;**164(4)**:822-9.
40. Rudolph C, Schnoor M, Eisemann N, et al. Incidence trends of nonmelanoma skin cancer in Germany from 1998 to 2010. *J Dtsch Dermatol Ges*. 2015;**13(8)**:788-97.
41. Bernard P, Dupuy A, Sasco A, et al. Basal cell carcinomas and actinic keratoses seen in dermatological practice in France: a cross-sectional survey. *Dermatology*. 2008;**216(3)**:194-9.
42. Schreuder K, Hollestein L, Nijsten TEC, et al. A nationwide study of the incidence and trends of first and multiple basal cell carcinomas in the Netherlands and prediction of future incidence. *The British journal of dermatology*. 2022;**186(3)**:476-484.
43. Callens J, Van Eycken L, Henau K, et al. Epidemiology of basal and squamous cell carcinoma in Belgium: the need for a uniform and compulsory registration. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2016;**30(11)**:1912-1918.
44. Jurciukonyte R, Vincerzevskiene I, Krilaviciute A, et al. Epidemiology of basal cell carcinoma in Lithuania, 1996-2010. *The British journal of dermatology*. 2013;**169(5)**:1100-5.
45. Celić D, Lipozencić J, Jurakić Toncić R, et al. The incidence of basal cell carcinoma in Croatia: an epidemiological study. *Acta Dermatovenerol Croat*. 2009;**17(2)**:108-12.
46. Videnović G, Miljuš D, Ilić D, et al. Nonmelanoma Skin Cancer in the Population of the City of Belgrade in the Period 1999-2011. *Srp Arh Celok Lek*. 2015;**143(5-6)**:290-5.
47. Bielsa I, Soria X, Esteve M, et al. Population-based incidence of basal cell carcinoma in a Spanish Mediterranean area. *The British journal of dermatology*. 2009;**161(6)**:1341-6.

48. Revenga Arranz F, Paricio Rubio JF, Mar Vázquez Salvado M, et al. Descriptive epidemiology of basal cell carcinoma and cutaneous squamous cell carcinoma in Soria (north-eastern Spain) 1998-2000: a hospital-based survey. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2004;**18(2)**:137-41.
49. Rubio-Casadevall J, Hernandez-Pujol AM, Ferreira-Santos MC, et al. Trends in incidence and survival analysis in non-melanoma skin cancer from 1994 to 2012 in Girona, Spain: A population-based study. *Cancer Epidemiol*. 2016;**45**:6-10.
50. Jung GW, Metelitsa AI, Dover DC, et al. Trends in incidence of nonmelanoma skin cancers in Alberta, Canada, 1988-2007. *The British journal of dermatology*. 2010;**163(1)**:146-54.
51. Pilgrim W, Hayes R, Hanson DW, et al. Skin cancer (Basal cell carcinoma, squamous cell carcinoma, and malignant melanoma): new cases, treatment practice, and health care costs in new brunswick, Canada, 2002-2010. *J Cutan Med Surg*. 2014;**18(5)**:320-31.
52. Demers AA, Nugent Z, Mihalcioiu C, et al. Trends of nonmelanoma skin cancer from 1960 through 2000 in a Canadian population. *Journal of the American Academy of Dermatology*. 2005;**53(2)**:320-8.
53. Karagas MR, Greenberg ER, Spencer SK, et al. Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. New Hampshire Skin Cancer Study Group. *Int J Cancer*. 1999;**81(4)**:555-9.
54. Asgari MM, Moffet HH, Ray GT, et al. Trends in Basal Cell Carcinoma Incidence and Identification of High-Risk Subgroups, 1998-2012. *JAMA Dermatol*. 2015;**151(9)**:976-81.
55. Athas WF, Hunt WC, Key CR. Changes in nonmelanoma skin cancer incidence between 1977-1978 and 1998-1999 in Northcentral New Mexico. *Cancer Epidemiol Biomarkers Prev*. 2003;**12(10)**:1105-8.
56. Harris RB, Griffith K, Moon TE. Trends in the incidence of nonmelanoma skin cancers in southeastern Arizona, 1985-1996. *Journal of the American Academy of Dermatology*. 2001;**45(4)**:528-36.
57. Custódio G, Locks LH, Coan MF, et al. Epidemiology of basal cell carcinomas in Tubarão, Santa Catarina (SC), Brazil between 1999 and 2008. *Anais brasileiros de dermatologia*. 2010;**85(6)**:819-26.
58. Abarca JF, Casiccia CC. Skin cancer and ultraviolet-B radiation under the Antarctic ozone hole: southern Chile, 1987-2000. *Photodermatol Photoimmunol Photomed*. 2002;**18(6)**:294-302.
59. Pandeya N, Olsen CM, Whiteman DC. The incidence and multiplicity rates of keratinocyte cancers in Australia. *Med J Aust*. 2017;**207(8)**:339-343.

