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Risk factors and diagnostic tools in the skin cancer era

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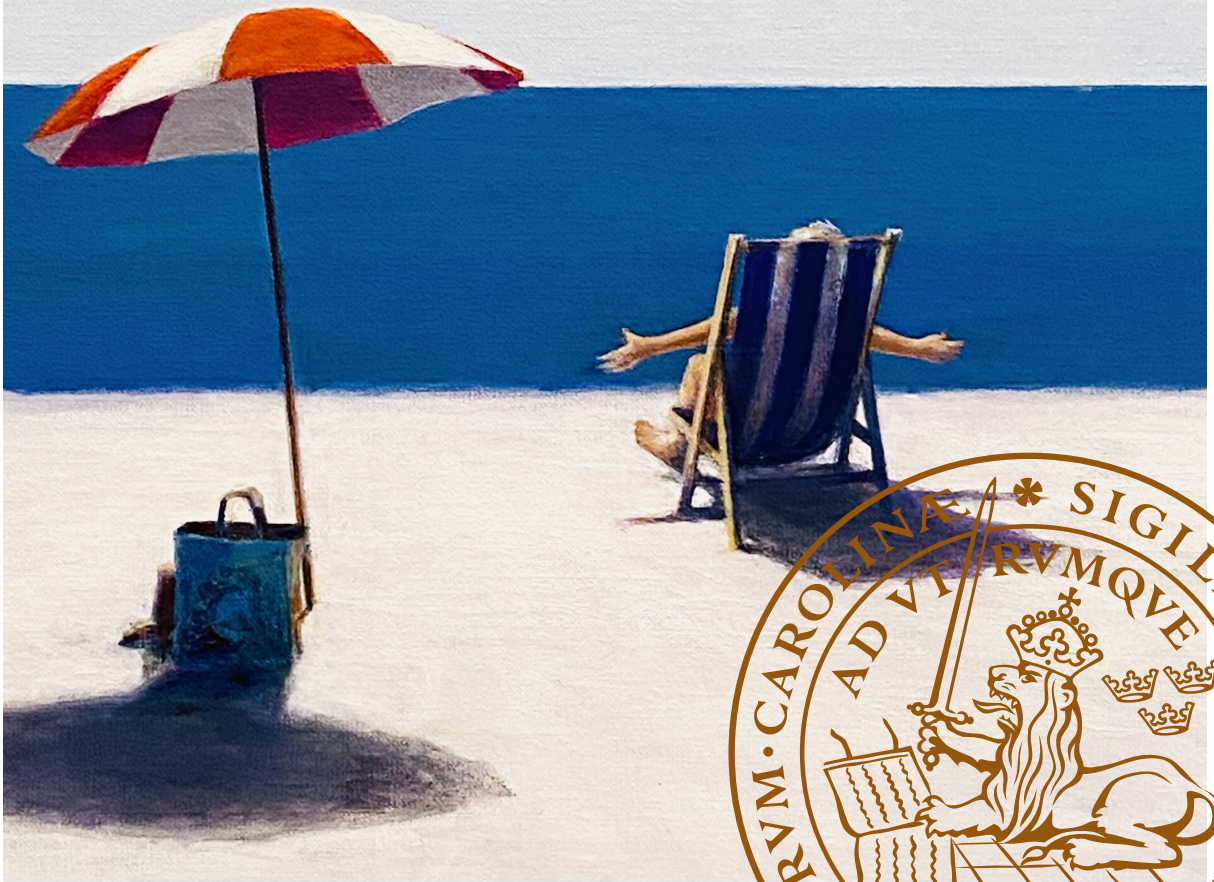

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Gustav Boelsgaard Christensen is currently working as a specialist, senior consultant and as Head of the Department of Dermatology and Venereology in Lund, Skåne University Hospital. His area of special interest is skin cancer.

His research areas includes epidemiology, risk factors and diagnostic tools in the field of skin cancer.

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Gustav Boelsgaard Christensen

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In papers I and III we utilized the large MISS-cohort, consisting of Swedish women with prospectively collected information on phenotypic traits and sun exposure. The cohort was matched with the National Cancer Registry and the Swedish Prescribed Drug Registry. In paper II, equivocal pigment lesions were, before excision, examined using a novel HSI device, to compare the accuracy of melanoma diagnosis, in relation to histopathological outcome. In paper IV, we used the population-based Swedish Melanoma Registry, including 1,000 AMs examining trends in incidence rates and melanoma-specific survival from 1990 to 2020).

In paper I, we showed that red and light blond hair and freckles, as well as immunosuppressive medication and sunbed use were risk factors for cutaneous squamous cell carcinoma (cSCC). In paper II, we examined 202 lesions with HSI, reaching a sensitivity of 96.7 % for detecting cMM and a specificity of 42.1 % for detecting benign pigmented skin lesions. In paper III, we showed that prescriptions of estrogen increased risk of Basal cell carcinoma (BCC), cSCC and melanoma (cMM). Prescription of loop diuretic medication was exclusively associated with risk of cSCC while thiazide use was associated with risk of cMM and BCC. In paper IV no significant change of incidence trends could be observed during the studied period. Male sex, age over 70 years and high tumor thickness were factors linked to lower melanoma specific survival.

In conclusion: several risk factors for skin cancer in women were detected, highlighting foremost the negative effect of sunbed use and use of estrogen. The non-invasive HSI device might be a valuable clinical tool for detecting cMM in the future. Lastly, incidence and mortality rates of AM in Sweden have remained steady over the last three decades, in stark contrast to cMM found on other body sites.

Key words: risk factors, sunbeds, incidence, UVR, cutaneous malignant melanoma, basal cell carcinoma, cutaneous squamous cell carcinoma, photosensitizing drugs, epidemiology, hyperspectral imaging.

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MADE IN SWEDEN

To Anna, Lykke, Ludvig and Smilla, you are my life.

Table of Contents

Abstract

In Sweden, the incidence rates concerning skin cancer are steadily increasing. To counteract this development, it is imperative to understand the epidemiology of the different skin cancers, the role of both UVR and skin type, risk factors and how to best diagnose skin cancer.

The aim of this thesis is to explore risk factors for skin cancer in women, including photosensitizing drugs, to test a novel diagnostic tool using hyperspectral imaging (HSI) on a fair skinned population in Sweden and to explore the epidemiology of acral melanomas (AM) in Sweden.

In papers I and III we utilized the large MISS-cohort, consisting of Swedish women with prospectively collected information on phenotypic traits and sun exposure. The cohort was matched with the National Cancer Registry and the Swedish Prescribed Drug Registry. In paper II, equivocal pigment lesions were, before excision, examined using a novel HSI device, to compare the accuracy of melanoma diagnosis, in relation to histopathological outcome. In paper IV, we used the population-based Swedish Melanoma Registry, including 1,000 AMs examining trends in incidence rates and melanoma-specific survival from 1990 to 2020).

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In conclusion: several risk factors for skin cancer in women were detected, highlighting foremost the negative effect of sunbed use and use of estrogen. The non-invasive HSI device might be a valuable clinical tool for detecting cMM in the future. Lastly, incidence and mortality rates of AM in Sweden have remained steady over the last three decades, in stark contrast to cMM found on other body sites.

Populärvetenskaplig sammanfattning

Huden är kroppens största organ och har flera funktioner. Den främsta funktionen är att vara en fysisk barriär mot UV-strålning, mekanisk påverkan och mot mikroorganismer som bakterier, svampar och virus. Huden ser även till att hålla ordning på kroppstemperatur och vätskebalans, samt att den bildar D-vitamin när solens strålar träffar huden. D-vitamin är nödvändig för att upprätthålla kalkbalansen i skelett och tänder. I huden finns också många nervceller, som regerar på smärta, tryck, beröring och temperatur.

Huden är grovt indelad i tre lager, överhuden (epidermis), läderhuden (dermis) och underhuden (subcutis). Hudceller, de så kallade keratinocyterna, hittas i överhuden där de bildar ett stryktåligt hornlager längst ut. Längst ner i överhuden finns basalcellslagret där keratinocyterna produceras. Här hittar vi också de pigmentproducerande melanocyterna som utgör ca en tiondel av cellerna i huden. I melanocyterna produceras pigmentet melanin som färgar huden och håret. Där finns två sorter, det rödgula pheomelanin och det brunsvarta eumelanin. Genom melanocyternas tentakler avlevereras melaninet till keratinocyterna, där melaninets huvuduppgift är att skydda keratinocyternas DNA i cellkärnan mot UV-strålning från solen. När huden träffas av solljus ökas produktionen av melanin som blir mörkare/brunare för att skydda mot UV-strålningen.

Ultraviolett (UV) strålning, får vi främst från solljus, men hittas även i solarier. Ca 95% av UV-strålningen utgörs av UVA och resterande av UVB. UV-strålning har skadliga effekter på huden, främst angriper den DNA i cellernas kärna som i sin tur skapar mutationer. När tillräckligt många mutationer inträffat kan detta leda till att en cell övergår till att bli en malign cancercell och delar sig ohämmat, förstör vävnader lokalt och till slut även metastasera. Detta är en komplicerad process i många steg. Det är vetenskapligt klarlagt att det är UV-strålningen som är den största orsaken till utvecklandet av alla typer av hudcancer. Det är samtidigt också vetenskapligt tydligt att individer med ljusare hudtyp drabbas oftare av hudcancer. Mörkare hudtyper kan också drabbas av hudcancer, men det är mycket ovanligare.

Hudcancer är ett samlingsnamn för cancer som uppkommer i huden. Det finns många typer av hudcancer som uppkommer ur olika typer av celler som finns i huden. När man använder termen hudcancer, menar man oftast de tre vanligaste hudcancrarna vi har, nämligen basalcellscancer, skivepitelcancer och malignt melanom. De två senare kan uppträda i andra vävnader än hud, men detta är ovanligare. Det är vetenskapligt klarlagt att hudcancer ökat i de flesta ljushyllta populationerna i världen. Detta är också sant för befolkningen i Sverige.

Basalcellscancer har sitt ursprung i keratinocyterna. Detta är den överlägset vanligaste hudcancern och drabbade ca 70000 svenskar 2021, jämnt fördelade mellan könen. Det är även den minst farliga av de tre. Den växer lokalt, oftast långsamt men kan invadera och förstöra vävnaden den växer i. Där finns olika typer av basalcellscancer, vissa mer lokalt aggressiva än andra. Basalcellscancer kan i princip inte sprida sig, förutom i vissa undantagsfall, men det är ytterst ovanligt.

Skivepitelcancer i huden utgår också från keratinocyterna, är lite mindre vanlig än basalcellscancer. Lite mer än 11000 drabbades av skivepitelcancer i huden år 2021 i Sverige där man såg en viss övervikt för män. Denna tumörform växer också långsamt, inte sällen som en skrovlig upphöjd knuta. Precis som basalcellscancer uppträder de ofta på kroppsdelar som utsatts för mycket sol, främst huvud-hals området samt underarmar och handryggar. Organtransplanterade, vilka står på långvarig immundämpande medicin, har en ökad risk att drabbas av skivepitelcancer. Även om det är ovanligt, så kan skivepitelcancer sprida sig. Ca 90 personer avled till följd av skivepitelcancer 2021.

Malignt melanom utgår i sin tur från de pigmentproducerande melanocyterna. Detta är den farligaste formen av hudcancer. Ca 4800 personer drabbades av melanom 2021, detta är en fördubbling av antalet fall jämfört med 20 år sedan. Trots denna massiva ökning, ligger antalet dödsfall på en jämn nivå över tid, med drygt 500 dödsfall per år. De flesta melanom uppkommer ”de novo”, men de kan också utvecklas ur vanliga leverfläckar. Oftast rör det sig om en pigmentering som långsamt växer till sig, ändrar färg och blir mörkare och oregelbunden. Det finns flera subtyper, i denna avhandling tittar vi bland annat närmare på melanom som uppkommer på händer och fötter, så kallade akrala melanom.

Alla typer av hudcancer ökar i den svenska befolkningen. För att kunna förstå varför detta sker är det viktigt att undersöka hur och vem som riskerar att bli drabbad. För detta krävs epidemiologiska studier som över tid tittar på hur många som drabbas, vem som drabbas, hur ofta och om där finns någon annan bakomliggande orsak till att vissa drabbas mer än andra. Genetiska variabler som hår-, ögon- och hudfärg går inte att påverka. Här vet vi att ljushyllta personer drabbas oftare av hudcancer. Andra variabler kan man däremot påverka, som till exempel hur man umgås med solen, om man använder solarium eller röker.

I denna avhandling har vi i två studier undersökt en stor grupp, en så kallad kohort, av slumpvis utvalda kvinnor från södra Sverige. 1990 bjöds 40000 kvinnor i åldrarna 25-65 in för att delta i studien, ca 30000 tackade ja och fick fylla i ett större frågeformulär om deras ögon- och hårfärg, ärftlighet för hudcancer, hur många födelsemärken de hade på en arm samt flertalet frågor om hur de reagerade på solljus och hur de umgås med

solen. Denna information matchades bland annat mot Nationella Cancerregistret, Dödsorsaksregistret och register om förskrivning av läkemedel.

I vår första delstudie (paper I i denna avhandling) undersökte vi riskfaktorer för skivepitelcancer. Här kunde vi se att deltagarna hade en ökad risk för att utveckla skivepitelcancer om man hade rött till ljusblont hår och om man hade fräknar. Vidare var det tydligt att risken ökade om man stod på immundämpande medicin samt att solarieanvändning ökade risken. Här kunde vi också visa att ju mer man använde sig av solarier, desto med skivepitelcancer fick man. I den andra studien av denna kohort (benämnd som paper III i denna avhandling), undersökte vi sambandet mellan fotosensiterande läkemedel och alla de tre vanligaste hudcancrarna. Fotosensiterande läkemedel ökar hudens känslighet för UV-strålning och gör att man lättare bränner sig, vilket i sin tur ger DNA skador och mutationer och ökar således risken för att utveckla en hudcancer. Många vanliga och ofta använda läkemedel har fotosentitiserande egenskaper. I den undersökt gruppen av kvinnor kunde vi konstatera att vi såg ett samband mellan postmenopausal (efter menstruationer slutat) behandling med östrogen och riskökning för alla tre hudcancrar. Vätskedrivande läkemedel används ofta för att behandla högt blodtryck. Med undergruppen tiazider kunde vi se ett samband med basalcellscancer och melanom. I den andra undergruppen med loop-diuretika såg vi ett samband med skivepitelcancer. Vidare undersöktes flera andra läkemedelsgrupper som inte visade lika tydliga resultat.

Med tanke på att hudcancerkurvorna pekar fortsatt uppåt är det viktigt att hitta och behandla hudcancern så fort det går. För att ställa diagnos finns flera hjälpmedel tillgängliga. Det vanligaste som används är dermatoskopi, vilket i princip är ett förstoringsglas med ljuskälla som man lägger an på huden över en misstänkt hudförändring eller hudcancer. Dermatoskopi ökar den diagnostiska träffsäkerheten jämfört med det blotta ögat. Det är billigt och enkelt att använda. Därtill har man utvecklat möjlighet att ta foto med dermatoskopitillsats, vilket gör det möjligt att följa misstänkta hudförändringar över tid på ett enkelt sätt. Men för att ställa diagnosen helt och fullt behövs fortsatt mikroskopisk undersökning av den bortskurna förändringen, så kallad patologisk bedömning. Således behövs det ett sätt att utan att skära bort förändringen kunna säkerställa om förändringen är god- eller elakartad. Det finns flera tekniker på marknaden, men ingen har riktigt slagit ut i den kliniska vardagen. Jämfört med dermatoskopi så är teknikerna otympliga, inte användarvänliga och tar lång tid. I vår studie undersökte vi en ny teknik grundad på hyperspektralmätning av pigmenterade hudförändringar på individer med ljusare hudtyp. Maskinen, HSI-03, är utvecklad i Japan och testad på en japansk population. Vi ville undersöka hur träffsäker maskinen var på en svensk befolkning, som generellt sett är mer ljushyllta än japaner. Vi kunde konstatera att träffsäkerheten för att ställa diagnosen melanom var hög, upp

mot 97%, vilket är högre nivåer än vad man kan komma upp i med dermatoskopi. Dock var träffsäkerheten vad gäller att ställa diagnosen ofarlig leverfläck bara ca 42%. Hyperspektraltekniken är i sin linda och behöver ta flera steg i sin utveckling för att kunna användas i den kliniska vardagen, men tekniken fungerade och kan vara ett framtida hjälpmedel för att ställa diagnos.

I den sista studien i denna avhandling undersöktes hur många och vem som drabbats av den specifika undergruppen melanom på händer och fötter under åren 1990-2020. Vi undersökte också överlevnad i denna undergrupp, som också kallas akrala melanom (AM). Data för vår studie kom från Nationella Melanom Registret. Här kunde vi se att insjuknande och dödlighet i AM var stabil över den undersökta tidsperioden, trots att AM kan vara svår att diagnosticera eftersom den inte sällan inte uppträder som vanliga melanom på huden. Antal insjuknande i AM står i bjärt kontrast till melanom uppkomna på andra områden av huden, som mer än dubblerats under samma tidsperiod. Sannolikt är inte AM lika känslig för UV-strålning. Mer kunskap om AM behövs för att så tidigt som möjligt ställa diagnos och behandla.

Vi har i denna avhandling täckt delar av det stora fält av forskning som finns inom hudcancer. Vi har kunnat visa att riskfaktorer för kvinnor spelar roll när det handlar om utvecklandet av hudcancer. Detta är viktig kunskap att förmedla, kanske främst vad gäller solarieanvändning eftersom vi vet att kvinnor använder det mer än män. Då skulle man kunna rikta informationskampanjer mot just solarieanvändning. Vissa länder har helt förbjudit solarium för kosmetiskt bruk, i Sverige har vi infört åldersrestriktioner. Med tanke på det ökande insjuknandet i hudcancer så kanske våra myndigheter måste tänka om och även här inför ett totalt förbud mot solarieanvändning. Våra fynd kan också användas som en del av en bredare kunskapsgrund när det gäller förskrivning av hormonbehandling innehållande östrogen till kvinnor. Kanske skall man informera om vikten av att skydda sig extra mot solen när man står på dessa behandlingar, med eller utan medicinering av vätskedrivande i form av tiazider eller loop-diuretika.

List of Papers

Paper I

Gustav Boelsgaard Christensen, Christian Ingvar, Linda Werner Hartman, Håkan Olsson, and Kari Nielsen.
Sunbed use increases cutaneous squamous cell carcinoma risk in women: a large-scale, prospective study in Sweden. ACTA Dermato-venereologica, Volume 99, 2019, Pages 878-883

Paper II

Gustav Boelsgaard Christensen, Takashi Nagaoka, Yoshio Kiyohara, Iva Johansson, Christian Ingvar, Atsushi Nakamura, Takayuki Sota, Kari Nielsen.

Clinical performance of a novel hyperspectral imaging device for cutaneous melanoma and pigmented skin lesions in Caucasian skin. Skin Research and Technology, Volume 27, Issue 5, Pages 803-809, September 2021

Paper III

Gustav Boelsgaard Christensen, Johan Kappelin, Jenny Sandgren, Kari Nielsen and Åsa Ingvar.

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

In manuscript

Paper IV

Teo Helkkula, Gustav Boelsgaard Christensen, Rasmus Mikiver, Åsa Ingvar, Karolin Isaksson and Kari Nielsen.

Acral Melanoma Incidence and Survival Trends in Sweden: Insights from a

Population-Based Study 1990-2020.

In manuscript

Related papers not included in thesis

Kato K, Nemoto M, Kimura Y, Kiyohara Y, Koga H, Yamazaki N Christensen G., Ingvar C., Nielsen K., Nakamura A., Sota T. and Nagaoka T.

Performance improvement of automated melanoma diagnosis system by data augmentation.

Advanced Biomedical Engineering. 2020 Mar 19;9:62-70.

Sanna A, Harbst K, Johansson I, Christensen G, Lauss M, Mitra S, Rosengren F, Häkkinen J, Vallon-Christersson J, Olsson H, Ingvar Å, Isaksson K, Ingvar C, Nielsen K, Jönsson G.

Tumor genetic heterogeneity analysis of chronic sun-damaged melanoma

Pigment Cell Melanoma Res 2020 May;33(3):480-489. doi 101111 / pmcr.1285.1 Epub 2019 Dec 23

Helkkula T, Christensen G, Ingvar C, Isaksson K, Harbst K, Persson B, Ingvar Å, Hafström A, Carneiro A, Gaspar V, Jönsson G, Nielsen K.

BioMEL: a translational research biobank of melanocytic lesions and melanoma

BMJ Open 2024; 0.e069694. doi 10.1136/bmjopen-2022-069694

Saleh K, Gebre-Medhin G, Christensen G

Pancreatic cancer occurrence in Ferguson-Smith syndrome

JAAD Case Rep. 2018 Jul; 4(6): 565–567. Published online 2018 Jun 12.

Authors contribution

Paper I

The author, Gustav Christensen (GC), took part in the scientific planning of the study and discussed the data management plan. Furthermore, GC had the main correspondence with the statistician to collaborate on the project. After some initial guidance from the supervisors and the statistician, GC compiled the statistics, the tables, figures and the interpretation of the data/results. GC wrote the draft and submitted the paper as the first author. GC was also the corresponding author in the peer review process before publication.

Paper II

GC took a main lead in the scientific planning of the study in cooperation with supervisors and researchers from Japan. Before the study started, GC undertook a research visit to the Japanese University to study and train the method and learn how to use the device. In Sweden, GC included all research objects (patients) and performed all the hyperspectral imaging on all patients of the study. Moreover, GC was the main contact person for the Japanese research partners, who worked together concerning statistics and presentation. Furthermore, GC wrote the draft and was the first author of the published article and was the corresponding author in the whole peer review process.

Paper III

GC participated in the study's scientific planning and came up with novel ideas about study design. GC was involved in the data extraction work, in cooperation with supervisors. GC had during the whole project the main correspondence with the statistician appointed for the project. GC independently compiled data and statistics and analysed the main results. Furthermore, GC was the first author of the published article and is the corresponding author also in this peer review process. The paper is currently under revision and has not yet been published.

Paper IV

GC took an important part in all scientific planning and study design, in cooperation with first author Teo Helkkula, co-authors and supervisors. He was involved in the process of ethical application. GC worked together with co-authors on statistical output from the appointed statistician. Together with author Helkkula, GC was involved in compiling data and analysing results. Furthermore, in this paper GC has been involved in the peer review process but not as the corresponding author. The paper is currently under revision and has not yet been published.

Preface

I started my dermatological career in 2007 when I joined the Department of Dermatology and Venereology in Lund, at Skåne University Hospital. After some hesitation in choice of medical specialty and a year away from the department, I returned as a resident in 2008. Initially trying to learn as much as possible about the vast number of dermatological diseases, I eventually gravitated towards subspecializing in the field of skin cancer. I thoroughly enjoy all aspects of dermatology and all the interaction you have with the patients over the whole age spectrum. However, patients with skin cancer seems to appeal to me the best, including the surgical aspects of treatment.

A couple of years into my residency, the head of the department, Dr Bertil Persson, brought me along for a scientific meeting with Lund Melanoma Study Group, a translational research group consisting of residents, specialists and professors from oncology, surgery, dermatology, ENT, pathology and biomedicine. I can still remember the headaches I got after those first meetings. The scientific discussions on results and new projects and namedropping went at a fast pace and in areas that were new to me. But I continued going to the meetings to observe and learn, and eventually we decided on a projects for me and we planned a research path with the goal of doctoral dissertation.

Together with my then main supervisor, professor Christian Ingvar, and my then co-supervisor, associate professor Kari Nielsen, we planned the first study and registration to become a PhD-student in 2014 at the Department of Clinical Sciences, Lund University. Parallel to this, I became a specialist in Dermatology and Venereology in 2013. A year later, I became the Head of the Department. This was just a temporary position for half a year until they found someone more fitting. As it was, I was asked to continue and I have now been in charge for almost 10 years. Naturally, this was not good news for my scientific endeavours and I cannot really recommend being head of a department and being a PhD-student.

So, my scientific progress has arguably been somewhat slow, but in a steady forward motion, soon expanding over 10 years. Our initial PhD-plan on which studies to proceed with changed somewhat under the way, which of course is not unusual over a span of a PhD-project. The scientific scope of this thesis is broad with three projects involving different topics of epidemiology concerning the three most common skin cancers. The fourth paper involved testing av novel non-invasive diagnostic device from Japan. This project also took me to Japan, visiting the researchers behind the device at Shizuoka Cancer Center at the foot of Mount Fuji.

My PhD-project has been a fantastic journey. It has not been all smiles all the time. Sometimes asking myself if it really is worth it. Often with a feeling of bad conscience of being able to do more research. During my prolonged scientific process, I have met so many interesting researcher devoted to their scientific work, truly believing in that they work for the benefit of not only the patient in front of them, but also the patients in the future. From a career perspective, I do not have to research. I am a senior consultant and Head of a department at a university hospital. So why do I research? Maybe because of a notion that I possibly could help my patients by expanding knowledge. An also, maybe to challenge myself.

In this thesis, I have tried to portray the main paths of development of skin cancer. Below, I will briefly explain the journey the thesis is set on to better understand our aims, results and findings of the papers of this thesis. Starting with the structure and purpose of the skin, illuminating the role of pigmentation in regard to skin cancer and why it can arise. The role of skin type and the impact of ultraviolet radiation on the skin cannot be underestimated and is here discussed further. The thesis continuous on with risk factors in skin cancer and the different types of skin cancer that has been in focus in the four papers, including a run-down of diagnostic tools in the clinical setting. This marks the end of the Introduction, and I thereafter show the different aspects of the four papers, including aims, methodology, results, discussion and our main conclusions.

Abbreviations

AK	Actinic keratosis
ACEi	Angiotensin converting enzyme inhibitor
AM	Acral melanoma
ALM	Acral lentiginous melanoma
ARB	Angiotensin receptor blocker
ATC	Anatomical Therapeutic Chemical classification system
BCC	Basal cell carcinoma
CCB	Calcium channel blocker
CI	Confidence interval
cMM	cutaneous Malignant melanoma
cSCC	cutaneous Squamous cell carcinoma
DDD	Dispensed daily doses
DN	Dysplastic nevus
DNA	Deoxyribonucleic acid
DOPA	Dihydroxyphenylalanine
FDA	Food and Drug Administration
FN	False negative
FP	False positive
HR	Hazard Ratio
HSI	Hyperspectral imaging
HRT	Hormone replacement therapy
IARC	International Agency for Research on Cancer
MN	Melanocytic nevi
LM	Lentigo maligna
LMM	Lentigo maligna melanoma
MISS	Melanoma Inquiry in Southern Sweden
MN	Melanocytic nevus
MELTUMP	Melanocytic tumour of uncertain malignant potential
MSM	Melanoma specific mortality
MSS	Melanoma specific survival
NM	Nodular melanoma
NMSC	Non-melanoma skin cancer
NSAID	Non-steroidal anti-inflammatory drugs
OC	Oral contraceptives
OTR	Organ Transplant Recipients
OR	Odds ratio
PPi	Proton pump inhibitor

PSL	Pigmented skin lesion
ROS	Reactive oxygen species
SAMPUS	Superficial atypical melanocytic proliferations of uncertain significance
SD	Standard deviation
SK	Seborrhoeic keratosis
SSM	Superficial spreading melanoma
SweMR	Swedish Melanoma Registry
TN	True negative
TP	True positive
UV	Ultraviolet
UVA	Ultraviolet A radiation
UVB	Ultraviolet B radiation
UVR	Ultraviolet Radiation
WHO	World Health Organization

Introduction

The human skin

The human skin consists of three layers divided into epidermis, dermis and subcutis (Figure 1). Being one of the largest organs of the body, the skin weighs about 4-5 kg and has a surface of about 1,5-2,0 m^2. The epidermis, the outermost avascular layer, consist of mainly keratinocytes and a smaller number of melanocytes, which are the pigment producing cells. The mechanosensory Merkel cells and the dendritic immunocompetent Langerhans cells and resident T-cells are also present in the epidermis. In the bottom of the epidermis, the keratinocytes proliferate at basal layer and then differentiate up through the epidermis, eventually losing its nucleus and ultimately forming a cornified layer. Finally, the keratinocytes shed off. This layer is thin, tough, and semipermeable and serves as a physiological barrier [1,2].

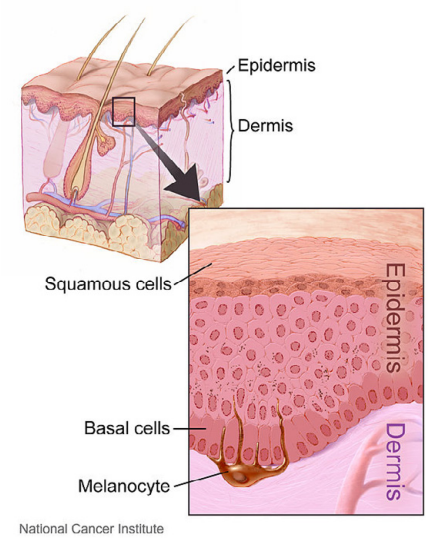

Figure 1: Anatomy of the skin. Author: Wikimedia Commons contributors, Publisher: Wikimedia Commons. Date of last revision: 3 November 2022 20:18 UTC. Date retrieved: 29 January 2024 08:34 UTC. Permanent.URL: https://commons.wikimedia.org/w/index.php?title=File:Layers_of_the_skin.jpg&oldid=702288430

Beneath the basal layer and the dermoepithelial junction comes the dermis, which is a vascularized connective tissue that supports the skin both structurally and nutritionally. A matrix of collagen and elastin fibers gives the skin strength and flexibility. In the dermis, we also find a complex network of hair follicles, sebaceous- and sweat glands, lymphatic structures, nerve endings, and blood vessels. This network is instrumental in providing nutrients and oxygen in order for the skin to work as intended[2]. The deepest layer of the skin is the subcutis. This layer consists of a looser connective tissue of adipocytes (Figure 2).

The skin of the human body has several capacities and purposes, and the three different layers work together. Foremost, it is a protective layer thar covers our body and serves as barrier against external elements such as microorganisms, ultraviolet radiation (UVR), toxins, and provides padding against mechanical trauma. It also has an important function as an insulator and thermoregulator and the prevention of water-loss. Vitamin D, that have several important functions in the body, is synthesized in the skin. In the skin, we have many types of nerve endings that gives us information about the surroundings we are in. The melanocytes in the epidermis produce the pigment that color our skin, hair, and eyes.

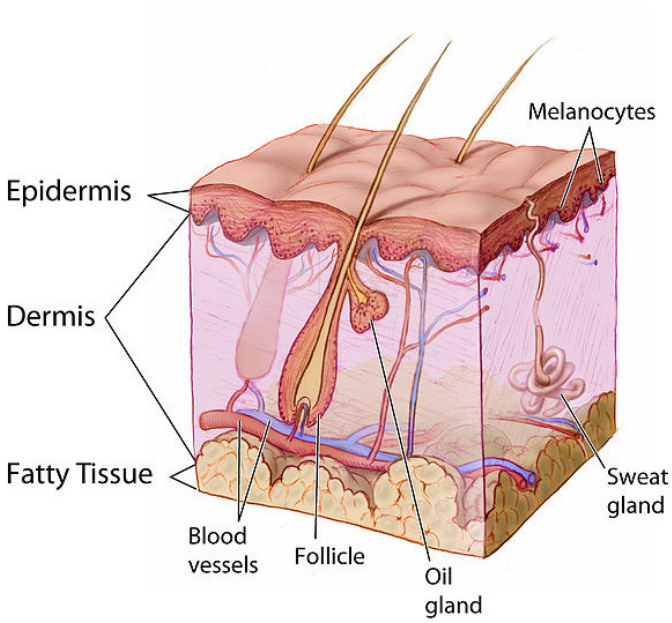

Figure 2: Anatomy The Skin - NCI Visuals Online.svg. Author: Don Bliss. Source: National Cancer Institute. File:Anatomy The Skin - NCI Visuals Online.jpg - Wikimedia Commons

Pigmentation of the Skin

Evolution and depigmentation

Since the origin of humans, the dark and protective pigmentation with strong tanning abilities have been selected through evolution in areas of high UVR[3]. Depigmentation to more fair skin tones has occurred multiple times in prehistory as our ancestors migrated into environments with lower and more seasonal UVR, also enhanced by unique sets of genes and cultural practices. There are different theories on why skin pigmentation started to differentiate. The predominating theory is the Vitamin D-folate hypothesis, postulating that changes in skin pigmentation occurred as an evolutionary adaptation to geographical variations in UVR[3,4]. When the early humans living near the equator lost their capacity for profuse hair growth, they developed darker pigmentation with skin rich in melanin in order to protect folate from photodegradation by the ambient UVR from the sun. Folate, a type of vitamin B, is essential for healthy pregnancies and childbirth[5], hence very important for reproductive health.

Migration into other geographical areas away from the equator where the UVR from the sun was not as harsh started about 60 000 years ago. Gradually depigmentation of the skin evolved in the migrating humans in order to ensure production of vitamin D in the skin [6]. Vitamin D_3 is produced in the skin when it is exposed to specific wavelengths of UVR in the UVB range. It can also be ingested naturally in some foods, notably oily fish. Vitamin D is like folate essential for reproductive health as shortage leads to rachitis, which impairs development of skeletal structures with soft and misshaped pelvis and long bones, specifically in early childhood. This can impair successful pregnancies, counterproductive to reproduction and evolution[3,5].

Melanocytes and melanin

The pigmentation of our skin comes from the dendritic melanocytes, dispersed in the skin's deeper parts of the epidermis along the basal layer, in the hair follicles, the uvea and also in mucosal linings and central nervous system. Interestingly, the density of melanocytes is the same regardless of the color of your skin [7], but it can vary from one individual to another and also differ depending on body site with a higher abundance in head and forearm[8]. A single melanocyte uses dendritic extensions to contact up to 36 surrounding keratinocytes, with this forming the epidermal melanin unit[9]. The pigment melanin is produced by the melanocytes in the melanosomes, which are organelles that trough a stepwise pathway of chemical reactions and maturation is

transferred to keratinocytes, cells of the uveal tract in the eyes and hair follicle cells (Figure 3)[10].

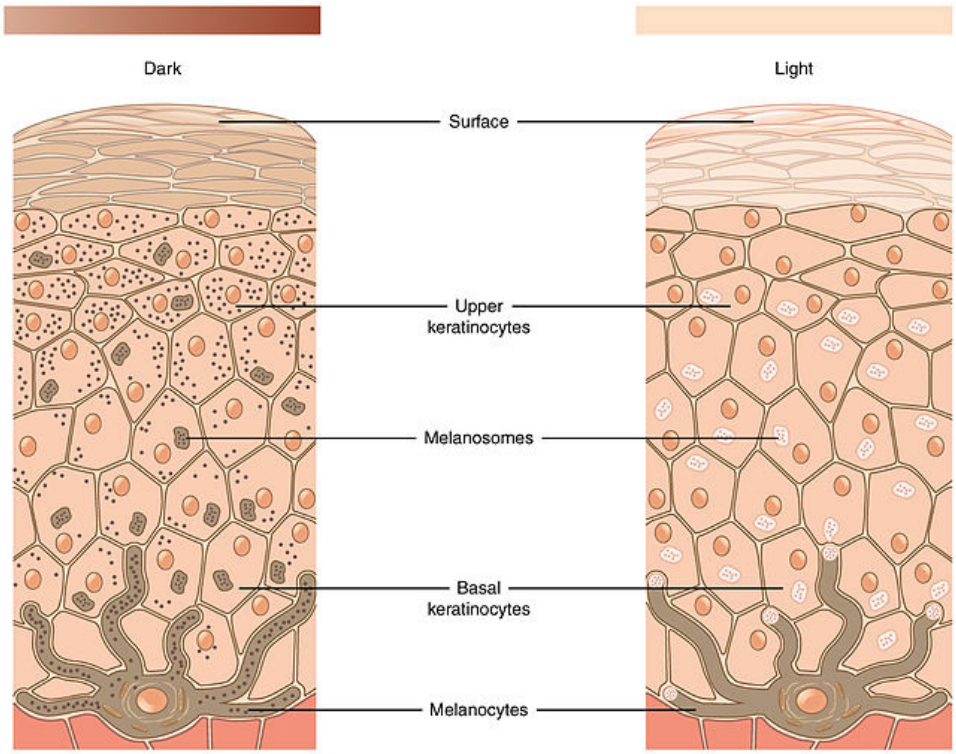

Figure 3: Melanocytes and melanin distribution in the epidermis. Illustration from Anatomy & Physiology, http://cnx.org/content/col11496/1.6/, Jun 19, 2013. © Creative Commons Attribution 4.0 International License (CC BY 4.0). Access for free at openstax.org.

There are three types of melanin in the skin, pheomelanin and two versions of eumelanin, which are produced in various amounts. The biosynthesis of both begins the same way. Simplified, tyrosine is converted into dihydroxyphenylalanine (DOPA). Tyrosinase, an enzyme, then converts DOPA into dopaquinone, which can follow a variety of pathways to form eumelanin or pheomelanin[11,12]. Eumelanin is found in two versions, one brown and one black, giving dark colors. Pheomelanin is reddish yellow[13]. It is the mixture of eumelanin and pheomelanin that will ultimately determine your skin color. To exemplify, individuals that have equal amount of eumelanin and pheomelanin will have red hair, and individuals with brown or black hair have varying amounts of black and brown eumelanin. Although we all roughly have the same number of melanocytes, the amount of melanin produced varies. Individuals with darker skin have more active melanocytes with several dendritic extensions and with

melanosomes that are large and degraded slowly. The activity of tyrosinase is higher resulting in more granules filled with melanin is displaced throughout the epidermis within the surrounding keratinocytes (Figure 3)[14,15].

Melanin and UVR

Besides giving us the color of our skin, hair and eyes, melanin's foremost and crucial function for humans is to protect us from the harmful UVR from the sun. Melanin carrying melanosomes reaching the keratinocytes position themselves superficially above the cell nuclei, which protect the DNA from the external UVR[14]. Eumelanin has a higher capability at blocking UVR than pheomelanin. Hence, the more eumelanin in the skin, the less permeable to UVR the epidermis is[16]. Conversely, individuals with more pheomelanin and lesser amounts of eumelanin, e.g., the fair-skinned, are much more sensitive to UVR and thus burn their skin more easily. Notably, the amounts of pheomelanin are similar between individuals regardless of dark or light skin, consequently meaning that it is the amount of epidermal eumelanin that determines an individual's sensitivity to UVR, the color of the skin, and risk of skin cancer[11].