60. Cancer counsil Australia. Skin cancer statistics and issues. 2020. [cited 2023 October 17th]. Available from: https://wiki.cancer.org.au/skincancerstats/UV_radiation#UV_Index.
61. Richmond-Sinclair NM, Pandeya N, Ware RS, et al. Incidence of basal cell carcinoma multiplicity and detailed anatomic distribution: longitudinal study of an Australian population. *The Journal of investigative dermatology*. 2009;**129(2)**:323-8.
62. Brougham ND, Dennett ER, Tan ST. Changing incidence of non-melanoma skin cancer in New Zealand. *ANZ J Surg*. 2011;**81(9)**:633-6.
63. Pondicherry A, Martin R, Meredith I, et al. The burden of non-melanoma skin cancers in Auckland, New Zealand. *The Australasian journal of dermatology*. 2018;**59(3)**:210-213.
64. Oh CM, Cho H, Won YJ, et al. Nationwide Trends in the Incidence of Melanoma and Non-melanoma Skin Cancers from 1999 to 2014 in South Korea. *Cancer Res Treat*. 2018;**50(3)**:729-737.
65. Ogata D, Namikawa K, Nakano E, et al. Epidemiology of skin cancer based on Japan's National Cancer Registry 2016-2017. *Cancer Sci*. 2023;**114(7)**:2986-2992.
66. Koh D, Wang H, Lee J, et al. Basal cell carcinoma, squamous cell carcinoma and melanoma of the skin: analysis of the Singapore Cancer Registry data 1968-97. *The British journal of dermatology*. 2003;**148(6)**:1161-6.
67. Mahmoud SF, Azadeh B. Basal cell carcinoma in Qatar. *Int J Dermatol*. 1996;**35(10)**:704-6.
68. Almaani N, Juweid ME, Alduraidi H, et al. Incidence Trends of Melanoma and Nonmelanoma Skin Cancers in Jordan From 2000 to 2016. *JCO Glob Oncol*. 2023;**9**:e2200338.
69. McLoone P, McLoone P, Imanbayev K, et al. The incidence and body site of skin cancers in the population groups of Astana, Kazakhstan. *Health Sci Rep*. 2018;**1(7)**:e51.
70. Sella T, Goren I, Shalev V, et al. Incidence trends of keratinocytic skin cancers and melanoma in Israel 2006-11. *The British journal of dermatology*. 2015;**172(1)**:202-7.
71. Norval M, Kellett P, Wright CY. The incidence and body site of skin cancers in the population groups of South Africa. *Photodermatol Photoimmunol Photomed*. 2014;**30(5)**:262-5.
72. Malalaniaina A, Lovasoa T, Mamisoa RI, et al. [Skin cancers in Madagascar: where do we stand?]. *Pan Afr Med J*. 2019;**34**:167.
73. Oseni GO, Olaitan PB, Komolafe AO, et al. Malignant skin lesions in Oshogbo, Nigeria. *Pan Afr Med J*. 2015;**20**:253.