Skin type

All skin has a color, which is true for eyes and hair as well. There is no base color when it comes to human skin, although terms like "ethnic skin" and "skin of color" have been used to depict skin rich in melanin. These labels are imprecise and do not convey the wide range of variation observed in moderately or darkly pigmented populations[17,18]. A classification of different skin types that is often used in dermatological terminology and research is the Fitzpatrick scale[19]. Originally designed to try to estimate the response to UVR in different skin types in order to apply the correct dose of UVA in patients receiving PUVA treatment. When using color of hair and/or eyes, some patients received too much UVA and burned their skin. Hence, Fitzpatrick developed a scale based on the patients self-reported skin reaction to the UVR from the sun. Initially, this numerical scale only consisted of the skin types I-IV, but was later complemented with V-VI[20] (Figure 4). The Fitzpatrick scale has rendered criticism due to lack of incorporating the diversity of skin reactions and downplaying risk of skin cancer, specifically in skin types V-VI[21-23]. The scale cannot encompass the enormous variety of skin complexion we see throughout the globe. However, no other classification of skin types has evolved and been established in the dermatological literature and research so far, thus making the Fitzpatrick scale both applicable, relevant, and accepted.

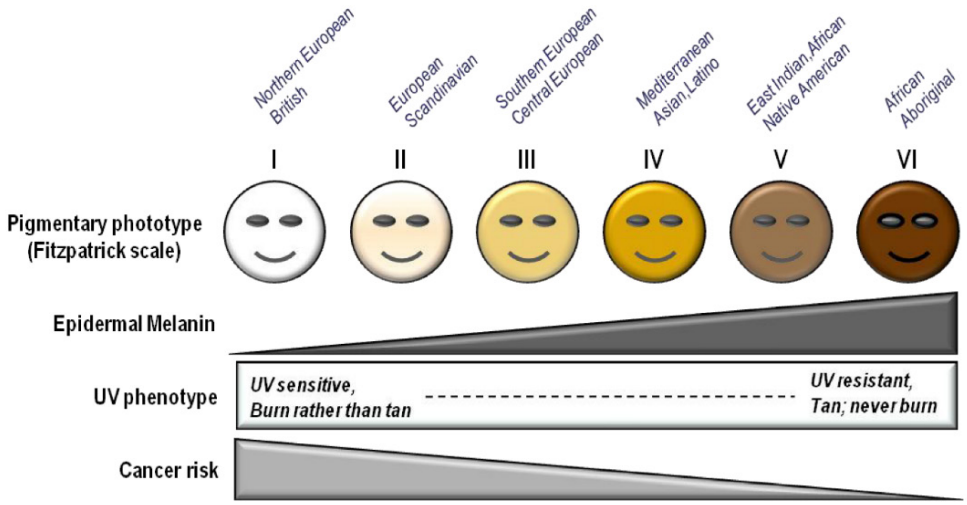

Figure 4. Skin type according to Fitzpatrick. I lighter skin tone and a tendency to burn in the sun indicates a lower skin type, while a darker skin tone and a low tendency to burn in the sun indicates a higher skin type. Picture adapted from John D'Orazio, Stuart Jarrett, Alexandra Amaro-Ortiz and Timothy Scott, CC BY 3.0 <https://creativecommons.org/licenses/by/3.0>, via Wikimedia Commons

UVR effects on skin

UVR

UV light or UV radiation (UVR) is emitted from the sun and from artificial UV sources, as sunbeds and sunlamps. The UVR spectrum is divided in three major parts: UVA (320-400 nm), UVB (290-320 nm) and UVC (100-290 nm). It is mainly solar UVA and UVB that reaches the earth. Solar UVC is absorbed by an intact ozone layer. Ambient sunlight consists of 90-95 % UVA and 5-10 % of UVB, with the latter being more energetic than the former. UVR, either emitted and ambient from the sun or coming from artificial sources such as sunbeds, can lead to skin inflammation, degenerative aging of the skin, and skin cancer. The wavelengths of UVA can reach through the epidermis deep into the dermis and can cause damage in both of these layers, whereas UVB is almost completely absorbed in the epidermis and is primarily affecting the cells within this layer[24] (Figure 5).

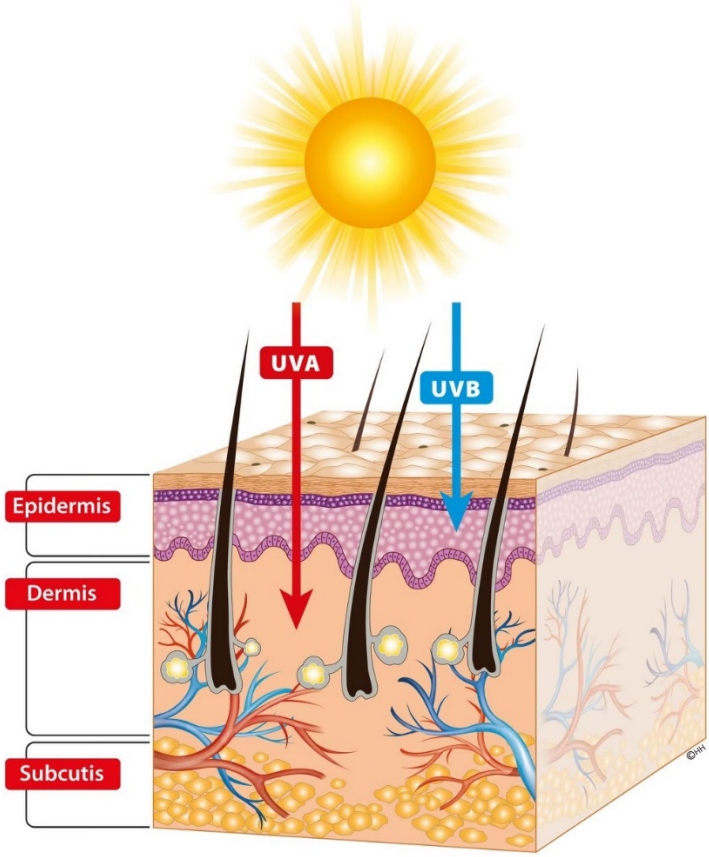

Figure 5: UVA and UVB skin penetration. Artwork: Hassan Hashemian.

UVR and tanning mechanism

The skin damage of UVR can be acute and near immediate in nature as well as prolonged, taking several years if not decades for the damage to show. The acute reactions are of course the inflammation seen when getting sunburned[25], including reactions such as redness, pain, formation of blisters and eventually peeling. Another acute reaction when the human skin is hit by UVR is the so called "tanning pathway", when the melanocytes induce further pigmentation as a protective measure in order to preserve DNA from damage by UVR. This leads to activation of the suppressor protein p53 in the epidermal keratinocytes, which in turn leads to a cascade of intracellular events including cleavage of pro-opiomelanocortin (POMC) in the keratinocytes into α-melanocyte stimulating hormone (α-MSH), which connects with melanocortin-1-

receptor (MC1R) on melanocytes[26]. This triggers the melanocyte to promote the production of microphthalmia-associated transcription factor (MITF), which regulates melanocyte survival and pigment production. MITF then targets many genes upregulating melanin synthesis, among others tyrosinase, and genes regulating trafficking and the transfer of foremost eumelanin containing melanosomes to neighbouring keratinocytes in the epidermis. Hence, the tanning response is an adaptation that provides a delayed protection from further DNA damage and carcinogenesis. Addressing carcinogenesis and the risk of developing a skin cancer, the variation of MC1R is essential. Hypomorphic MC1R variants are seen in individuals with lighter skin tones and/or red hair, often of European/Caucasian descent, and are associated with poor tanning responses [27,28].

The poor ability to tan in fair-skinned individuals can be illuminated by the use of Minimal erythematous dose (MED) [29]. MED is defined as the least amount of UVB radiation that causes reddening and inflammation of the skin 24–48 h after exposure (*i.e.*, the lowest UV dose that causes sunburn). The more sensitive an individual is to UVR, the lower the MED of his/her skin.

UVR and DNA damage

UVR can reach cells in the epidermis and dermis, where DNA is the main target, hitting the DNA in the cell nuclei results in several type of damages, the most prevalent being photoproducts. Most common examples are formation of cyclobutane-pyrimidine dimers (CPD) and 6-4 photoproducts (6-4PP)[30]. These products are mostly formed by the effects of UVB. These lesions can distort the DNA-helix, hence impeding transcription and replication. One gene that can be affected is the suppresser oncogene p53, which is important for DNA-repair and apoptosis of damaged cells. UVA also has mutagenic capacities via an indirect pathway generating different reactive oxygen species (ROS), which creates formations of CPD in the DNA. Another deleterious reaction is an oxidation process in the DNA, when singlet oxygen reacts with UVA and form free radicals that can then influence DNA, RNA, lipids, and protein in the skin cells and impair their intended function[11,31,32]. DNA have through evolution found ways to counteract the damage that our cells continuously face. There are several ways of DNA-repair. One major mechanism is the base excision repair (BER), very simplified, it removes and replaces small base lesions in the DNA in a stepwise fashion. This mechanism is foremost used for repairment after damage caused by free radicals. The nucleotide excision repair (NER) mechanism is more complex and repair DNA damage such as CPD and 6-4PP. The damage is more severe and the NER pathway first identifies the afflicted DNA, recruiting a multiprotein repair complex, excising the

damaged parts, then replacing it using a template. Interestingly in this context is that aging of the skin is associated with an observed decrease of NER and BER efficiency[33].

Skin cancer

The term skin cancer is often used in a general sense, meaning all cancers derived from the skin. When expressed in this general way, the different types of cancers that arises in the skin are intermixed and can be confused with each other. This in turn, can lead to misunderstanding of the severity of the cancer and what it can lead to as there are several types of skin cancers, which develop from different cell types, and hence show somewhat different risk factors and biological behaviour. There are several types of skin cancers which develop in different cell types with somewhat different risk factors.

The three most common skin cancers are basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (cSCC) and cutaneous malignant melanoma (cMM). There are of course also other cancers that arise from cells in the skin, such as Merkel cell carcinoma, atypical fibroxanthoma and dermatofibrosarcoma protuberans. However, these cancers emerge more seldom and have much lower numbers of incidence than BCC, cSCC, and cMM. In this thesis, we have concentrated on and studied different aspects of BCC, cSCC, and cMM.

Risk factors for skin cancer

Defining risk factors and challenges

What is risk? Risk can be defined as "the probability of an event during a specified period of time" [34]. This means, in principle, that anything we do can render a risk of an event to happen. Knowledge and risk are intertwined and it is knowledge of our surroundings that can help us with day-to-day risk management. An often-used example in this context is smoking and lung cancer, when new insight came to light trough research, we started to see smoking as a risk. Studying skin cancer and risk factors, we have through a vast amount of research output identified several factors that can increase the risk of developing skin cancer. The risk of developing a skin cancer is multifactorial and dependent on environmental as well as genetic factors. Importantly, we might change behaviour if we have knowledge of which outcome a certain risk factor can have. It is still almost impossible to change our congenital genetic risk factors. However, environmental factors might be influenced and are therefore important to evaluate and clarify further.

Environmental risk factors

The most important environmental skin cancer risk factor is UVR, either from the rays of the sun itself or artificially from sun beds or for medical purposes in the form of narrow-band UVB or PUVA (psoralen + UVA)[11,35-43]. As early as 1956, a migration study from Lancaster et al[44], concluded that fair skinned individuals from Northern Europe moving to areas more ambient UVR will have an increased risk for skin cancer. The most important extrinsic factor that was different between the studied individuals was the UV exposure in the different latitudes, and the corresponding intensity of UVR, in the different locations. Other migrant studies have reached similar conclusions, specifically for cMM[45-47]. Although migrant studies propose an association between exposure of UVR and skin cancer, there are scientific challenges concerning dose and timing of UVR exposure and the risk of skin cancer. Moreover, it is difficult to study the long lag time until the outcome, the skin cancer, develops. The problem to study exposure and risks arises foremost in retrospective studies, where participants have to recall their UVR exposure and sunburn history many years before, sometimes decades ago. However, the research in this field is ever growing and evidence is mounting that UVR constitutes the main risk factor for all of the three major skin cancers studied in this thesis: BCC, SCC and cMM[48].

Figure 6: Secret Beach, Mirissa Sri Lanka. Photo: Gustav Christensen

Behaviour as an environmental risk factor

There are other environmental factors linked to UVR. Studies have shown that a sun seeking behaviour and intermittent sun exposure, as sunbathing vacations, are risk factors for skin cancer. A society's preference on what constitutes a beautiful look can lead to behaviours that increases the risk of a sun seeking behaviour. Being tanned is still considered as a desirable look, since it is associated with "a healthy and rich lifestyle". Indeed, Swedes are sun loving people, elucidated by international studies on tanning and sun protection[49,50]. The studies show a lower degree of sun-protection and that a higher level of tanning was more preferable in Sweden compared to other countries. Interestingly, Swedes are generally well informed about the connection between the UVR and the risk of skin cancer, but a Swedish survey still convey the picture that a tan is attractive and sun exposure makes you feel good[51]. In the same survey, it was evident that tanning and exposure to the sun was took place at outdoor bathing areas abroad, with about 60% spending 4-5 hours outdoors when the UVR from the sun is strongest. Hence, travelling on vacation to sunnier countries to swim and sunbath is a behavioural risk factor to developing a skin cancer. At least for Swedes (Figure 6).

Sunbed use

Another important source of UVR is the use of sunbeds for cosmetic tanning. The aim of the tanning was foremost for cosmetic purposes, but also the misconception that a pre vacation tan would be beneficiary[52]. The artificial UVR coming from sunbeds have the same harmful effect on human skin as solar UVR. Research is clear that sunbed use is a risk factor for developing skin cancer, showing increasing risk for BCC, cSCC and cMM[41,48,53-56]. Furthermore, sunbeds can emit 1.5 higher doses of UVR than can be seen from the sun at noon on a summers day at intermediate latitudes[57] and there are scientific evidence of a dose-response association for cMM[58] and for BCC and cSCC[55]. Additionally, sunbed use in adolescence and as young adults (<35 years) seem to increase the risk even further[55,59]. Adolescents and young female adults use sunbeds more[60,61]. The mounting evidence of the detrimental effects of sunbed use led the WHO's International Agency for Research on Cancer (IARC), officially classifying that tanning devices emitting UVR are carcinogenic to humans[48,62].

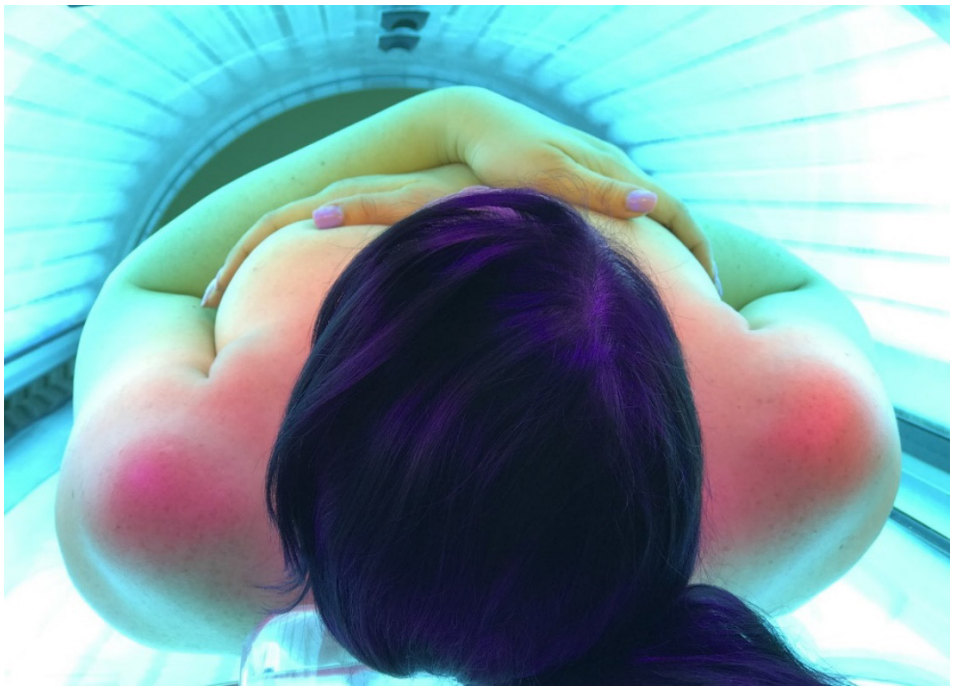

Figure 7: Sunbed tanning. Photo: Tomasryant. Creative Commons Attribution-Share Alike 3.0

Countries have had different approaches on regulation of sunbed use, some with no regulations, other with age restrictions at different ages and some countries with outright bans. Brazil was the first country to ban commercial use of sunbeds in 2009, with Australia following 2016[63]. Together with legislative measures, many countries have also had national campaigns informing of the negative effects of artificial tanning in sunbeds[56,64]. Interestingly, it can be concluded that prevalence of sunbed use have decreased since the IARC statement [63,65]. Together with legislation, perhaps has the knowledge of the risks with artificial tanning had an impact on behaviour in adolescents and young adults. This is an important step in order to decrease the risk of skin cancer and thus reaching higher public health effects years ahead, but more can be done whereas many countries still have no restrictions[66].

Ionizing radiation

Ionizing radiation is also an environmental risk factor for skin cancer. It is often used for medical purposes in the form of gamma-rays or as x-rays and have shown to be implicated in formation of specifically BCC, and to a lesser extent to cSCC[67-69].

Immunosuppressive medication

Another environmental risk factors to consider is the use of immunosuppressant medication in organ transplant recipients (OTR), i.e. patients with a solid organ transplant, such as lungs, kidney, heart or liver. A life-long immunosuppressant medication down-regulates immunologic responses which impairs cellular repair in the skin, making it more susceptible to developing skin cancer[42,70]. cSCC is the skin cancer that is the most frequent and when compared to the general population, studies show very large increased risk in organ transplant patients, but also BCC and cMM are more frequent in OTRs[70-72]. As a result of improved survival post transplantation, one long-term effect is that cSCC is the most common malignancy in these patients[73,74]. Therefore, it is of outmost importance that these organ transplant recipients are offered follow-up regimes via close cooperation between organ specialists and dermatologists.

Photosensitizing drugs

There are many types of widely used medicines that have been studied in relation to skin cancer because of their photosensitizing capacities. The pharmacodynamics of these drugs can give various chemical changes in the skin that induce a higher sensitivity to UVR., There are mainly two reaction patterns for photosensitization in the skin: the most common is acute phototoxicity, and less frequent is a photoinduced allergy[75-77]. When it comes to assessing medications with a possible phototoxic effect, the use of antihypertensive drugs has been studied most, specifically diuretics[78-85]. Several other types of widely used medications have also been studied, such as hormonal replacement therapy (HRT)[86-90], NSAIDs[91-93], proton pump inhibitors[94], antibiotics[80,93,95] and antidiabetics[96]. Studies of the relationships between exposure to photosensitizing drugs and skin cancer have yielded various and conflicting results. The studies are often retrospective or lack adjustment for important confounders such as sun exposure and sun sensitivity. With that said, there is emerging scientific evidence concerning the diuretic hydrochlorothiazide can be a risk factor for skin cancer. Recently, the US Food and Drug Administration (FDA) has put forward a label change due to a slight increase in cSCC and BCC, but with no recommendation of stopping the use of this well-established anti-hypertensive medication[97]. So far, the consensus is that the individual risk of a poorly treated hypertension out-weighs the risk of developing skin cancer. However, it is important to further evaluate this potential risk factor, in different settings and cohorts, to be able to accurately discuss any future adjustments of clinical guidelines.