74. Flohil SC, van Tiel S, Koljenovic S, et al. Frequency of non-histologically diagnosed basal cell carcinomas in daily Dutch practice. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2013;**27(7)**:907-11.
75. Flohil SC, Proby CM, Forrest AD, et al. Basal cell carcinomas without histological confirmation and their treatment: an audit in four European regions. *The British journal of dermatology*. 2012;**167 Suppl 2**:22-8.
76. Backman E, Oxelblom M, Gillstedt M, et al. Basal cell carcinoma: Epidemiological impact of clinical versus histopathological diagnosis. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2023;**37(3)**:521-527.
77. Wallberg P, Skog E. The incidence of basal cell carcinoma in an area of Stockholm County during the period 1971-1980. *Acta dermato-venereologica*. 1991;**71(2)**:134-7.
78. Peris K, Fargnoli MC, Garbe C, et al. Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines. *Eur J Cancer*. 2019;**118**:10-34.
79. Rosso S, Zanetti R, Martinez C, et al. The multicentre south European study 'Helios'. II: Different sun exposure patterns in the aetiology of basal cell and squamous cell carcinomas of the skin. *British journal of cancer*. 1996;**73(11)**:1447-54.
80. 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. *The British journal of dermatology*. 2011;**165(3)**:612-25.
81. Dixon AJ, Dixon BF. Ultraviolet radiation from welding and possible risk of skin and ocular malignancy. *Med J Aust*. 2004;**181(3)**:155-7.
82. de Gruijl FR. Skin cancer and solar UV radiation. *Eur J Cancer*. 1999;**35(14)**:2003-9.
83. Rünger TM. Role of UVA in the pathogenesis of melanoma and non-melanoma skin cancer. A short review. *Photodermatol Photoimmunol Photomed*. 1999;**15(6)**:212-6.
84. Cancer research UK. Genes, DNA and cancer, 2023 [cited 2024 April 21st]. Available from: https://www.cancerresearchuk.org/about-cancer/what-is-cancer/genes-dna-and-cancer.
85. Wehner MR, Shive ML, Chren MM, et al. Indoor tanning and non-melanoma skin cancer: systematic review and meta-analysis. *Bmj*. 2012;**345**:e5909.

86. Christensen GB, Ingvar C, Hartman LW, et al. Sunbed Use Increases Cutaneous Squamous Cell Carcinoma Risk in Women: A Large-scale, Prospective Study in Sweden. *Acta dermato-venereologica*. 2019;**99(10)**:878-883.
87. Nielsen K, Måsbäck A, Olsson H, et al. A prospective, population-based study of 40,000 women regarding host factors, UV exposure and sunbed use in relation to risk and anatomic site of cutaneous melanoma. *Int J Cancer*. 2012;**131(3)**:706-15.
88. Stern RS. The risk of squamous cell and basal cell cancer associated with psoralen and ultraviolet A therapy: a 30-year prospective study. *Journal of the American Academy of Dermatology*. 2012;**66(4)**:553-62.
89. Moloney FJ, Comber H, O'Lorcain P, et al. A population-based study of skin cancer incidence and prevalence in renal transplant recipients. *The British journal of dermatology*. 2006;**154(3)**:498-504.
90. Krynitz B, Olsson H, Lundh Rozell B, et al. Risk of basal cell carcinoma in Swedish organ transplant recipients: a population-based study. *The British journal of dermatology*. 2016;**174(1)**:95-103.
91. Jensen AO, Svaerke C, Farkas D, et al. Skin cancer risk among solid organ recipients: a nationwide cohort study in Denmark. *Acta dermato-venereologica*. 2010;**90(5)**:474-9.
92. Silverberg MJ, Leyden W, Warton EM, et al. HIV infection status, immunodeficiency, and the incidence of non-melanoma skin cancer. *J Natl Cancer Inst*. 2013;**105(5)**:350-60.
93. Jensen A, Olesen AB, Dethlefsen C, et al. Chronic diseases requiring hospitalization and risk of non-melanoma skin cancers--a population based study from Denmark. *The Journal of investigative dermatology*. 2008;**128(4)**:926-31.
94. Khandpur S, Porter RM, Boulton SJ, et al. Drug-induced photosensitivity: new insights into pathomechanisms and clinical variation through basic and applied science. *The British journal of dermatology*. 2017;**176(4)**:902-909.
95. Lankerani L, Baron ED. Photosensitivity to exogenous agents. *J Cutan Med Surg*. 2004;**8(6)**:424-31.
96. Honari G. Photoallergy. *Rev Environ Health*. 2014;**29(3)**:233-42.
97. Karagas MR, Stukel TA, Umland V, et al. Reported use of photosensitizing medications and basal cell and squamous cell carcinoma of the skin: results of a population-based case-control study. The Journal of investigative dermatology. 127. United States2007. p. 2901-3.
98. Kaae J, Boyd HA, Hansen AV, et al. Photosensitizing medication use and risk of skin cancer. *Cancer Epidemiol Biomarkers Prev*. 2010;**19(11)**:2942-9.

99. Swedish National Board of Health and Welfare. Statistik om läkemedel 2021. 2022. [cited 2023 October 25th]. Available from: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/statistik/2022-4-7842.pdf.
100. Blowey DL. Diuretics in the treatment of hypertension. *Pediatr Nephrol*. 2016;**31(12)**:2223-2233.
101. Götzinger F, Reichrath J, Millenaar D, et al. Photoinduced skin reactions of cardiovascular drugs-a systematic review. *Eur Heart J Cardiovasc Pharmacother*. 2022;**8(4)**:420-430.
102. International Agency for Research on Cancer Monograph Working G. Some drugs and herbal products. 2015;**108**.
103. Shin D, Lee ES, Kim J, et al. Association Between the Use of Thiazide Diuretics and the Risk of Skin Cancers: A Meta-Analysis of Observational Studies. *J Clin Med Res*. 2019;**11(4)**:247-255.
104. Pedersen SA, Gaist D, Schmidt SAJ, et al. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: A nationwide case-control study from Denmark. *Journal of the American Academy of Dermatology*. 2018;**78(4)**:673-681 e9.
105. Adalsteinsson JA, Muzumdar S, Waldman R, et al. Association between hydrochlorothiazide and the risk of in situ and invasive squamous cell skin carcinoma and basal cell carcinoma: A population-based case-control study. *Journal of the American Academy of Dermatology*. 2021;**84(3)**:669-675.
106. Morales DR, Pacurariu A, Slattery J, et al. Association between hydrochlorothiazide exposure and different incident skin, lip and oral cavity cancers: A series of population-based nested case-control studies. *Br J Clin Pharmacol*. 2020;**86(7)**:1336-1345.
107. León-Muñoz LM, Duarte-Salles T, Llorente A, et al. Use of hydrochlorothiazide and risk of skin cancer in a large nested case-control study in Spain. *Pharmacoepidemiol Drug Saf*. 2021;**30(9)**:1269-1278.
108. Schneider R, Reinau D, Stoffel S, et al. Risk of skin cancer in new users of thiazides and thiazide-like diuretics: a cohort study using an active comparator group. *The British journal of dermatology*. 2021;**185(2)**:343-352.
109. Rouette J, Yin H, Pottegård A, et al. Use of Hydrochlorothiazide and Risk of Melanoma and Nonmelanoma Skin Cancer. *Drug Saf*. 2021;**44(2)**:245-254.
110. 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. *The British journal of dermatology*. 2012;**167 Suppl 2**:1-13.
111. Jensen AO, Thomsen HF, Engebjerg MC, et al. Use of photosensitising diuretics and risk of skin cancer: a population-based case-control study. *British journal of cancer*. 2008;**99(9)**:1522-8.