Host factors

Skin cancer is mostly a disease of the fair skinned, predominantly with blue eyes, red/blond hair and freckles with poor tanning abilities[35,36,38,98-100]. These traits, including the propensity to easily burn on sun exposure, are linked to loss-of-function variations in the MC1R gene and increased risk of mainly cMM, but also BCC and cSCC[101,102]. Importantly, skin cancer can also arise in individuals with darker complexion, but to a much lesser extent then fair-skinned. The number of nevi on the body is also an important factor to elucidate. Having over 100 nevi on the body, increases the relative risk of cMM tenfold, when comparing to individuals with few nevi[103]. A high nevi count can also be attributed to previous sun exposure as a child[104-106], which can complicate the true relationship between nevi and melanoma since UVR might be a confounder in the relationship between number of acquired nevi and cMM.

Evolution is to a large extent driven by DNA mutations, which are changes in the DNA sequence in the cells of an organism. DNA mutations evolve from errors in the replication of DNA during cell division, exposure to mutagens such as UVR or also viral infection. We are not replicas of our parents, rather we are a mix of the genetic blueprint passed down through the generations. Hence, between 7 to 15 % of melanomas are considered familial and factors that influence risk of cMM in a family are diverse, including shared sun exposure experiences, amount of ambient UVR, skin type and genetic variants [107,108]. Mutations in predisposing tumor genes in affected families, often leads to formation of multiple tumours earlier in life than in the general population. Concerning cMM, the high-risk germline mutation of CDKN2A, is coupled with high penetrance within the affected families[109,110]. Mutation in CDKN2A, a tumour suppressor gene, can give as much as a 65-fold increased risk of melanoma[110]. The families with these known mutations are paramount to find and offer full-body examination and photography including digital dermoscopy one to two times a year[111]. A Swedish study from 2022 have shown that inclusion in dermatological surveillance of families CDKN2A mutations resulted in less advanced cMM and better melanoma specific survival[112]. The CDKN2A mutation is the most common germline mutation concerning cMM. There are several other less common germline mutations with difference in penetrance concerning familial cMM, including TERT, MC1R, BAP1, CDK4, ACD, TERF2IP and MITF[108].

In cancers developing from keratinocytes, we see the genetic disorder of Gorlin's syndrome, also called basal cell nevus syndrome. These patients develop multiple BCC due to a mutation in the patched 1 tumor suppressor gene, PTCH1, which regulates the hedgehog-signalling pathway[113,114]. Research into this mutation and its pathway have led to new successful medicines to treat patients with this syndrome as well as locally advanced and metastatic BBC[114]. Lastly, Xeroderma pigmentosum (XP), has a

genetic defect DNA-repair system, specifically the nucleotide excision repair (NER) mechanism[11,115]. The skin of the XP-patients is very UVR sensitive, leading to UVR derived mutations that the failed cellular DNA-repair system is unable to handle, which in turn results in mostly cSCC formation. The impact of impaired DNA-repair can also be seen in XP-patients with skin type V-IV living in a tropical region, having more skin cancers than controls[116].

Epidemiology of skin cancer

In 2020, 1.5 million cases of skin cancers were estimated to be diagnosed worldwide, making skin cancer as a group the most common malignancy in humans. Roughly, cMM constitutes 1 in 5 cancers found on the skin with about 325 000 cases diagnosed globally in 2020[117,118]. The incidence of BCC, cSCC and cMM are predominantly seen in fair-skinned populations, which are more in risk of damage from UVR. Skin cancer can also occur in darker skin types, but they are considered rare[119]. Concerning cancers arising from the keratinocytes, BCC and cSCC, comparing incidence from different countries or geographical areas are harder since. Many countries lack comprehensive registries with detailed data on specific keratinocyte tumours, which instead often are grouped together as non-melanoma skin cancer (NMSC). Albeit this, studies show similar increasing incidence rates as for cMM[39,120].

In the 1950's, cMM was an unusual cancer. Since the Second World War, incidence of cMM has been rising steadily in fair-skinned individuals. Looking at incidence rates of melanoma across the world in 2020, there are about 25 new cases per 100 000 population in Europe, 30 cases per 100 000 population in the USA, and 60 cases per 100 000 population in Australia and New Zealand[121]. Making projection for the future, trends of increasing total MM incidence are seen in the US (fair skinned population), United Kingdom, Sweden and Norway. On the contrary, incidence stabilization is seen in New Zealand and decreasing incidence in Australia[122]. Overall figures of diagnosed cMM, will further increase in coming decades, specifically in older patients. In younger generations, it is likely to stabilize or even decline [122]. The discussion on why there appears to be this shift in trend in young patients is ongoing. Maybe enlightenment concerning the risks of UVR exposure has had an effect? The international trends are evident. The trends of increasing incidence are also true for Sweden during the last decades, concerning all three skin cancers detailed below.

Basal cell carcinoma – BCC

BCC is the most common malignancy by far and incidence is growing, specifically in population mainly consisting of skin types I-II[38,120,123,124]. In 2021, BCC was the most common form of cancer in Sweden, with about 70 000 diagnosed cases in 50 000 patients, equally distributed between men and women. Median age was 74 years of age (Figure 8)[125].

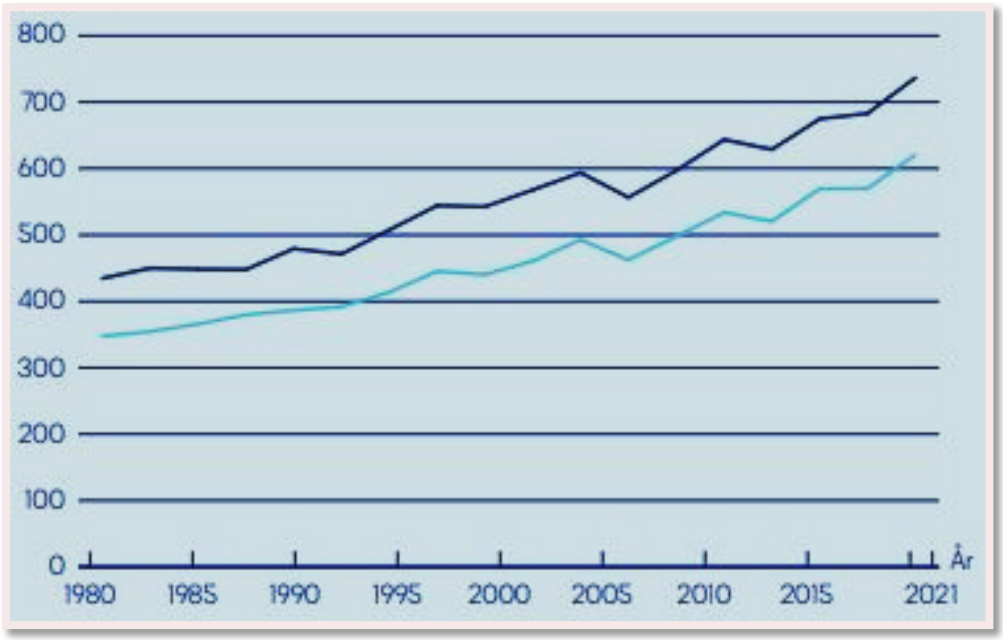

Figure 8: Number of BCC per 100 000 inhabitants in Sweden, age
standardized according to the Swedish population 2021. Men in dark blue, women in light blue. Courtesy of National Board of Health and Welfare (Socialstyrelsen).

BCC resembles the cells of the basal layer in the epidermis histologically and arise from the resident keratinocyte progenitor cells found in the interfollicular epidermis as well as the upper infundibulum[126]. Most of the mutations concerning BCC are UVR induced (UVB)[127,128]. Close to all BCCs show activation of the Hedgehog signalling pathway outlined above, and animal models show that this pathway alone is sufficient for tumorigenesis[128,129].

BCC evolves primarily, but not exclusively, on areas of the skin that is chronically sun damaged such as the head-neck area followed by the trunk[38,124]. BCC arises most commonly in the sixth-eight decades of life, hence age is an independent risk factor[128].

Clinically BCC is a localized nonhealing, slowly enlarging skin lesion which can bleed or itch, but can also grow without symptoms. Left untreated, BCC grows locally and can ultimately destroy tissues of skin, cartilage and bone. Extremely seldom, BCC can metastasize. There are several subtypes of BCC which can be distinguished clinically and histologically. There can be international differences in how BCC is classified. In Sweden we use the Sabbatsberg/Glas classification, where BCCs are categorized according to growth pattern as nodular, superficial, micronodular/infiltrative and morphoeic[130]. Knowing the growth pattern of the BCC is of crucial importance in order to treat the patient successfully via different modes of treatment actions.

- Nodular BCC: slow growing, often shiny, pearly papule or nodule with a smooth surface with arborizing telangiectasias, not seldom eventually ulcerating. This subtype is the most common of all BCC, up to 50% of all BCC. Arises foremost on the head and neck area, but also on trunk. Considered low aggressive.
- Superficial BCC: also slow growing, often slightly infiltrated erythematous thin plaque or patch with crusts or scales, often well-circumscribed. This is the second most common BCC, about 20-30 % of all cases of BCC, and they are primarily diagnosed on the trunk and rendered as low aggressive in nature.
- Micronodular/infiltrative BCC: this subtype can exhibit both nodular, flat or depressed plaque which can be poorly defined, indurated with shiny white/pale to pink/red color. It can also present with ulceration, crusts and erosions and most cases are found in the head and neck area. These BCCs are viewed as intermediately aggressive.
- Morpheiform BCC: as for all types of BCC, it is slow growing as a sclerotic plaque with borders that are poorly defined and are hard to visualize. Often found the head and neck area and recognized as more aggressive.

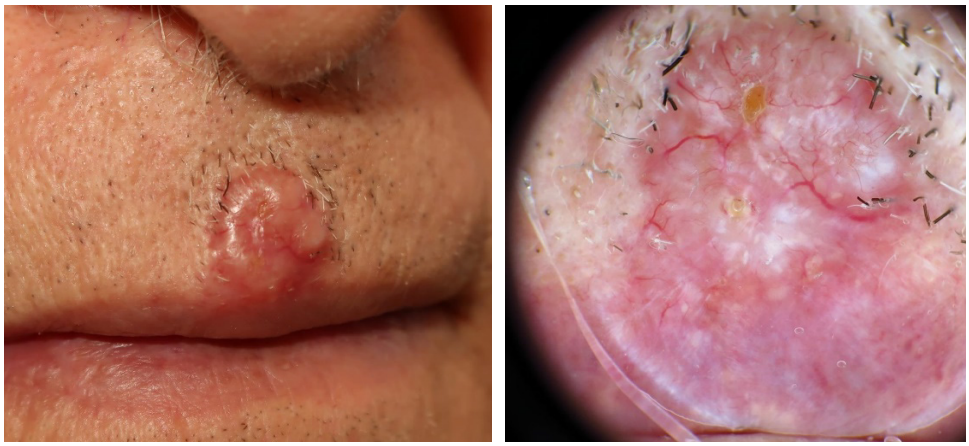

Figure 9: Nodular BCC, clinical and dermoscopic image. Published with permission of the patient. Photo: Joakim Nilsson, Department of Dermatology and Venereology, Skåne University Hospital, Lund.

There are several treating options concerning BCC. The subtype of BCC and the specific location is very important to consider when choosing treatment modality. A superficial BCC can be successfully treated with cryo therapy (with or without initial curettage), CO_2 laser, 5-fluorouracil cream, photodynamic therapy and surgery. Surgery, including Mohs micrographic surgery, is often the preferred way of treating nodular, infiltrative and morpheiform BCC, specifically in the head-neck area. Ionizing radiation can also be an alternative mode of action in difficult cases. Severe locally advanced or metastatic BCC can be treated with Hedgehog inhibitors. If Hedgehog inhibitors are intolerated or the disease progresses, treatment with immunotherapy anti-PD1 inhibitor can be used[131,132].

Cutaneous Squamous Cell Carcinoma – cSCC

SCC of the skin, cutaneous SCC (cSCC), is the second most common skin cancer and, just as for cMM and BCC, the incidence is growing in lighter skin types[133]. For cSCC in Sweden 2021, roughly 10 100 patients were diagnosed, making it the second most common cancer in men and women. Although, there has been at steep increase in cSCC during the for last decades (Figure 10), the specific mortality has stayed the same[125].

Figure 10: Number of cSCC per 100 000 inhabitants in Sweden, age standardized according to the Swedish population 2021. Men in dark blue, women in light blue. Mortality in dotted line. Courtesy of National Board of Health and Welfare (Socialstyrelsen).

cSCC is derived from the keratinocytes found in the epidermis and primarily found on chronically sun damaged skin[134]. SCC is one of the cancers with the highest mutation rate. cSCC is often delt into SCC in situ, also known as Bowen's disease, and invasive cSCC.

- SCC in situ/Bowen's disease: this form is found in the epidermis and is slow growing with erythematous, well-demarcated, scaly patch or plaque which can be ulcerated. Often located in sun-exposed areas, such as the head and neck and extremities, but can be found on all parts of the body, although very seldom on soles or palms. The symptoms can be minor in absence of ulceration. About 5 % of SCC in situ can evolve into an invasive cSCC[135,136]. The peak of incidence is in the seventh decade.
- Invasive cSCC: the clinical appearance of cSCC depends foremost on the degree of differentiation of the lesion. Well differentiated cSCC exhibits often as scaly dome-shaped nodule or as infiltrating plaque. Poorly differentiated cSCC can be displayed as soft, ulcerated, or hemorrhagic lesions[134,137]. Invasive cSCC can be found on any anatomical area, it is primarily found on sun

exposed areas such as head and neck up to 55% and dorsal areas of hands and forearms up to 18% of cases.

- Majorlin's ulcer: this is an unusual form of cSCC, often arising in chronic ulcers such as leg ulcers or in burn wound on the lower extremities. This variant is a more aggressive form of cSCC, with metastasis to lymph nodes in 32% of cases when diagnosed[138].
- HPV-related cSCC: Human papilloma virus can elicit the development of cSCC in situ and invasive cSCC and often found in perianal, genital and subungual areas. Not seldom, the patient has had a history of warts that have been refractory to treatment[137,139,140].

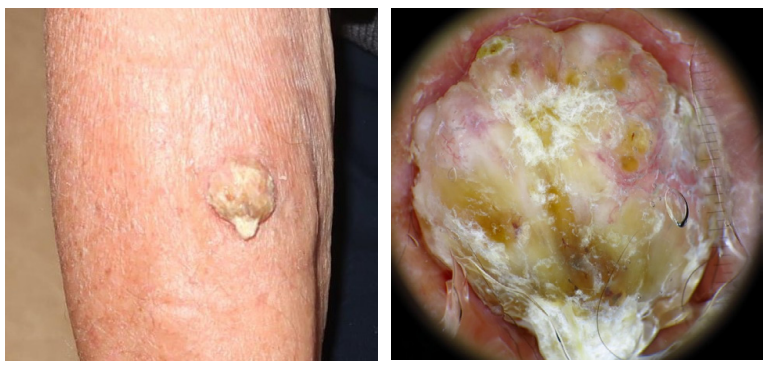

Figure 11: clinical example of cSCC on right arm, clinical and dermoscopic image. Published with permission of the patient. Photo: Joakim Nilsson, Department of Dermatology and Venereology, Skåne University Hospital, Lund.

As all skin cancers, invasive cSCC can be locally destructive in affected tissue and has the potential to locally recur after surgical treatment or radiation. It also has the ability to metastasize. Depending on the risk of recurrence, invasive cSCC can be defined as low-risk or high-risk. Smaller well differentiated cSCC are generally low-risk, whereas there are several clinical and histological features that define high-risk SCC[141,142]:

- Size and location, >20 mm on trunk and extremities, >10 mm on forehead, neck, cheeks and scalp, > on face, ears, genitalia, feet and hands
- Undefined borders
- Recurrent lesion
- OTRs
- Previous radiotherapy or site of chronic inflammation

- Rapidly growing lesion
- Neurologic symptoms
- Pathological risk factors are not clearly differentiated lesion, adenoid, adenosquamous or desmoplastic subtypes, Clark level IV, modified Breslow thickness > 4 mm.

Invasive cSCC can metastasize. Both local recurrence, regional and distant metastasis incidence is about 5 %[143]. Risk factors for metastasis are immune-suppression, incomplete primary excision, local recurrence, poor differentiation of tumor, perineural or lymphovascular invasion, longer duration of tumor and larger tumor diameter[144].

Cutaneous Malignant Melanoma – cMM

Malignant melanoma arises from melanocytes. in any organ where melanocytes are present, but primarily it develops in the melanocytes of the epidermis. As for BCC and SCC, incidence of cMM is increasing in many parts of the world, specifically in fair skinned populations[41], with highest rates in Australia and New Zeeland[145]. Interestingly, a shift has occurred in Australia and the US with stabilizing or declining incidence rates in younger birth cohorts[122]. However, the fact is that the incidence in older age groups are projected to increase together with the parallel effect of higher death rates[146]. Looking at cMM in the Swedish context, we follow suit internationally when coming to increase in incidence the last 40 years. In fact, cases have doubled the last 20 years. 4800 cases of invasive cMM were diagnosed 2021 and 525 people died due to cMM. The mortality has been roughly the same during the years[125], although new research show better melanoma specific survival the years 2011-2020 compared with 1990-2000[147].

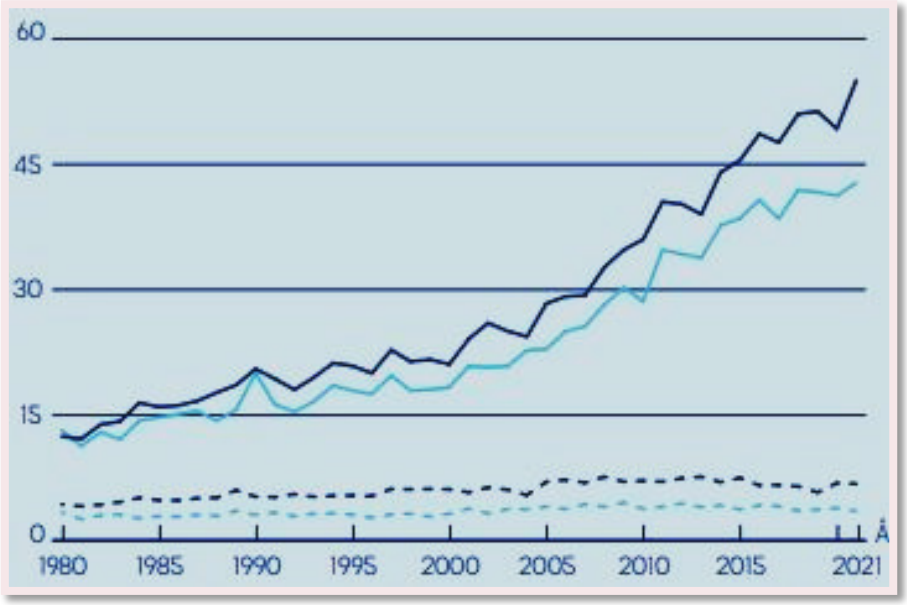

Figure 10: Number of cMM per 100 000 inhabitants in Sweden, age standardized according to the Swedish population 2021. Men in dark blue, women in light blue. Mortality in dotted lines. Courtesy of National Board of Health and Welfare (Socialstyrelsen).

Although the risk of cMM increases with age, it is also one of the most common cancers in young adults[148]. Site of origin of cMM correlate best with the genetic somatic profile of the tumor, where cMM arising from sun damaged skin have a higher mutational burden compared to cMM developing from skin that is not damaged by UVR[149]. cMM that is found in skin that through life has undergone intermittent sun exposure are more likely to have a mutation in BRAF, which is an important proto-onco gene and detectable in 45-50 % of cMM, compared with melanomas occurring on chronically sun-exposed skin[150,151]. Younger patients are more prone to have cMM with BRAF mutation. On the other hand, in older patients with subtype of nodular melanoma, mutation of oncogene NRAS, are more common, specifically on body sites with chronic UV-damaged skin[152].

The WHO has made a generalized classification melanomas of the skin, uvea and mucosa, using distinctive features clinically, histopathologically, genetic and epidemiological coupled with progression and specific body sites and chronic sun damage (CSD)[153]. Traditionally, cMM is presented there in 4 clinical-pathological subtypes of cMM:

- Superficial spreading melanoma (SSM): SSM constitutes 70% of all cMM , making it the most common subtype. It can be found on all body sites, but in women primarily on legs and in men more often on the back. It presents as a flat, slow growing pigmented lesion that can become irregular in shape and form[154]. Mostly arising de novo, this subtype does not seldom arise in a pre-existing nevus. Furthermore, SSM tend to develop in sun-exposed skin, albeit it is considered low cumulative CSD subtype [155] (Figure 11, 12).

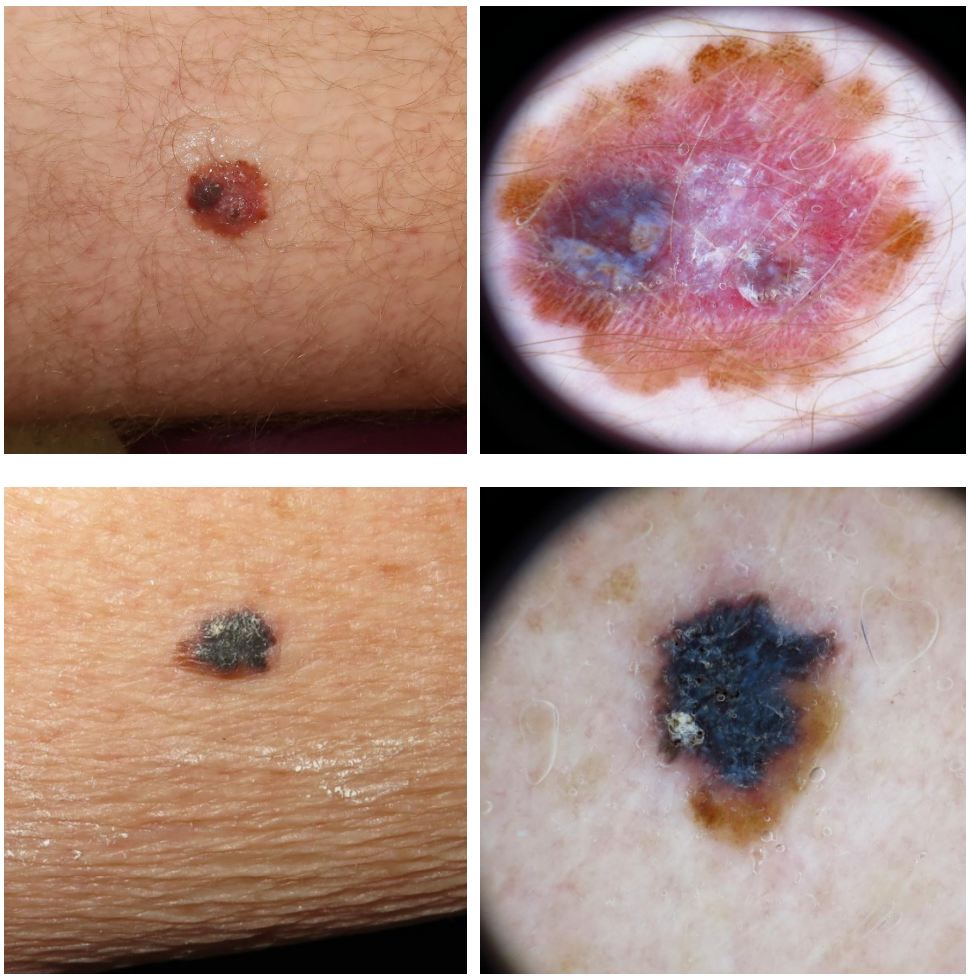

Figure 11 and 12: Two examples of Superficial spreading melanoma (SSM), clinical and dermoscopic images. Published with permission of the patient. Photo: Joakim Nilsson, Department of Dermatology and Venereology, Skåne University Hospital, Lund.

- Nodular melanoma (NM): this subtype, which constitutes about 20 % of all cMM [154], arises de novo and has a faster vertical growth rate invading the dermis early, often presenting as a symmetrical tumor, which is pigmented or amelanotic and can lack typical clinical signs of melanoma and consequently are often not recognized as such. NM is relatively small in diameter initially, but due to the vertical growth pattern reaches a tumor thickness (Breslow thickness) that could be associated with a high mortality rate [153,156].
- Lentigo maligna (LM)/Melanoma in situ/Lentigo maligna melanoma (LMM): this subtype tends to be more prone to appear on skin areas with more severe sun damage, such as the head and neck area. Thus, making it a high CSD melanoma. LM is intra-epithelial precursor and grow in a radial fashion (Figure 13) without becoming invasive, a phase that can last for many years[157]. Often diagnosed as larger, slow growing pigmented macula, with time becoming increasingly irregular and hence easier to detect clinically. Some LM will eventually start to grow vertically, becoming an invasive LMM. Both in the clinical and histological setting, it can be hard to define borders of the tumor, leading to wider margins when being excised[158]. LMM represents 5-10% of all cMM[154].

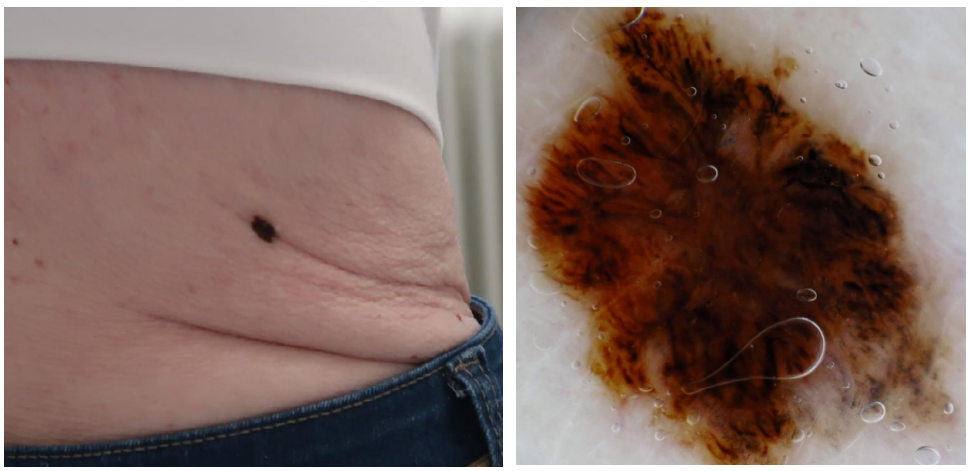

Figure 13: Melanoma in situ, clinical and dermoscopic images. Published with permission of the patient. Photo: Joakim Nilsson, Department of Dermatology and Venereology, Skåne University Hospital, Lund.

- Acral lentiginous melanoma (ALM): this is the histopathological subtype that originates from the skin of acral sites of the body, the palms, the soles and the nail beds[118]. Here, the difference between ALM and Acral melanoma (AM) needs to be addressed. AM is defined as any cMM arising on acral sites. ALM is predominantly found histopathological subtype on acral sites (Figure 14). ALM and AM are sometimes intermixed, misunderstood and/or misused leading to lacking specification in studies. Because AMs often can be hypopigmented, they are frequently misdiagnosed, leading to significant delays in treatment[159]. AM also tend to exhibit greater tumor depths (Breslow thickness) and mortality rates than other cutaneous melanoma subtypes[160,161]. Interestingly, AM development is not considered to be influenced by UVR. AM accounts for about 3% of all MM in fair-skinned populations. In populations with darker skin types, the proportion is significantly higher[162].

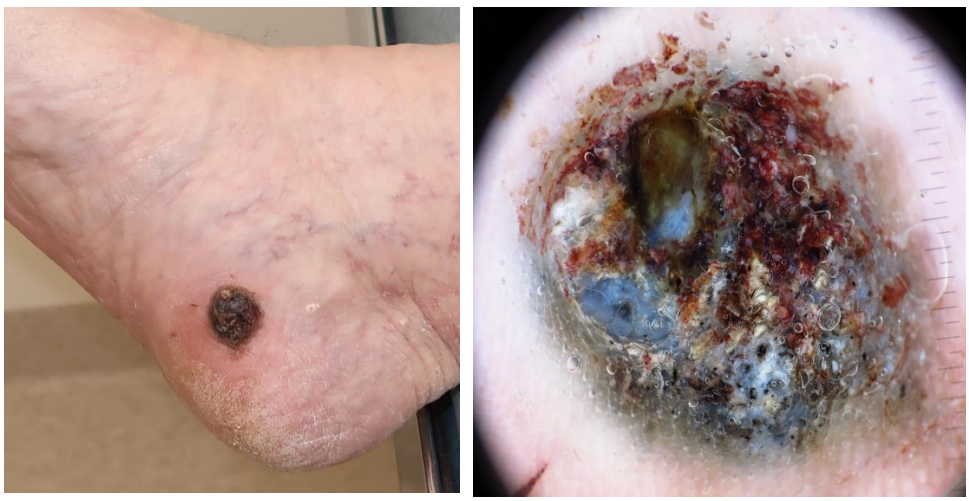

Figure 14: Acral melanoma (AM) on the foot, clinical and dermoscopic images. Published with permission of the patient. Photo: Joakim Nilsson, Department of Dermatology and Venereology, Skåne University Hospital, Lund.

As with all skin cancers, but generally more important for cMM because of the malignant potential it holds, early detection and complete surgical removal of the tumor is paramount. Gold standard for final diagnosis (today) is the histopathological evaluation of the excised tumor, and the histopathological diagnosis/primary tumor stage. The pathology report includes information about subtype classification, tumor depth according to Breslow, presence of ulceration and surgical margins. This tumoral information makes staging of cMM possible[163]. Interestingly, in absence of lymph node status, Breslow depth is the most important prognostic marker[153,164].

Diagnostic tools for skin cancer

As outlined above, the earlier skin cancers are treated, i.e. in as early stage as possible, the less likely they are to destruct local tissue, metastasize, and cause death. Therefore, early and correct diagnostics are essential. In a clinical setting, physicians first use the naked eye in order to judge which lesion on the patient that needs further diagnostic evaluation. The next step is often to use dermoscopy, a magnifying device with enhanced light, for a more accurate diagnosis. Regarding melanoma detection, naked-eye examination only reaches a sensitivity of about 60%. However, trained dermoscopists can increased sensitivity to about 80%-95% with the aid of dermoscopy[165-167]. The histopathologic examination of an excised suspicious lesion is the current gold standard for skin cancer diagnosis, but it has disadvantages in that it is an invasive procedure and it takes time to get the results. Furthermore, histopathology is not always clear and there can be significant discordance between pathologists, especially concerning pigmented skin lesions[168]. Thus, there is a demand for novel non-invasive diagnostic systems that can differentiate between malignant and benign skin lesions and challenge the current gold standard. New techniques must be quick and easy to use in the day-to-day clinical practice and deliver continuous and credible high sensitivity and specificity in order to correctly diagnose between a suspicious skin tumor or a benign skin lesion. There are several innovations and novel techniques that are tried and tested continuously in the field of non-invasive diagnostics of skin cancer:

- Dermoscopy: cheap, handheld and easy to use in most clinical settings. Trained dermoscopists can reach up to 95 % sensitivity. There are several algorithms developed in order to help clinicians to structurally examine and judge suspicious lesions. Ultimately, all other non-invasive techniques will have to compete with dermoscopy (Figure 15).
- Teledermoscopy: a technical development of dermoscopy using photo taken through a dermoscope is a part of the evolving teledermatology and has proved useful in triage of referrals[169]. Using this technique, patients can also avoid the expense and inconvenience of go to specific clinics. Teledermoscopy can be a valuable tool due to its visual nature, capturing precise dermoscopic images, especially for clinicians and their patients in rural or remote areas, where face-to-face visits are hard to facilitate[170]. Teledermoscopy can monitor the course of the disease, not only suspicious skin lesions, but also inflammatory skin disease[171]. The field of teledermoscopy is growing and will play a more important role in the future due to its cost effectiveness and easy use (Figure 15).

- Computer aided diagnostics (CAD): this is the next step of non-invasive techniques using dermoscopic images, aided by artificial intelligence (AI), and have potential to revolutionize several fields in medicine and assisting in greater diagnostic accuracy. CAD is a field of AI where the system learns to interpret visual images through deep learning models[172]. In the field of dermatology, AI systems have shown to be on par with or better in performance the seasoned dermatologists in diagnosing skin conditions[173,174].
- Total Body Photography (TBP): this modality is preferably used in high-risk individuals with risk of developing MM, where the whole body is photographed together with digital dermoscopic pictures of suspected pigmented lesions. These patients often have a follow-up once or twice per year, enabling clinicians to continuously re-examine lesions of interest. This combination of techniques has been shown to detect MM early[175,176] (Figure 15).

Figure 15: Picture above showing different types of dermoscopes, including a smartphone with an attached dermoscope for teledermoscopy. Lower picture showing a Total Body Photography (TBP) device. Photo: Gustav Christensen

- Reflectance confocal microscopy (RCM): a technique using a laser light source on a tissue sample, which is reflected into an opening that can filter out surrounding light. This creates a thin horizontal section. The sections can be stacked together in a vertical fashion, thus creating images of cellular structure on par with histologic evaluation[177,178]. To note, depending on size of lesion, the imaging can take approximately between 2-45 minutes and cannot visualize past the papillary dermis. In an outpatient clinic, it has its limits.
- Optical confocal tomography (OCT): using near-infrared light on the selected tissue, it can a generate 2-D cross-sectional images of tissue microstructure. Compared to RCM, this technique can go deeper, but not show individual cellular structures. However, it can make images of the layered structure of the skin, including epidermis, papillary and reticular dermis together with hair follicles. In OCT images, you search for disruption of the pattern of normal skin in order to detect skin cancer, specifically best for BCC detection[179].
- Electrical impedance spectroscopy (EIS): based on the principle that malignant transformation can alter the electrical impedance of cells. The apparatus compares electric impedance of suspected lesions with normal skin. Each measurement takes about 10 seconds. Sensitivity scores on MM and NMSC have been high in some studies, but low in specificity[180].
- Pigmented lesion assay (PLA): This technique analyses the genetics of lesions and not microscopic structure. PLA is a non-invasive biopsy, using an adhesive patch which is placed on the suspected lesion. Here, it collects a thin layer of stratum corneum tissue that contains genetic information from the cells of the skin, specifically LINC (RNA158) and PRAME, which is the analysed to evaluate if the lesion genetically expresses signs of MM or not[181]. This a time-consuming process and so far, it has not found its place in the clinical setting.
- Hyperspectral imaging (HSI): this technique collects and processes information from across the electromagnetic spectrum. The human eye is able to see visible light in three bands of red, green, and blue. HSI make it possible to look into many more bands and furthermore, enables its user to identify spectral features that are not visible for common cameras or the human eye. As a result, you can for example get a spectral analysis, with a Spectral angle (SA) map, and histograms of SA, where the warmer colors correspond to a higher spectral angle (Figure 16)[182]. These specific features are related to the optical properties of the analysed materials, such as human skin[183,184]. The technique is used in a variety of fields, including satellites, archaeology, art conservation, crime scene investigations and biomedicine[183]. The machines are not that easy to use in the clinic because of size,

although a measurement takes only about 20 seconds. To truly be competitive with dermoscopy and the future of dermoscopic images assisted by AI, future HSI devices must be more easily used, and reach high scores not only in sensitivity.

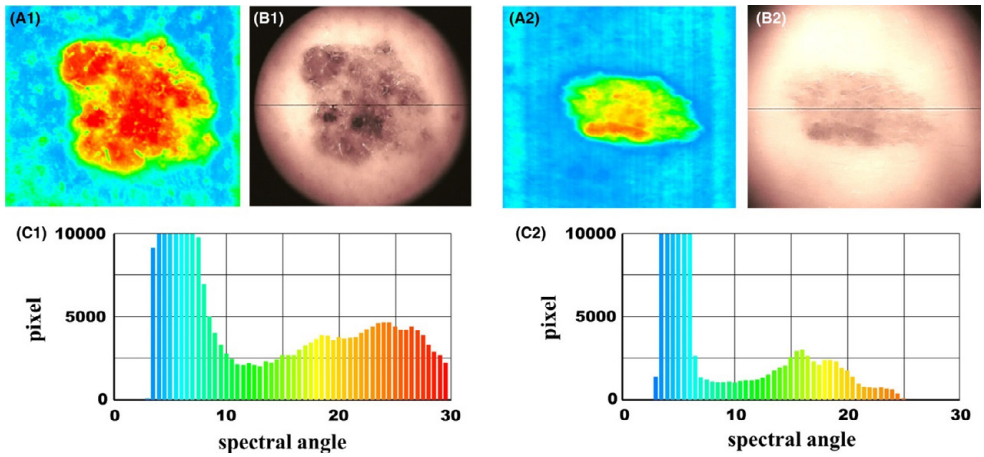

Figure 16: Typical analysis example hyperspectral image from device MSI-03 (paper II[182]) for cMM (1) and a benign nevus (2). (A) Spectral angle (SA) map. The warmer colors correspond to a higher spectral angle. (B) Charged Coupled Device (CCD) monitor image. (C) Histogram of spectral angle. The colour of the bar matches the spectral angle map. Distinctive of melanoma is higher and wider spectral angles. Bye due permition of © Wiley.

The MISS cohort

In two of the four papers of this thesis(paper I and III), we used the Melanoma Inquiry in Southern Sweden (MISS) cohort. This prospective cohort was established in 1990-1992. The study design stipulated that the cohort should not include women with any prior diagnosis of invasive cancer. Therefore, eligible women were first controlled with the Regional Cancer Registry. In total, 40,000 Swedish-born women (1000 per calendar year from 1925 to 1965) with no previous history of cancer were invited through random computerized selection from the National Population Registry and were invited (by letter) to join the initial cohort. The non-responders were sent one reminder. At baseline, all women lived in Southern Sweden's healthcare region, consisting of the regional counties of Skåne, Blekinge, Kronoberg and the Southern half of Halland. Participants provided written informed consent. At baseline, participants answered a validated and detailed questionnaire originally constructed in the late eighties[185-188]. Many questions concerned UVR exposure from sun tanning behaviour, sunburn history, sunbed use, sunscreen use, travelling habits and also information on phenotypic traits such as hair color, eye color, freckles and nevi count

on the left arm. Furthermore, it covered questions about lifestyle and sporting habits, parity, smoking habits, alcohol consumption, prescribed drugs as well as questions about marital status, educational level and residence during life. Additionally, there were also questions of heredity for cMM. The first questionnaire (baseline) was sent out 1990, with follow-up questionnaires sent to participants in year 2000 and 2010. The nature of the questions in the questionnaire makes them applicable not only for studies of melanoma but for BCC and cSCC and other diseases as well. The MISS cohort has therefore been utilised in several publications[90,185,188-190]

All MISS cohort participants, by using the unique Swedish personal identification number, have regularly been linked to both the Regional and National Cancer Registries, as well as to the National Cause of Death Registry, in order to receive detailed information on incidence of malignancies, and when applicable, the time and cause of death. Depending on the aim of different research studies, the participants of the MISS cohort were also linked with the National Birth Registry, the National Prescribed Drug Registry and the National Patient Registry.