112. Pottegård A, Hallas J, Olesen M, et al. Hydrochlorothiazide use is strongly associated with risk of lip cancer. *J Intern Med*. 2017;**282(4)**:322-331.
113. Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. *Circulation*. 1998;**97(14)**:1411-20.
114. Alrashidi A, Rhodes LE, Sharif JCH, et al. Systemic drug photosensitivity-Culprits, impact and investigation in 122 patients. *Photodermatol Photoimmunol Photomed*. 2020;**36(6)**:441-451.
115. Koronellos N, Yapijakis C, Katoulis A, et al. Association study indicates combined effect of interleukin-10 and angiotensin-converting enzyme in basal cell carcinoma development. *Arch Dermatol Res*. 2021;**313(5)**:373-380.
116. Yapijakis C, Koronellos N, Spyridonidou S, et al. Association of angiotensin-converting enzyme gene insertion/deletion polymorphism with decreased risk for basal cell carcinoma. *Arch Dermatol Res*. 2013;**305(4)**:333-9.
117. Christian JB, Lapane KL, Hume AL, et al. Association of ACE inhibitors and angiotensin receptor blockers with keratinocyte cancer prevention in the randomized VATTC trial. *J Natl Cancer Inst*. 2008;**100(17)**:1223-32.
118. Moscarelli L, Zanazzi M, Mancini G, et al. Keratinocyte cancer prevention with ACE inhibitors, angiotensin receptor blockers or their combination in renal transplant recipients. *Clin Nephrol*. 2010;**73(6)**:439-45.
119. Schmidt SA, Schmidt M, Mehnert F, et al. Use of antihypertensive drugs and risk of skin cancer. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2015;**29(8)**:1545-54.
120. Elliott WJ, Ram CV. Calcium channel blockers. *J Clin Hypertens (Greenwich)*. 2011;**13(9)**:687-9.
121. Venkata C, Ram S. Beta-Blockers in Hypertension. *The American Journal of Cardiology*. 2010;**106(12)**:1819-1825.
122. Tang H, Fu S, Zhai S, et al. Use of antihypertensive drugs and risk of keratinocyte carcinoma: A meta-analysis of observational studies. *Pharmacoepidemiol Drug Saf*. 2018;**27(3)**:279-288.
123. Kiiski V, de Vries E, Flohil SC, et al. Risk factors for single and multiple basal cell carcinomas. *Archives of dermatology*. 2010;**146(8)**:848-55.
124. Falk M, Anderson CD. Influence of age, gender, educational level and self-estimation of skin type on sun exposure habits and readiness to increase sun protection. *Cancer Epidemiol*. 2013;**37(2)**:127-32.
125. Eriksson H, Lyth J, Mansson-Brahme E, et al. Low level of education is associated with later stage at diagnosis and reduced survival in cutaneous malignant melanoma: a nationwide population-based study in Sweden. *Eur J Cancer*. 2013;**49(12)**:2705-16.
126. Balakrishnan S. Basal cell carcinoma – Pathology. *J Skin Sex Transm Dis*. 2022;**4**:164-70.

127. Bigler C, Feldman J, Hall E, et al. Pigmented basal cell carcinoma in Hispanics. *Journal of the American Academy of Dermatology*. 1996;**34(5 Pt 1)**:751-2.
128. Gloster HM, Jr., Neal K. Skin cancer in skin of color. *Journal of the American Academy of Dermatology*. 2006;**55(5)**:741-60; quiz 761-4.
129. Reiter O, Mimouni I, Gdalevich M, et al. The diagnostic accuracy of dermoscopy for basal cell carcinoma: A systematic review and meta-analysis. *Journal of the American Academy of Dermatology*. 2019;**80(5)**:1380-1388.
130. Ahnlide I, Zalaudek I, Nilsson F, et al. Preoperative prediction of histopathological outcome in basal cell carcinoma: flat surface and multiple small erosions predict superficial basal cell carcinoma in lighter skin types. *The British journal of dermatology*. 2016;**175(4)**:751-61.
131. Reiter O, Mimouni I, Dusza S, et al. Dermoscopic features of basal cell carcinoma and its subtypes: A systematic review. *Journal of the American Academy of Dermatology*. 2021;**85(3)**:653-664.
132. Paoli J, Gyllencreutz JD, Fougelberg J, et al. Nonsurgical Options for the Treatment of Basal Cell Carcinoma. *Dermatol Pract Concept*. 2019;**9(2)**:75-81.
133. Backman EJ, Polesie S, Berglund S, et al. Curettage vs. cryosurgery for superficial basal cell carcinoma: a prospective, randomised and controlled trial. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2022.
134. Bichakjian CK, Armstrong A, Baum C, et al. Guidelines of care for the management of basal cell carcinoma. *Journal of the American Academy of Dermatology*. 2018;**78(3)**:540-559.
135. Tarstedt M, Wennberg A-M. Fotodynamisk terapi ger nya behandlingsmöjligheter vid ytlig hudtumör. *Lakartidningen*. 2007;**104(6)**.
136. Wang H, Xu Y, Shi J, et al. Photodynamic therapy in the treatment of basal cell carcinoma: a systematic review and meta-analysis. *Photodermatol Photoimmunol Photomed*. 2015;**31(1)**:44-53.
137. Arits AH, Mosterd K, Essers BA, et al. Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. *The Lancet Oncology*. 2013;**14(7)**:647-54.
138. Trakatelli M, Morton C, Nagore E, et al. Update of the European guidelines for basal cell carcinoma management. *European journal of dermatology : EJD*. 2014;**24(3)**:312-29.