Ingvar et al[189] conducted a study to see if the Hawthorne effect could be seen when following the MISS cohort. In short, the Hawthorne effect is when participants change behaviour due to attention from study personnel and/or just being a part of a prospective study[191]. It is known from some former research studies that participants that agree to partake in research studies also tend to have better overall health, lower mortality rates, higher socioeconomic status and do not smoke as much then the persons who does not agree to participate[192,193]. In the context of the MISS cohort, it could mean participants changed behaviour concerning UVR exposure or made healthier life-style changes because they knew that they were observed. However, since the cMM incidence did not differ between the participants and the background population, the study confirmed that the results were not influenced by an observer effect[189]. The conclusion being that the MISS cohort was found to represent a true and valid sample of the Swedish population, which supports the results of former studies on risk factors pertaining cMM.

Aims

The overall aim of this thesis is to enhance the understanding of risk factors for BCC, SCC, and cMM in women, to study the incidence trends in acral melanoma and evaluate a novel diagnostic non-invasive tool for cMM. The specific research questions asked in our studies are detailed below.

Paper I

Which influence has host characteristics (colour of hair and eyes, freckles and nevi count) and environmental factors (medicine intake, educational level, smoking habits and UV exposure) on cSCC risk in women?

Paper II

How efficient and accurate is a HSI device in diagnosing cMM among pigmented skin lesions in patients with fair skin?

Paper III

Do commonly prescribed photosensitizing drugs increase skin cancer risk in women?

Paper IV

How has incidence trends and melanoma-specific survival (MSS) rates changed for acral melanoma in the Swedish population during three decades, from 1990 to 2020?

Material and methods

Background

This thesis has a wide scope and the studies conducted have used different statistical methods to investigate our aims. We have also been using a diverse selection of patients and cohorts, depending on the specific study. Nonetheless, there are some common grounds for the studies of this thesis.

Registries

One of the fundaments of this thesis is the use of population-based registries. In Sweden, the registration of the whole population is managed by the Swedish Tax Agency. Everyone registered in Sweden through the Swedish National Population Registry is assigned a unique 12-digit personal registration number which follows the person their entire life. This personal identity number, with the date of birth included, enables the Population Registry to access information on where a person lives and works, their family relations, emigration in or out of the country and lastly death. This type of continuous census though the personal identity number, also have the great benefit in the way it enables researchers to match to diverse sets of other registries, including cancer registries.

The Swedish National Cancer Registry is a population-based mandatory registry under the National Board of Health and Welfare, and was established in 1958[194]. In this registry, the personal identity number is registered together with the specified malignant diagnosis, tumor site, tumor-specific histology, sex, diagnosing hospital and diagnosing doctor, and corresponding date of diagnosis. Reporting to the registry is mandatory, and the National Board of Health and Welfare requires a strategy of double registration, pertaining that the diagnosing physician and the responsible pathologist report all new cases of cancer to the registry. The National Cancer Registry is also linked with the Swedish Cause of Death Registry, where information can be found about time of death and cause of death and diagnosis contributing to the death of the patient. The

unique personal identity number makes these types of registries a reliable source of data enabling scientific research. In this thesis we primarily used extracted data from the National Cancer Registry in our MISS cohort studies (papers I and III). Furthermore, all data from the Swedish Melanoma Registry (Paper IV) is continuously matched to the National Cancer Registry and National Death Registry to be up to date.

The Swedish Melanoma Registry (SweMR)[195] is a nationwide quality registry, collecting valuable clinical and histopathological data about all diagnosed cutaneous invasive melanomas in Sweden. Reporting to SweMR is not mandatory but incited to. Hence the coverage about tumor-specific factors, compared to the National Cancer Registry, is almost 100 %. One advantage of SweMR, compared to the National Cancer Registry, is the corresponding clinical information about all the melanomas. SweMR is continuously matched with the National Cause of Death Registry, which makes extracted data very valuable. In paper IV we used the SweMR to extract data about all acral melanomas diagnosed in Sweden 1990-2020.

The National Prescribed Drug Registry is a registry under The National Board of Health and Welfare, where comprehensive data about doses, ATC-codes and other relevant information correlated to prescribed medications in Sweden are registered in relation to an individual's personal registration number. The Registry started in 2005 and data from this Registry was used in paper III, to explore photosensitizing medicines as potential risk factors for skin cancer.

Study participants

Since the four papers of this thesis studies different aspects of skin cancer, the participants of the four studies were identified and enrolled in different ways.

In papers I and III, we used the prospective MISS cohort, detailed in previous section. In short, at baseline 40,000 Swedish-born women were invited to join the initial cohort.

In paper II, the study was performed in the Department of Dermatology and Venereology at Skåne University Hospital, Lund, Sweden, Inclusion started in September 2014 and ended in June 2016. It was part of the diagnostic procedures of the established BioMEL biobank project (www.bioMEL.org). This projects aim was to collect clinical and molecular information on suspected pigmented skin lesions (PSL), including cMM, before and after excision. Patients with a PSL planned for excision, were consecutively offered to join the study before the planned excisional biopsy for diagnosis. All patients provided written informed consent. The enrolled patients were

Caucasians, corresponding to Fitzpatrick skin types I-II. Exclusion criteria were based on previous studies with hyperspectral imaging[196-198].

In paper IV, the patients were selected from the Swedish Melanoma Registry (SweMR). This comprehensive nationwide population-based quality registry including nearly all invasive cMM from 1990, with clinical and histopathological information[199]. In paper IV, all individuals in Sweden diagnosed with invasive melanoma on an acral site (palm, sole, or subungual) from 1990 to 2020 were included.

Ethical considerations

Progress of societies have always been dependent on new findings and new thoughts. In a modern context, scientific research is paramount in order to achieve more general knowledge and for development of new technical innovations for the good of mankind. Here, ethics has played an increasingly important role to uphold codes of conduct in research. Medical research is of course no exception. History has taught us the value of having ethical rules and legislative regulations to counteract medical research that harm individuals or groups that partake in the studies. Examples are numerous of research projects that did not meet ethical requirements. The "four principals" of beneficence, justice, autonomy and non-maleficence are often used as a framework in medical ethics. Beneficence mean that the practitioner/physician should always act in the best interest of the patient. Justice deals with the question of the scarcity of health resources and who is entitled to what treatment. Autonomy, the right for the patient to refuse or chose treatment or participation in studies. Finally, non-maleficence pertains to not be the cause of harm. These principles are indicative for medical research a well.

All medical studies involve a various number of ethical issues, dilemmas and/or problems. The aspects can differ and deal with many questions such as patient safety, the use of sensitive information on participants, using biological material from participants and also animal experiments. Hence, to ensure the "four principals" of medical ethics are met, a diversity of laws and regulations are in place in order to safeguard the interest of the participants in medical studies and to counteract research misconduct, plagiarism, including fabrication and/or falsification.

Nearly all studies involving humans in Sweden will have to go through an application to the Swedish Ethical Review authority (Etikpövningsnämnden). All four studies of this thesis have gone through this process and been accepted (see Ethical approval below). In paper I and II we used an established cohort of women since 1990. All participants signed an informed consent. All participants could withdraw from the

study at any time, without needing to explain their reason, which facilitates the process if anyone regretted the participation after inclusion. All participation was strictly voluntarily and data has been presented in a way that could not disclose a specific participant. However, the data gathered is considered sensitive sin nature since it deals with personal information about medication, educational level, sun exposure, pregnancy and parity, smoking and more on each participant. Therefore, all legal data management requirements were fulfilled and during data handling the data was pseudonymized to minimize the risk of identification further. The collaboration of professional statisticians, mostly from Clinical Forum South, in this as well as in the further studies in this thesis, guaranteed discussion about the accurate statistical methods and accurate presentation of data. Importantly, we discussed data management and planned analyses before the respective study and we were adherent to these plans, to avoid doubtful ad hoc analyses.

In paper II, we also gathered informed consent from the participants of the study to avoid recruiting individuals that did not want to participate. The study was a part of a the larger BioMEL study, which focuses on cMM. The patients came to the clinic and were examined. If a suspicious skin lesion was found, including melanoma, the patients were informed about the outlines of the study and consequently asked if they were interested in partaking in the study. In this circumstance, it can be argued that the patients were in a vulnerable position since they were just informed that they have a suspicious lesion that needed to be excised. In worst case, it could be a cMM. Could this perceived vulnerability lead to the notion that the patients who said yes had to or felt they were forced to join the study? We simply do not know. However, very few patients said no to join the study when asked. All participants have received information on how to proceed in order to opt out of the study.

In paper IV we used pseudonymized date retracted from the SweMR. In this study we cooperated with the statistician in SweMR, and therefore data was never used outside SweMR, but held within the registry. As acral melanomas is a rare subtype of melanoma, with a known high mortality, it is important to assess risk factors and clarify trends in incidence and survival in a cohort that is big enough to generate statistical power and not produce research without significance. We used all available data on Swedish acral melanoma patients in modern time, which could be of help when planning health activities, prevention campaigns and how to impact and improve the care of these patients in the future. Therefore we think that the research based on sensitive data, and the results could be of benefit of future patients, and thus fulfilling the criteria of “be of use” instead of “be of harm” for the included participants.

Another aspect of ethics in medical research is critical evaluation of your scientific work. This is discussed in length in each paper in this thesis and is an integral part of the

research process, constantly evaluating if our findings are worth publication and can be a part of a larger general interest. Furthermore, it is important that you publish your findings, even if the study at hand does not find any positive associations. Finding no association is also a scientific finding.

Ethical approval

All studies in this thesis were in accordance with ethical standard of the institutional research committee and with the Helsinki declaration and its later amendments.

For paper I and III, The Institutional Ethics Review Board of Lund University and the Swedish Ethical Review Authority approved the study (LU-34-1992, LU-632-2003, LU-781-2005, LU-849-2005, LU-190-2007, LU-644-2015 and LU-02914-2022).

For paper II, BioMEL was approved by the Ethical Board of Lund University (2013/101).

For paper IV, the study was approved by the Swedish Ethical Review Authority (Dnr 2020-03870).

Study design and statistical analyses

Paper I

The participants were continuously cross-checked with the National and Regional Cancer Registry for the occurrence of any kind of cancer, including cSCC. The follow-up time was measured from the inception of the study until the diagnosis of first primary cSCC, death, emigration, or the end of the study period (20 years).

Self-reported use of drugs/medications were grouped according to the ATC classification system and the participants of the cohort were coded as "users" if they have been prescribed the medication for more than a month and received the drug at the pharmacy and the rest of women as "non-users" for the specific drug. Questionnaire based data on phenotypic characteristics included information about hair colour, eye colour, amount of freckles, and numbers of naevi on one arm. Moreover, we used data about smoking habits, number of pregnancies, former and present locations of living, the level of education, information about outdoor work and the use of sunbeds and UV lamps.

Statistical analysis

Incidences of cSCC were presented for each level of the hypothesized risk factors. In order to estimate the increased risk associated with each factor, we used a univariable cause-specific Cox regression analysis using age as the timescale, i.e., subjects enter the analysis at their baseline age (age at which they completed the questionnaire) and exit at their event, censoring age or death. By using age as the timescale, confounding risk factors by age were already eliminated in the univariable analyses. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI) and p-values.

To investigate the independent contribution of each risk factor, we used a multivariable Cox regression analysis. In both the multivariable and univariable Cox analyses, the proportional hazards assumption was tested using Schoenfeld's test (tests with $p < 0.05$). Statistical calculations were performed in cooperation with a professional statistician.

Paper II

Patients, recruited in the dermatological routine care when a pigmented skin lesion (PSL) was suspicious and was recommended excision to rule out melanoma were offered inclusion. All participants were fair-skinned. Before surgical diagnostic excision of the PSL the lesion was imaged by dermoscopy and a Hyperspectral imaging device, MSI-03, with a wavelength range of 400-800 nm and a wavelength resolution of 2.4 nm (Mitaka Kohki Co., Ltd.). Assessing the PSL did neither affect the lesions or the following clinical management of the patients. All excised lesions were sent for ordinary histopathological diagnosis and were later also re-evaluated by a certified dermatopathologist. The discrimination index of a lesion (DI) was derived from the corresponding HSI data as a continuous numerical value. The DI reflected the lesional irregularity and randomness, via a variety of spectra included in the device. The HSI data together with final histopathological diagnosis, was compared to the DI for all lesions.

Statistical analysis

The PSLs were during statistical analyses divided into three groups: a malignant melanoma group (cMM), a benign PSL group and a malignant non-melanoma skin cancer group (NMSC).A receiver operating characteristics (ROC) analysis was used to compare the performance of the HSI device regarding Caucasian PSLs and to determine the DI irrespective of skin types. The alpha level was set at 0.05. The 95% confidence interval (CI) was obtained using the Clopper-Pearson exact CI[200]. Sensitivity and specificity endpoints were evaluated at a certain cut-off level of DI. All

statistical calculations were performed using BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan).

Paper III

The MISS-cohort was linked to the Swedish Cancer Registry, the regional pathology registers, and the National Swedish Prescribed Drug Register (SPDR). Participants were followed from 1 January 2008 until either diagnosis of skin cancer, emigration, death, or end of follow-up on 31 December 2018. Women diagnosed with skin cancer before the study began were excluded. Only primary diagnoses of cSCC, BCC or cMM were used in the analyses. Participants were considered to be exposed to the included drugs if one or more prescriptions were registered in their name. Reported phenotypic factors and UV exposure variables were extracted from the mentioned MISS questionnaires (1990 and 2000).

After a literature review, drugs with a photosensitizing effects were identified and the following classes of drugs were finally included: antidiabetics, diuretics, β-blockers, calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), proton pump inhibitors (PPi), NSAIDs, antibiotics, and hormonal replacement therapies. The drugs were grouped according to the Anatomical Therapeutic Chemical (ATC) classification system.

Statistical analysis

Multivariable Cox regression analyses were performed using complete cases, controlling for known risk factors (including host and environmental factors) using drug exposures as time-dependent covariates. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk associated with each of the studied skin cancers with ever-never use of each photosensitizing drugs were analysed . To evaluate the dose-effect relationship the prescription quantity of defined daily dose (PDDD) was extracted from the SPDR. We defined PDDD as the number of standard daily doses of a drug, when used for its primary indication, included in a single prescription. The sum of a person's PDDD was divided by the duration of the treatment (last date - first date of prescription + 30 days that is a common length of a prescription) and split in quartiles. Each skin cancer was analysed separately, and each drug group, subgroup, and dose variable were added to a base model with 13 possible confounding variables (phenotypic traits and UVR exposure). Tests for proportional hazards were performed for statistically significant variables. Using a two-sided statistical test, statistical significance was recognized when $P < 0.05$. Bonferroni adjustments were also performed in the ever-never analyses, by dividing the p-value with the number of

models analysed (n=19), and statistical significance was recognized when the Bonferroni-adjusted $P < 0.05$. Analyses were performed using SAS Enterprise Guide, version 8.3 (SAS Institute, Inc.)[201].

Paper IV

This registry-based study included all patients in Sweden diagnosed with invasive melanoma on an acral site (palm, sole, or subungual) from 1990 to 2020. Data was extracted from the National Swedish Melanoma Registry (SweMR) as formerly described. Incidence trends and melanoma specific survival (MSS) were calculated. We observed these individuals' MSS from the diagnosis date until either their demise from melanoma, the first instance of death from other causes, diagnosis of a second melanoma, or the end of follow-up on 31 December 2020. The SweMR database provided clinicopathological information (age, sex, tumor data, tumor (T) stage, histopathological subtype) as well as data about cause of death.

Statistical analyses

Acral melanoma (AM) cases were reported as absolute numbers and age-standardized incidence rates per 100,000 person-years. An annual percent change (APC) calculation was performed using joinpoint regression, to assess changes in incidence rates. The APC calculation started from 1996, since SweMR registration was not yet fully nationwide during the initial years. For the analysis of time-dependent changes in clinicopathological features and MSS, the study period spanning from 1990 to 2020 was divided into three segments: period 1 (1990–2000), period 2 (2001–2010), and period 3 (2011–2020).

Multinomial logistic regression was employed to examine differences in tumor characteristics over time, with period 1 (1990–2000) as the reference period. In paper IV, the results are presented as odds ratios (ORs) and 95% CIs. Kaplan-Meier curves were plotted for overall MSS and separated by sex for different periods. To identify risk factors for melanoma-specific mortality (MSM), we conducted a multivariable Cox proportional hazard regression, incorporating variables such as sex, age, Breslow thickness, histopathological subtype, and period of diagnosis. Stratification was done for age and Breslow thickness to examine whether changes in prognosis were restricted to specific groups. Hazard ratios (HRs) are presented with 95% CIs and p-values from two-tailed tests. A significance level of <0·05 was used. Statistical analyses were conducted using R Statistical Software (v4.0.3; RCore Team 2020) and Joinpoint Trend Analysis Software (v.4.6.0.0; the National Cancer Institute) and performed in close collaboration with a statistician at the SweMR.

Results

Paper I

In this study, we aimed to investigate which influence phenotypic traits and environmental factors have on risk for developing a cSCC in women. 29460 women agreed to participate in the study, hence a response rate at 74%, compared to the initial 40 000 invited women. After further exclusions there remained 29421 women, of which 333 were diagnosed with a cSCC (124 of which were invasive cSCC and 209 tumours were SCC in situ).

In the univariable analysis, we compared the incidence of cSCC with its potential risk factors. We could show influence on cSCC incidence of sunbed use (ever vs never), HR 1.55 95% CI 1.24–1.95) and for sunbed use up to three times per year vs never use HR 1.34 95% CI (0.96–1.87). Sunbed use between four and 10 times per year vs never use showed a HR 1.55 95% CI (1.14–2.10), and sunbed use over 10 times per year vs never use showed a HR of 1.88 (1.34–2.63). Furthermore, associations were shown with freckles HR 1.53 95% CI (1.23–1.91), red hair HR 2.00 95% CI (1.12-3.56), red or light blond hair HR 1.63 95% CI (1.16-2.31), use of OC HR 1.30 95% CI (1.03-1.65) and use of immunosuppressive medications for over one month HR 2.51 95% CI (1.47-4.29). The independent effects of the risk factors were determined using a multivariable analysis, using a 95% CI (Table 1). To account for possible age-dependent differences, we adjusted according to birth cohort (four groups). In the multivariable analysis, sunbeds HR 1.18 per step in score 95% CI (1.04-1.32), red or light blond hair HR 1.58 95% CI (1.06-2.34, freckles HR 1.43 95% CI (1.11-1.85) and immunosuppressive medication HR 2.16 95% CI (1.06-4.39) were associated with increased HR for cSCC.

Additionally, we detected a positive association between cSCC incidence and sunbed use (HR 1.18; 95% CI 1.04-1.32) for each score level (0-3). Using a more detailed multivariable analysis, we further elucidated this trend by including sunbed use as a factor on these four levels and compared the sunbed users to those that of never users: sunbed use 0-3 times/year (HR 1.38; 95% CI 0.95-2.0), 4-10 times/year (HR 1.47; 95% CI 1.02-2.1), and >10 times/year, (HR1.62; 95% CI 1.09-2.42). The increased

risk of cSCC for sunbed users compared to never-users is illustrated graphically in (Figure 17).

Table 1: Multivariable Cox regression analysis of risk factors for cSCC, based on 247 events in 22 690 women (complete case analysis).