139. Codazzi D, Van Der Velden J, Carminati M, et al. Positive compared with negative margins in a single-centre retrospective study on 3957 consecutive excisions of basal cell carcinomas. Associated risk factors and preferred surgical management. *J Plast Surg Hand Surg*. 2014;**48(1)**:38-43.
140. Bozan A, Gode S, Kaya I, et al. Long-term Follow-up of Positive Surgical Margins in Basal Cell Carcinoma of the Face. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]*. 2015;**41(7)**:761-7.
141. Sussman LA, Liggins DF. Incompletely excised basal cell carcinoma: a management dilemma? *Aust N Z J Surg*. 1996;**66(5)**:276-8.
142. Richmond JD, Davie RM. The significance of incomplete excision in patients with basal cell carcinoma. *Br J Plast Surg*. 1987;**40(1)**:63-7.
143. Silverman MK, Kopf AW, Bart RS, et al. Recurrence rates of treated basal cell carcinomas. Part 3: Surgical excision. *J Dermatol Surg Oncol*. 1992;**18(6)**:471-6.
144. Armstrong LTD, Magnusson MR, Guppy MPB. Risk factors for recurrence of facial basal cell carcinoma after surgical excision: A follow-up analysis. *J Plast Reconstr Aesthet Surg*. 2017;**70(12)**:1738-1745.
145. Farhi D, Dupin N, Palangie A, et al. Incomplete excision of basal cell carcinoma: rate and associated factors among 362 consecutive cases. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]*. 2007;**33(10)**:1207-14.
146. Kumar P, Watson S, Brain AN, et al. Incomplete excision of basal cell carcinoma: a prospective multicentre audit. *Br J Plast Surg*. 2002;**55(8)**:616-22.
147. Ceder H, Ekström A, Hadzic L, et al. Clinicopathological Factors Associated with Incomplete Excision of High-risk Basal Cell Carcinoma. *Acta dermato-venereologica*. 2021;**101(7)**:adv00496.
148. Hansen C, Wilkinson D, Hansen M, et al. Factors contributing to incomplete excision of nonmelanoma skin cancer by Australian general practitioners. *Archives of dermatology*. 2009;**145(11)**:1253-60.
149. Bogdanov-Berezovsky A, Cohen AD, Glesinger R, et al. Risk factors for incomplete excision of basal cell carcinomas. *Acta dermato-venereologica*. 2004;**84(1)**:44-7.
150. Kimyai-Asadi A, Goldberg LH, Jih MH. Accuracy of serial transverse cross-sections in detecting residual basal cell carcinoma at the surgical margins of an elliptical excision specimen. *Journal of the American Academy of Dermatology*. 2005;**53(3)**:469-74.
151. Shriner DL, McCoy DK, Goldberg DJ, et al. Mohs micrographic surgery. *Journal of the American Academy of Dermatology*. 1998;**39(1)**:79-97.