Variable	HR	95% CI	*P-value*
Freckles	1.43	1.11-1.85	0.006
Sun-bed use (per step in linear score 0-3)	1.18	1.04-1.32	0.008
Red or light blond hair	1.58	1.06-2.34	0.023
Use of immunosuppressive medication >1 month	2.16	1.06-4.39	0.034
Use of NSAID (>1 month)	0.63	0.39-1.02	0.059
Occupational outdoor working	0.81	0.59-1.11	0.2
Ever-user of oral contraceptives	1.18	0.86-1.51	0.4
Ever-user of hormone replacement therapy	1.12	0.85-1.54	0.4
High number of nevi	0.87	0.56-1.31	0.5
Ever-smoker	0.93	0.72-1.20	0.6
Tertiary education	0.92	0.72-1.19	0.6
Ever lived in a sunny climate	1.13	0.54-2.24	0.8
More than two pregnancies	1.03	0.80-1.34	0.8
Birth cohort (vs 1926-1935)			0.17
1936-1945	1.23	0.84-1.79	
1946-1955	1.36	0.68-2.73	
1956-1965	3.26	1.09-9.72	

A global Schoenfelds test displayed no evidence of departure from proportional hazards (p=0.63).
HR, hazard ratio; CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs.

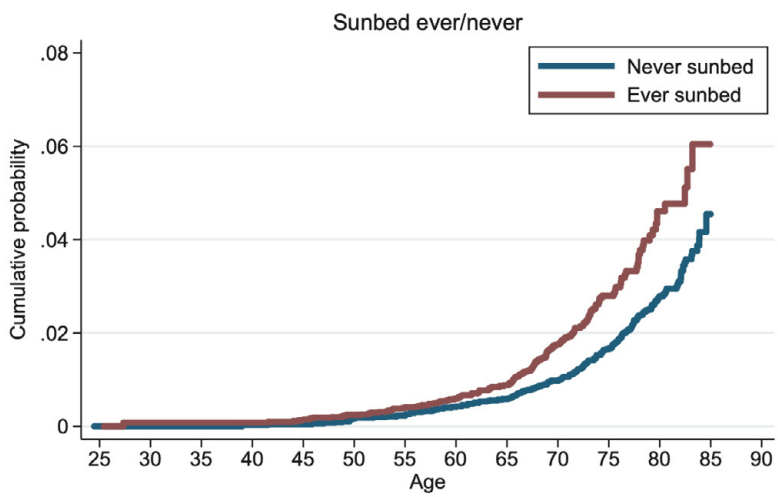

Figure 17. Curves showing the relationship between the cumulative incidence of cutaneous squamous cell carcinoma (cSCC) in ever- users and never-users of sunbeds and in relation to age[36]. By due permisson of © Acta Dermato-Venereologica.

Paper II

In the study at hand, we aimed to test the efficiency and accuracy of a novel HSI device in diagnosing cMM among pigmented skin lesions in patients with fair skin. A total of 186 participants with 207 PSLs were originally enrolled in the study. Median age of participants was 62 years (range: 15-96 years), 98 males (53%), 88 females (47 %).

Of the 207 lesions registered at baseline, 5 lesions were excluded due to non-eligibility because of placement on non-target skin (acral volar skin) for four patients and one patient because of a background other than normal skin. Five PSLs were histopathologically classified as "non-melanoma skin cancer" and were excluded in further calculations regarding cMM and PSLs.

The eligible and evaluable PSLs were divided into two groups. In the melanoma-group there were 90 lesions, including 53 cMM, 34 melanoma in situ, one case of MELTUMP (melanocytic tumour of uncertain malignant potential) and two cases of SAMPUS (superficial atypical melanocytic proliferations of uncertain significance). The benign group consisted of 107 benign PSLs, including melanocytic nevi with none to severe dysplasia, seborrheic keratosis and other benign lesions (Table 2).

Table 2 Observed sensitivity, specificity, and true and false positive/negative values for pigmented skin lesions (PSLs) of Caucasians.

Diagnosis	Total (n)	TP	FN	SE(%)
MM-group	90	87	3	96.7
Invasive melanoma	53	52	1	98.1
In situ melanoma	34	33	1	97.1
MELTUMP/SAMPUS	3	2	1	66.7
Diagnosis	**Total (n)**	**TN**	**FP**	**SP(%)**
Benign PSL*	107	45	62	42.1
Benign MN	33	15	18	45.5
MN with severe dysplasia	15	6	9	40.0
MN with moderate dysplasia	22	7	15	31.8
MN with mild dysplasia	19	8	11	42.1
Seborrheic keratosis	9	4	5	44.4
Other benign lesions	9	5	4	55.6
Diagnosis	**Total (n)**	**TP**	**FN**	**SE(%)**
Non-melanoma skin cancer (NMSC)	5	3	2	60.0
Pigmented BCC	3	2	1	66.7
SCC	2	1	1	50.0

SE: sensitivity, SP: specificity, TP: true positive, FN: false negative, TN: true negative, FP: false positive, BCC: basal cell carcinoma. MN: melanocytic nevus, MM: malignant melanoma, SCC: squamous cell carcinoma, *Benign PSL=excluding all NMSC and MM. MELTUMP: melanocytic tumour of uncertain malignant potential, SAMPUS: superficial atypical melanocytic proliferations of unknown significance

For each lesion the hyperspectral analysis was summarised in a Discrimination index (DI) in order to be able to compare the hyperspectral analyses between different groups of lesions. The boxplot graph show the distribution of DI from the MM (solid squares) and benign PSL (solid circles) groups (Figure 18). In the panel the median, the 25th percentile and 75th percentile of DI for each group are also indicated by horizontal bars. The difference in DI for the two groups was statistically significant ($p<0.001$), and the cut off level for cMM was set to 4.669. This level was chosen to fulfil the criteria to include most melanomas and also exclude most benign lesions.

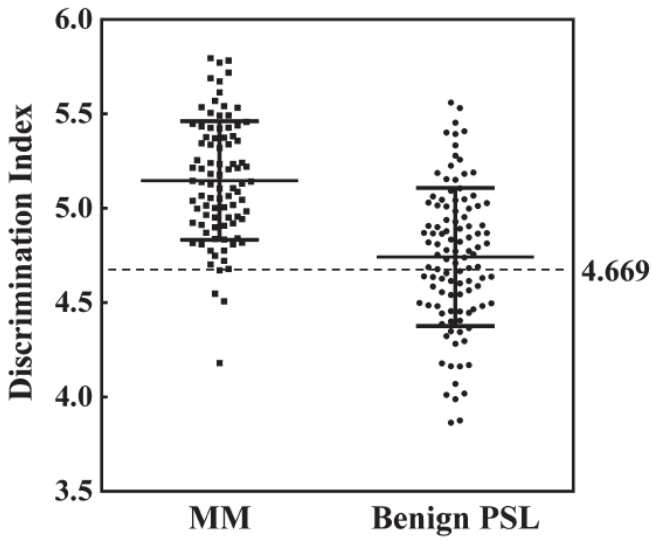

Figure 18: Distribution of the discrimination index (DI) for malignant melanoma (MM) and the other benign pigmented skin lesions (Benign PSL) from skin types I-II[182]. In the panel the median, the 25th percentile and 75th percentile of DI for each group are also indicated by horizontal bars. The difference in DI for the two groups was statistically significant ($p<0.001$). By due permission of © Wiley.

The sensitivity for the two groups was 96.7% (95% CI: 90.6% - 99.3%), and the specificity was 42.1% (95% CI: 32.6% - 52.0%) respectively. Out of the 90 lesions in the melanoma group, the following three lesions were by the device classified as false negatives: one case of lentigo maligna on head/neck area, one case of superficial spreading melanoma (SSM) on the frontal trunk (0.3 mm Breslow thickness), and one case of SAMPUS (Superficial Atypical Melanocytic Proliferations of Unknown Significance) on the lower extremities. These cases correspond to the bottom three DI plots in the MM group in the boxplot (Figure 18).

Receiver operating characteristics (ROC) (Figure 19) curves obtained using DI relative to the diagnostic gold standard (histopathological diagnosis). The circles represent the

ROC curves for Caucasian pigmented skin lesions sets. The area under the curve (AUC) reveals that the HSI system has practical potential as a clinical adjunct tool, as the AUC was 0.800 (95% confidence interval (CI): 0.740 - 0.861).

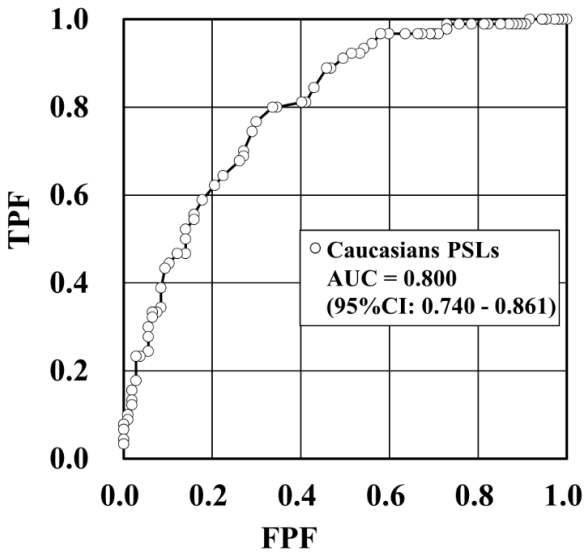

Figure 19: Receiver operating characteristics (ROC) curves obtained using discrimination index (DI) relative to the histopathological gold standard[182]. The circles represent the ROC curves for Caucasian pigmented skin lesions sets. The area under the curve (AUC) reveals that the evaluated HSI system has practical potential as a clinical adjunct tool. TPF: true positive fraction, FPF: false positive fraction, CI: confidence interval. **By due permission of © Wiley.**

Paper III

The aim of this study was to investigate if commonly prescribed photosensitizing drugs increase risk of skin cancer in women. Once again utilizing the MISS cohort, a total of 29,515 women were included at first. We thereafter excluded 3405 participants due to emigration, death, or prior skin cancer before the start date of this study, leaving 26,110 women of which 21,062 had complete data. During the study, 1308 primary BCC, 528 primary SCC and 257 primary cMM were registered. Prescription of medications with phototoxic characteristics were matched with the data in the MISS cohort.

In this study we primarily evaluated skin cancer risk as an adjusted HR with a 95% CI for each photosensitizing drug group, compared with the never-use group (Table 3). Female hormone-use, like estrogen- and progesterone-based drugs, significantly increased the risk of all assessed skin cancer types: BCC (HR 1.24; 95% CI 1.11-1.39), cSCC (HR 1.23; 95% CI 1.03-1.47) and cMM (HR 1.31; 95% CI 1.01-1.69), but

association persisted only with BCC after Bonferroni adjustment Sub-analyses of progesterone, estrogen and combination treatment revealed that this effect was dominated by the estrogen component.

Moreover, diuretic use significantly increased the risk of cSCC, but not of BCC or cMM. Subgroup analyses showed that the risk of cSCC was significantly associated with the use of loop diuretics (HR 1.6; 95% CI 1.3-2.0), but not with the other two drug groups (thiazide diuretics and other diuretics). However, thiazide use increased the risk of both BCC (HR 1.25; 95% CI 1.09-1.44) and cMM (HR 1.41; 95% CI 1.03-1.93). After Bonferroni adjustment, the association between thiazide treatment and risk of cMM became non-significant.

The other anti-hypertensive drugs, ACEi, ARB, β-blockers and CCB, were not associated with skin cancer risk. Photosensitizing antibiotics (tetracycline, sulphonamides, fluoroquinolones, and nitrofuran derivates) were related to increased risks of BCC (HR 1.14; 95% CI 1.02-1.28) and cSCC (HR 1.35; 95% CI 1.13-1.62), although the former being non-significant after Bonferroni adjustment.

To further assess causality, dose-dependent responses of selected photosensitizing drugs were evaluated. Dose of estrogen showed a positive correlation to risk of BCC. Compared to never users of estrogen, the risk of BCC increased 60% in the group using the highest dose (HR 1.6; 95% CI 1.30-1.96). A similar trend was found to risk of cM but not of cSCC.

Similarly, loop diuretics showed a dose-response trend with risk of cSCC. Compared to never-users, the HR gradually increased from 0.94 to 2.3 as dose increased from low to high. Moreover, use of CCB increased the risk of all skin cancers at the two higher dose quartiles, but this was significant only for BCC and, at the second-highest dosing level, for cSCC. Use of β-blockers modestly increased HR of all skin cancers only at the highest dosing levels.

Interestingly, low-dose NSAID significantly decreased the risks of BCC (HR 0.70; 95% CI 0.57-0.86) and cSCC (HR 0.55; 95% CI 0.39-0.79), but high-dose was associated with increased risks of BCC (HR 1.73; 95% CI 1.47-2.02) and cSCC (HR 1.57; 95% CI 1.22-2.02).

Table 3. Risk of skin cancer development in relation to ever-use compared to never-use of photosensitizing medication, categorized by group and, when possible, subgroups of medication and skin cancer type.

	BCC	cSCC	cM
Photosensitizing medication	**HR (95% CI)[§]**	**HR (95% CI)[§]**	**HR (95% CI)[§]**
Estrogen, Progesterone, and combination	1.24 (1.11 – 1.39)**	1.23 (1.03 – 1.47)*	1.31 (1.01 – 1.69)*
Estrogen	1.25 (1.11 – 1.40)**	1.23 (1.03 – 1.48)*	1.35 (1.03 – 1.75)*
Progesterone	1.23 (0.88 – 1.72)	1.01 (0.51 – 2.00)	0.52 (0.21 – 1.27)
Estrogen/Progesterone comb.	1.22 (0.97 – 1.53)	1.05 (0.69 –1.60)	1.14 (0.70 – 1.85)
Diuretics	1.12 (0.99 – 1.27)	1.53 (1.27 – 1.84)**	1.20 (0.90 – 1.60)
Thiazides	1.25 (1.09 – 1.44)**	1.17 (0.95 – 1.44)	1.41 (1.03 – 1.93)*
Loop diuretics	0.92 (0.78 – 1.10)	1.60 (1.29 – 1.98)**	0.92 (0.61 – 1.40)
Other diuretics	1.00 (0.81 – 1.24)	1.30 (0.98 – 1.71)	0.93 (0.55 – 1.58)
CCB	1.05 (0.91 – 1.21)	1.16 (0.95 – 1.41)	1.16 (0.84 – 1.61)
ACEi, ARB	0.94 (0.83 – 1.07)	1.03 (0.85 – 1.24)	0.96 (0.72 – 1.30)
β-blockers	1.00 (0.88 – 1.13)	1.10 (0.91 – 1.32)	1.17 (0.88 – 1.55)
Antibiotics	1.14 (1.02 – 1.28)*	1.35 (1.13 – 1.62)**	1.26 (0.97 – 1.63)
Antidiabetics	0.88 (0.69 – 1.12)	1.05 (0.76 – 1.46)	0.64 (0.33 – 1.24)
PPi	1.02 (0.91 – 1.15)	1.22 (1.02 – 1.46)*	0.98 (0.75 – 1.29)
NSAID	1.12 (1.00 – 1.25)	1.08 (0.90 – 1.28)	1.26 (0.98 – 1.63)

[§]Hazard ratio (HR) of ever-use of photosensitizing medication compared to never-use, presented with 95% confidence intervals (CI) regarding basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (cSCC) and cutaneous melanoma (cM).

*Significant p-value < 0.05.

**Significant p-value < 0.05 after Bonferroni correction for multiple testing.

CCB (Calcium channel blockers), ACEi (Angiotensin converting enzyme inhibitors), ARB (Angiotensin receptor blockers), β-blockers (Beta-blockers), PPi (Proton pump inhibitors), NSAID (Non-steroidal anti-inflammatory drugs).

Paper IV

In this study, we aimed to study incidence trends and melanoma-specific survival (MSS) for acral melanoma from 1990 to 2020 in the Swedish population. We used nation-wide data extracted from SweMR, as formerly described. Between 1990 and 2020, 1000 acral melanomas (AMs) were recorded in 999 people (Table 4). Diagnostic periods were divided in three, to be able to compare with recent Swedish studies and treatment guidelines of melanoma. Notably, a slight increase in absolute numbers of AM was observed from period 1(1990-2000) to period 3 (2011-2020). In period 1, 289 AM was recorded, compared to 308 in period 2 (2001-2010) and 403 in period 3. The median age at diagnosis was 69, 71, and 72 years for each respective time period. AMs were more prevalent in females during all three decades.

Over time, the ratio of AMs decreased in younger and middle-aged groups (<40, 40–59, and 60–69 years) and increased in older groups (70–79, and ≥80 years). Because of different ways of registration of tumour body sites pre- and post-2009, the exact AM locations were only documented in period 3. However analysis of this time period showed that only 25% of AMs developed on the palm or subungual finger and 75% on the sole or subungual toe. The most common histological subtype was ALM (about 40%), followed by SSM. No substantial variation was noted in different tumour thickness categories (Breslow thickness). Approximately half of the AMs had a tumour thickness of >2.0 mm, consistent across all periods. Similar numbers were noted for tumour thicknesses of 2.1–4.0 and >4.0 mm (Table 4).

Table 4: Clinicopathological features of acral melanoma (AM) in Sweden in years 1990-2020.

Diagnostic period	1990–2000	2001–2010	2011–2020	Total
Total number of AMs	289	308	403	1000
Sex (%):				
Male	132 (45.7)	119 (38.6)	170 (42.2)	421 (42.1)
Female	157 (54.3)	189 (61.4)	233 (57.8)	579 (57.9)
Age, years (%):				
<40	22 (7.61)	23 (7.5)	19 (4.7)	64 (6.4)
40–59	63 (21.8)	62 (20.1)	74 (18.4)	199 (19.9)
60–69	67 (23.2)	60 (19.5)	76 (18.9)	203 (20.3)
70–79	78 (27.0)	79 (25.6)	126 (31.3)	283 (28.3)
≥80	59 (20.4)	84 (27.3)	108 (26.8)	251 (25.1)
Median age [IQR][§]	69 [57;77]	71 [58;81]	72 [60;80]	71 [59;80]
Histopathological subtype (%):				
ALM	104 (36.0)	131 (42.5)	183 (45.4)	418 (41.8)
LMM	5 (1.7)	4 (1.3)	6 (1.5)	15 (1.5)
SSM	71 (24.6)	60 (19.5)	98 (24.3)	229 (22.9)
NM	63 (21.8)	50 (16.2)	42 (10.4)	155 (15.5)
Other	42 (14.5)	53 (17.2)	55 (13.6)	150 (15.0)
Missing	4 (1.4)	10 (3.3)	19 (4.7)	33 (3.3)
Site (%):*				
Palm or subungal finger	0 (0.0)	14 (4.6)	95 (23.6)	109 (10.9)
Sole or subungal toe	0 (0.0)	56 (18.2)	308 (76.4)	403 (40.3)
Acral site, unspecified	289 (100.0)	238 (77.3)	0 (0.0)	333 (33.3)
Breslow thickness, mm (%):				
0.1–1.0	64 (22.1)	53 (17.2)	86 (21.3)	203 (20.3)
1.1–2.0	55 (19.0)	63 (20.5)	77 (19.1)	195 (19.5)
2.1–4.0	67 (23.2)	73 (23.7)	100 (24.8)	240 (24.0)
>4.0	76 (26.3)	86 (27.9)	108 (26.8)	270 (27.0)
Missing	27 (9.3)	33 (10.7)	32 (7.9)	92 (9.2)

T category:				
T1	64 (22.1)	53 (21.2)	86 (4.7)	203 (20.3)
T1a	25 (8.7)	29 (9.4)	50 (12.4)	104 (10.4)
T1b	31 (10.7)	19 (6.2)	34 (8.4)	84 (8.4)
T2	55 (19.0)	63 (20.5)	77 (19.1)	195 (19.5)
T2a	31 (10.7)	41 (13.3)	55 (13.6)	127 (12.7)
T2b	16 (5.5)	17 (5.5)	22 (5.5)	55 (5.5)
T3	67 (23.2)	73 (23.7)	100 (24.8)	240 (24.0)
T3a	22 (7.6)	22 (7.1)	37 (9.2)	81 (8.1)
T3b	34 (11.8)	48 (15.6)	60 (14.9)	142 (14.2)
T4	76 (26.3)	86 (27.9)	108 (26.8)	270 (27.0)
T4a	9 (3.1)	17 (5.5)	23 (5.7)	49 (4.9)
T4b	57 (19.7)	68 (22.1)	79 (19.6)	204 (20.4)
Missing	27 (9.3)	33 (10.7)	32 (7.9)	92 (9.2)

[§]Median age, presented together with inter-quartile range (IQR).
AM (acral melanoma), ALM (acral lentiginous melanoma), LMM (lentigo maligna melanoma), SSM (superficial spreading melanoma), NM (nodular melanoma).