152. Nätterdahl C, Kappelin J, Persson B, et al. Risk factors for complicated Mohs surgery in the South Sweden Mohs Cohort. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2022;**36(7)**:1113-1117.
153. Lo JS, Snow SN, Reizner GT, et al. Metastatic basal cell carcinoma: report of twelve cases with a review of the literature. *Journal of the American Academy of Dermatology*. 1991;**24(5 Pt 1)**:715-9.
154. Flohil SC, Koljenović S, de Haas ER, et al. Cumulative risks and rates of subsequent basal cell carcinomas in the Netherlands. *The British journal of dermatology*. 2011;**165(4)**:874-81.
155. Ciążyńska M, Pabianek M, Sławińska M, et al. Risk Factors and Clinicopathological Features for Developing a Subsequent Primary Cutaneous Squamous and Basal Cell Carcinomas. *Cancers (Basel)*. 2022;**14(13)**.
156. Gordon LG, Rowell D. Health system costs of skin cancer and cost-effectiveness of skin cancer prevention and screening: a systematic review. *European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)*. 2015;**24(2)**:141-9.
157. Tinghog G, Carlsson P, Synnerstad I, et al. Societal cost of skin cancer in Sweden in 2005. *Acta dermato-venereologica*. 2008;**88(5)**:467-73.
158. National Board of Health and Welfare. Läkemedelsregistret. 2023 [cited 2023 October 30th]. Available from: https://www.socialstyrelsen.se/statistik-och-data/register/lakemedelsregistret/.
159. WHO Collaborating Centre for Drug Statistics Methodology. International language for drug utilization research. 2023. [cited 2023 October 30th]. Available from: https://www.whocc.no/.
160. National Board of Health and Welfare. Patientregistret. 2023. [cited 2023 October 30th]. Available from: https://www.socialstyrelsen.se/statistik-och-data/register/patientregistret/.
161. National Board of Health and Welfare. Cancerregistret 2023 [cited 2023 October 30th]. Available from: https://www.socialstyrelsen.se/statistik-och-data/register/cancerregistret/.
162. National Board of Health and Welfare. Dödsorsaksregistret 2023 [cited 2023 October 30th]. Available from: https://www.socialstyrelsen.se/statistik-och-data/register/dodsorsaksregistret/.
163. Statistics Sweden. Longitudinell integrationsdatabas för sjukförsäkrings- och arbetsmarknadsstudier (LISA) [cited 2023 October 30th]. Available from: https://www.scb.se/vara-tjanster/bestall-data-och-statistik/bestalla-mikrodata/vilka-mikrodata-finns/longitudinella-register/longitudinell-integrationsdatabas-for-sjukforsakrings--och-arbetsmarknadsstudier-lisa/.

164. Statistics Sweden. Mikrodata för Registret över totalbefolkningen (RTB) [cited 2023 October 30th]. Available from: https://www.scb.se/vara-tjanster/bestall-data-och-statistik/bestalla-mikrodata/vilka-mikrodata-finns/individregister/registret-over-totalbefolkningen-rtb/.
165. Björk J. *Praktisk epidemiologi för medicin, vård och folkhälsa.* 1 ed: Liber; 2019.
166. Bray F, Colombet M, Mery L, et al. Cancer Incidence in Five Continents Volume XI, 2021 [cited 2023 November 1st]. Available from: https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Scientific-Publications/Cancer-Incidence-In-Five-Continents%C2%A0Volume-XI-2021.
167. R Core Development Team. R: A language and environment for statistical computing. In: R Foundation for Statistical Computing. Vienna, editor. 2021.
168. Rich JT, Neely JG, Paniello RC, et al. A practical guide to understanding Kaplan-Meier curves. *Otolaryngol Head Neck Surg*. 2010;**143(3)**:331-6.
169. Spruance SL, Reid JE, Grace M, et al. Hazard ratio in clinical trials. *Antimicrob Agents Chemother*. 2004;**48(8)**:2787-92.
170. Koletsi D, Pandis N. Conditional logistic regression. *Am J Orthod Dentofacial Orthop*. 2017;**151(6)**:1191-1192.
171. Björk J. *Praktisk statistik för medicin och hälsa*. 1 ed: Liber; 2010.
172. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria2019 [cited 2020 Jan 16]. Available from: https://www.R-project.org/.
173. Kim HY. Statistical notes for clinical researchers: Chi-squared test and Fisher's exact test. *Restor Dent Endod*. 2017;**42(2)**:152-155.
174. Aickin M, Gensler H. Adjusting for multiple testing when reporting research results: the Bonferroni vs Holm methods. *Am J Public Health*. 1996;**86(5)**:726-8.
175. National Cancer Institute. World (WHO 2000-2025) Standard, [cited 2023 November 1st]. Available from: https://seer.cancer.gov/stdpopulations/world.who.html.
176. Bath-Hextall F, Leonardi-Bee J, Smith C, et al. Trends in incidence of skin basal cell carcinoma. Additional evidence from a UK primary care database study. *Int J Cancer*. 2007;**121(9)**:2105-8.
177. de Vries E, Louwman M, Bastiaens M, et al. Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973. *The Journal of investigative dermatology*. 2004;**123(4)**:634-8.
178. 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(1)**:6-10.

179. Boldeman C, Jansson B, Dal H, et al. Sunbed use among Swedish adolescents in the 1990s: a decline with an unchanged relationship to health risk behaviors. *Scand J Public Health*. 2003;**31(3)**:233-7.
180. Flohil SC, van der Leest RJ, Arends LR, et al. Risk of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma: a systematic review and meta-analysis. *Eur J Cancer*. 2013;**49(10)**:2365-75.
181. Richmond-Sinclair NM, Pandeya N, Williams GM, et al. Clinical signs of photodamage are associated with basal cell carcinoma multiplicity and site: a 16-year longitudinal study. *Int J Cancer*. 2010;**127(11)**:2622-9.
182. Kappelin J, Green AC, Ingvar A, et al. Incidence and trends of basal cell carcinoma in Sweden: a population-based registry study. *The British journal of dermatology*. 2022;**186(6)**:963-969.
183. van Iersel CA, van de Velden HV, Kusters CD, et al. Prognostic factors for a subsequent basal cell carcinoma: implications for follow-up. *The British journal of dermatology*. 2005;**153(5)**:1078-80.
184. Bresler SC, Padwa BL, Granter SR. Nevoid Basal Cell Carcinoma Syndrome (Gorlin Syndrome). *Head Neck Pathol*. 2016;**10(2)**:119-24.
185. Black JO. Xeroderma Pigmentosum. *Head Neck Pathol*. 2016;**10(2)**:139-44.
186. Brøndum-Jacobsen P, Nordestgaard BG, Nielsen SF, et al. Skin cancer as a marker of sun exposure associates with myocardial infarction, hip fracture and death from any cause. *Int J Epidemiol*. 2013;**42(5)**:1486-96.
187. Tseng HW, Shiue YL, Tsai KW, et al. Risk of skin cancer in patients with diabetes mellitus: A nationwide retrospective cohort study in Taiwan. *Medicine (Baltimore)*. 2016;**95(26)**:e4070.
188. Birkeland SA, Løkkegaard H, Storm HH. Cancer risk in patients on dialysis and after renal transplantation. *Lancet*. 2000;**355(9218)**:1886-7.
189. Ruiter R, Visser LE, Eijgelsheim M, et al. High-ceiling diuretics are associated with an increased risk of basal cell carcinoma in a population-based follow-up study. *Eur J Cancer*. 2010;**46(13)**:2467-72.
190. Siiskonen SJ, Koomen ER, Visser LE, et al. Exposure to phototoxic NSAIDs and quinolones is associated with an increased risk of melanoma. *Eur J Clin Pharmacol*. 2013;**69(7)**:1437-44.
191. Neufcourt L, Zins M, Berkman LF, et al. Socioeconomic disparities and risk of hypertension among older Americans: the Health and Retirement Study. *J Hypertens*. 2021;**39(12)**:2497-2505.
192. Leng B, Jin Y, Li G, et al. Socioeconomic status and hypertension: a meta-analysis. *J Hypertens*. 2015;**33(2)**:221-9.

193. Nardone B, Majewski S, Kim AS, et al. Melanoma and Non-Melanoma Skin Cancer Associated with Angiotensin-Converting-Enzyme Inhibitors, Angiotensin-Receptor Blockers and Thiazides: A Matched Cohort Study. *Drug Saf*. 2017;**40(3)**:249-255.
194. Ramdas K, van Lee C, Beck S, et al. Differences in Rate of Complete Excision of Basal Cell Carcinoma by Dermatologists, Plastic Surgeons and General Practitioners: A Large Cross-Sectional Study. *Dermatology*. 2018;**234(3-4)**:86-91.

Printed by Media-Tryck, Lund 2024 NORDIC SWAN ECOLABEL 3041 0903

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Clinical Sciences

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2024:53
ISBN 978-91-8021-546-6
ISSN 1652-8220