The ORs for AM per age group were notably higher in the third period for age groups 70-79 (2.16, 95% CI 1.04–4·48) and ≥80 years (2.30, 95% CI 1.09–4.86) compared to the reference age group (<40 years). In the second time period, females presented a higher OR of AM (1.46, 95% CI 1.02–2.07) than males, a trend which did not continue into the third period. Referring to the first period, the second and third periods showed significantly lower ORs for subtype NM. No significant differences were found in ORs for other histopathological subtypes or the distribution of tumour thickness across the study periods.

The age-standardised incidence rates per 100,000 person-years were 0.37 for 1996-2000, 0.33 for 2001-2010 and 0.38 for 2011-2020. Incidence trends from 1996-2020, presented as age period cohort (APC), was 0.94 for females and -0.33 for males with 0 joinpoints.

Melanoma specific survival (MSS) was also divided into the three studied periods (Figure 20). Neither of the 5-year MSS curves for the total population of the study nor the curves for males and females indicated any significant difference between the periods. Concerning melanoma specific mortality (MSM), the multivariable Cox regression analysis demonstrated a near 30% risk reduction for MSM among females than males (HR 0.73, 95% CI 0.57-0.95). The MSM significantly rose with advancing age, especially within the 70–79 and 80 and above age groups. It also increased significantly with higher Breslow thickness. Finally, the histopathological subtypes of SSM and NM, compared to ALM, displayed an association with an increased risk of MSM.

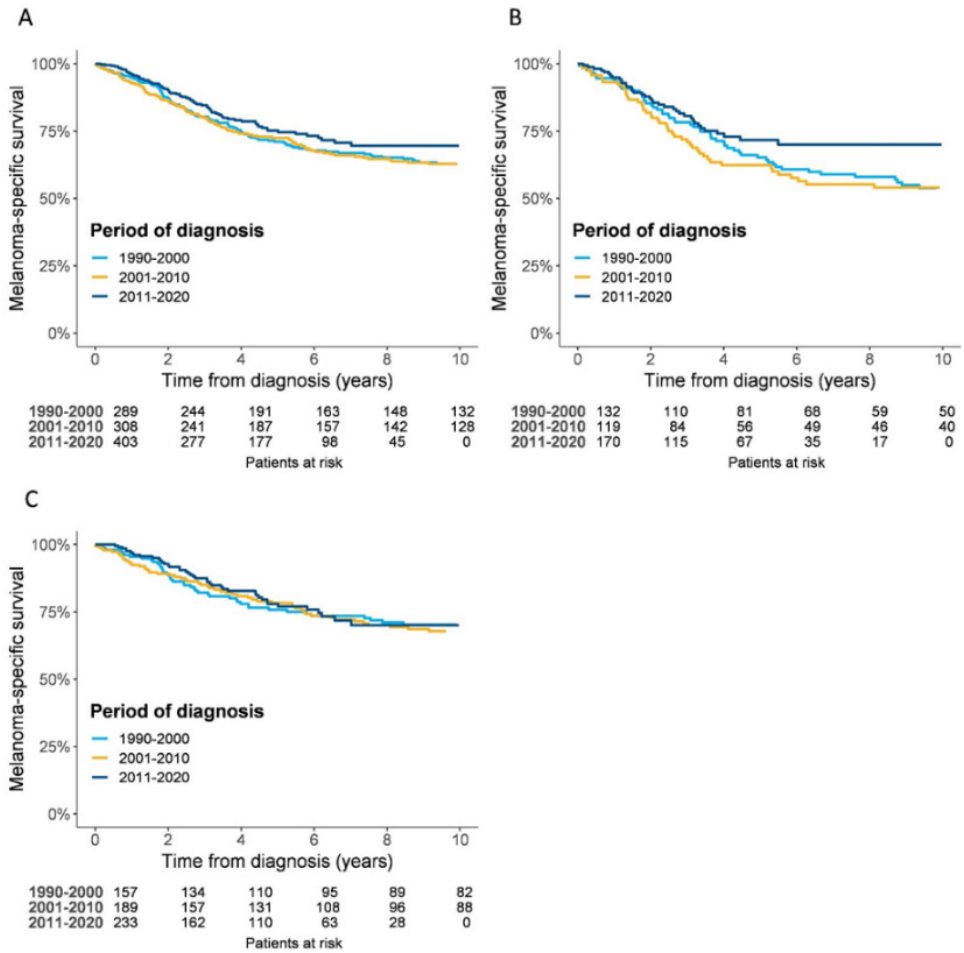

Figure 20: Kaplan-Meier curves displaying 5-year melanoma-specific survival 1990-2020 for A) total study population, B) males and C) females.

Methodological considerations and general discussion

Paper I

Methodological considerations

The main strength of this study is its prospective design including a large cohort of women with data collected over a long period of time. Furthermore, cross-referencing with the reliable National Swedish Cancer registry and other registries is also a strength.

One obvious limitation is that the MISS-cohort only consists of women, hence generalization of our findings cannot extend to male patients. For example, only few women in our cohort worked outdoor and this could underly the absence of an association between outdoor work with chronic exposure to UVR, which has been shown in earlier studies on males[35,120,202]. Furthermore, participants in the MISS-cohort come from the same geographical area and are predominantly skin type I-II, making conclusions applicable on similar populations. The data is based on a questionnaire constructed in the early nineties, there could be information lacking on confounders, such as changes in self-reported exposure. This means that we could not adjust for all possible confounders, for instance the use of sun protecting agents and their possible effect on the risk. Also, we have not been able to look at family history of cSCC as a risk factor in our study.

Discussion

The main findings of our study is that sunbed use, having freckles or red or light blond hair and using immunosuppressive drugs are independent risk factors for developing cSCC. This is in line with the literature[35,39,203-209] and confirms the distinct relationship between cSCC risk and sunbed use.

There were several perceived risk factors where we found no association of risk for cSCC. We detected no evidence for smoking being a risk factor. Earlier studies have

shown conflicting results[210-212]. Furthermore, there was no influence of risk OC, which aligns with risk of OC lack association in earlier studies[213,214].

Studying phenotypic traits, fair skinned individuals with red to blond hair have been reported as being at elevated risk of developing cSCC and cMM[39,207-209], which our study confirms. The inability to tan, corresponds to this populations predominant production of yellow reddish pheomelanin instead of brown-black eumelanin. This confirmed risk factor calls for an improved primary prevention strategy for this population[215,216].

Several studies have shown that the risk of cSCC is markedly increased following organ transplantation[205,206,217], which is in line with our study. This highlights the importance of continuous dermatological surveillance. Additionally, equally important is education about primary prevention for patients with long-term immunosuppression.

UVR is the most important known risk factor for cSCC[35,39,218], cMM, and BCC[35,98,203]. Confirming the contribution of sunbeds use and increased risk of cSCC is important since this risk factor can be influenced by information and regulation[61,219]. Sweden has enacted some age regulations in 2018 concerning sunbed use, while age limits for sunbeds have already been enacted in several other countries such as Italy and Australia[61,220,221]. This must be seen as promising and as a proactive preventive strategy.

Men tend to use sunbeds less than women[61]. In Sweden, the incidence of cSCC is somewhat higher in men than in women. Would the difference in incidence be higher between men and women if they used sunbeds in equal amounts? We do not know the answer to this question. However, we confirm that when sunbed use increases, so does the risk of developing cSCC. Once more this dose-response relationship illuminates the negative health impact of using sunbeds.

Paper II

Methodological considerations

The study was performed in a tertiary care clinic specialized in skin cancer from September 2014 through June 2016. The overall project aim of BioMEL (www.biomel.org) was to collect clinical and molecular information on clinically or dermatoscopically suspected pigmented skin lesions (PSL), including cMM, before and after excision. Here, selection bias can be discussed. The included patients had all a suspected pigmented lesion and were consecutively asked to join the study and not

randomly selected for this study, which can lead to unrepresentative sampling. Since the aim of the present study, Paper II, was to test a novel hyperspectral device in a clinical setting with skin types I-II, we set out to enrol participants in a real-life clinical setting. Hence, the device was also tested in a real-life setting making the results generalizable to similar contexts.

A major strength was that the clinical examination data, and histopathological data, was blinded to the data manager calculating the DI, and that the individual patient was used as its own control for calibrating the measurement of the PLS with normal adjacent skin.

Discussions

As with almost all cancers, finding and treating a cMM as early as possible is very important[222,223]. Working as dermatologist, there is often no problem in distinguishing advanced cMM from benign nevi using the naked eye or dermoscopy. However, the intermediary or "early" malignant lesions often have some features of malignancy coupled with benign hallmarks, that make both clinicians and pathologists unsure about whether the lesion is benign or not[224]. Thus, there is a balance between the risk of missing cMM and performing unnecessary excisions of benign PSLs. New reliable and objective diagnostic tools are needed.

Originally, the specific HSI device in our study was initially evaluated for melanoma detection/ PSL discrimination in a Japanese population. The Swedish population are mainly regarded as Fitzpatrick skin types I-II, while Japanese usually are regarded as Fitzpatrick skin types III-IV[19,20,225]. We studied the performance of the MSI-03 device in a Swedish population. Our main finding was that the device achieved a high sensitivity (96.7%) for melanoma detection, which is higher than the level seen in previous studies on dermoscopy, the current gold standard method for non-invasive preoperative preliminary diagnosis of cMM[166]. However, as our study was not designed as head-to-head comparison between HSI and dermoscopy we did not evaluate the accuracy of dermoscopy in the corresponding lesions.

There were three lesions that were false negatives according to the device, one in situ melanoma, one SAMPUS and one cMM with a Breslow thickness of 0.3 mm. All three PSL were assumed to be biologically less aggressive and showed a low DI in their HSI measurement. Importantly, the results indicate that it is essential to weigh in more lesional and patient related facts before a patient with an equivocal PSL is dismissed. In the future, if the HSI device will be used in the clinic and a lesion is judged to be benign and therefore not excised, it is always important to give the examined patients advice

about repeated self-examinations and to stress that one must seek medical advice if the examined and/or other PSLs change. This is in line with the advice we give today after dermoscopy and the following judgement of a lesion being benign.

Seborrheic keratosis (SK) can often be easily diagnosed, but they can occasionally mimic cMM, and therefore warrant unnecessary excision. Having a non-invasive device that could discriminate the difficult SK cases from cMM is desirable. In this study, the device classified a great proportion of seborrheic keratosis (SK) as false positives. However, this misclassification is in line with other established technologies used in the preoperative detection of melanoma[226,227].

A strength is that the DI was derived from the corresponding lesional HSI and solely compared with the corresponding histopathological result. Also, all lesions and patients were enrolled in a tertiary dermatology clinic, probably mirroring more equivocal PSLs that presents in specialized dermatological clinics, but still the sensitivity was high. Additionally, the AUC for PSLs in this study was considered high (0.8).

Looking at specificity, the HSI device reached only 42.1% for the benign PSLs. Using dermoscopy, the specificity for melanoma detection often reaches about 80%[166]. Nevertheless, this level of specificity is in line with that of other diagnostic devices that are established on the market, such as optical scanners[226] and electrical impedance spectroscopy[227]. In order to be relevant as a future diagnostic tool, specificity of this specific hyperspectral device (MSI-03) must increase. This has already been achieved when combining techniques of HSI and AI, reaching much higher levels of specificity[228,229].

Paper III

Methodological considerations

As with paper I, a strength in this study is that the MISS-cohort was followed prospectively with collection of unbiased data on known risk factors. Hence, our data is population-based, valid and also generalizable to women in comparable populations.

Research in the field of effects of photosensitizing medication is foremost retrospective, with an inherent risk for recall bias, seldom with adjustments for risk factors that are very important when investigating commonly used drugs that can interact with UVR. Furthermore, several studies often referenced have methodological limitations such as grouping different types of skin cancer or different drugs[81,230-232], short follow-up

time[81,233] and suboptimal control of confounders such as sun sensitivity and sun exposure[79,80,84,85,234-236]. These types of pharmacological studies tend to be complex in nature and prone to confounding factors and bias[237].

This study also has limitations. Again, generalization of the results is hampered since participants are only women and only from a single geographic area. Furthermore, we cannot be certain the participants in the study consumed the drugs as prescribed because the information about drug intake is limited to the drugs that were prescribed and dispensed. For statistical reasons, we grouped drugs with similar therapeutic effect, which means that conclusions could not be made for the individual drugs. Also, we did not consider the confounding effects of associated treatments, which is an issue in an aging population with polypharmacy and skin cancer. Confounding by indication cannot be ruled out, given that individuals with underlying diseases are known to be at a greater risk of a skin cancer diagnosis, since they are more frequently visiting their physicians. Lastly, we used exposure information from the baseline questionnaire, not considering possible behavioural changes during the long study period which could have affected the outcome.

Discussion

We found a strong association between estrogen use and risk of skin cancer, particularly BCC. We also found that risk of BCC was related to the use of thiazide diuretics, while risk of cSCC was related to the use of loop diuretics. Furthermore, we found that NSAID use might have a curvilinear association with both BCC and cSCC.

Our major finding highlights the plausible role of female hormones in skin carcinogenetic processes. Estrogen have photosensitizing properties[77,238], can increase skin thickness as well as improving wound healing in post-menopausal women[239]. Furthermore, cMM incidence is greater in women compared to men before the age of 45 to 65 years, depending on population, but lower at more advanced ages[240]. Also, cMM is the most common cancer during pregnancy[241,242]. Interestingly, early menarche and late onset of menopause were associated with higher risk of cMM[243]. Hence. greater estrogen levels over time can influence risk. When separating the hormonal drugs, we could detect that the effect was foremost due to the estrogen component in hormone treatments. This aligns with other research on estrogen and risk of cMM[88-90], BCC and cSCC[86,89,214]. However, research output in this field is conflicting with several studies describing no association[87,243-246]. We also show that risk of BCC was elevated with higher dose of estrogen, which were not as convincing for cM and cSCC. Lacking adjustment for menarche, parity, age at menopause and use of oral contraceptives is a

limitation of this study. Nevertheless, estrogen use clearly influenced all studied skin cancer types.

In the research field of photosensitizing drugs, diuretics and its possible impact on risk of skin cancer have rendered many publications[78-85,236,247,248]. The heterogeneous group of diuretic drugs are foremost used to treat hypertension and several have photosensitizing properties[76,77,234,238]. In this study, we found that loop diuretics were strongly associated with cSCC risk, confirmed by a clear dose-response relationship, which is not evident in other studies[78-80,84]. Loop diuretics did not affect the risks of BCC or cMM, contradictory to one study, which showed an increased risk for cMM[247]. Several studies have shown an association between thiazides, specifically HCTZ, and risk of skin cancer[82,83,236,248-250]. We also detected an association between thiazide use and BCC (HR 1.25; 95% CI 1.09-1.44) with evidence of a dose-response relationship. We further found a similar result for cMM (HR 1.41 for ever use), but no dose-response relationship. This agrees with the meta-analysis by Gandini et al[78]. Surprisingly, and in contrast to previous meta-analyses,[82,237,248] we found no significant association between thiazide use and the risk of cSCC. The results of our study does not settle the debate about thiazide use and the risk of skin cancer. It is important to consider the overall health benefits of thiazide use before recommending any changes to an antihypertensive treatment, given that the overall benefits likely outweigh the small risk of skin cancer.

Conflicting results have also been found for two other large aggregates of antihypertensive drugs: β-blockers and CCB[80,84,90,251,252]. The meta-analyses from Gandini et al[78] showed increased risk of all three skin cancers with intake of CCB, and from Tang et al [85] showed an increased risk of cMM with β-blocker use. We saw no convincing evidence of association with CCB or β-blockers. If anything, the results point to risk being associated with increased CCB and β-blocker doses. These results could be confounded by polypharmacy, and the risks associated with other pharmaceuticals, such as diuretics, could increase with combination treatments in these groups.

Treating hypertension, ARB and ACEi have photosensitizing abilities[75-77,253]. Schmidt et al.,[84] found an increased risk of cMM with long-term use of ARB, but not with ACEi. To date, little evidence of an association between ACEi/ARB risk of skin cancer is available[78,84,85,230-233,235,250-252]. In this study, we found neither an increase nor a decrease in skin cancer risk with the use of ACEi/ARB.

Although they are photosensitizing, antibiotics are often used for short periods, hence analyses are challenging. We could see a positive association between ever use of these antibiotics and risk of BCC and cSCC, but not cMM. This is in line with Kaae et al.,

who studied the effect of short-term drug use[80]. Other studies have shown that tetracyclines are associated with BCC, but not cSCC or cMM[95], and that quinolones are associated with cMM risk[93]. Thus, it is difficult to draw any substantial conclusions from our results.

The antidiabetic drugs metformin and glibenclamide were unrelated to skin cancer risk in our cohort, which contrasts with Chang and colleagues[96], who found a modestly reduced risk of skin cancer with metformin use. Concerning skin cancer and PPi, which treats gastritis and have photosensitizing properties[94], the literature provides little insight. In this study, the HR for risk of cSCC was increased with PPi use, however adjusting for multiple testing the significance was lost, and no dose-response relationship was found. Again, our results could be confounded by polypharmacy, and further research is warranted.

Studies on NSAID use and risk of skin cancer have shown divergent results[91-93,254]. We could not detect an association and our ever-never analysis showed no association between skin cancer and NSAID use, except possibly in a curvilinear way, particularly for BCC. In a meta-analysis performed by Ma et al.,[92] NSAIDs were found to be significantly associated with BCC and cSCC, but not with cMM. Notably, we found increased risk of skin cancer in the higher dose groups, but this result could be confounded by unregistered associated autoimmune processes such as arthritis.

Paper IV

Methodological considerations

The main strength of this study is the fact that it is population-based with data gathered over a considerable amount of time. Additionally, the detailed collected data on AM is retracted from a comprehensive nationwide population-based quality registry, Swe-MR, which make comparison and also validation of results possible. Consequently, it will lead to a better understanding of the epidemiology of AM in a Swedish context.

As most epidemiological studies on skin cancer in the Swedish population, a possible limitation is that the study population is fair-skinned, thus making our findings primarily applicable to other fair-skinned populations. Moreover, our data is hampered by incomplete registrations of specific variables in the initial period, although these missing values only constitutes a minor fraction of the data. Finally, we were unable to compare tumours on hands and feet due to the lack of precise tumour location details during the entire study period.

Discussion

The study, including all AM patients in SweMR from 1990-2020, demonstrated an absolute increase in AM cases. However, there were no significant shifts in the age-standardised incidence rates or MSS. In individuals over 70 years of age, AM cases displayed an increasing trend, which aligns with overall melanoma statistics in Sweden[255]. This can be understood as a product of an ageing population. Factors associated with an increased MSM were found to be age over 70 years and a Breslow thickness over 1.0 mm. Most AM patients were female and they had a lower MSM risk compared to males.

The comprehensive registration in SweMR allows for meticulous evaluation of time patterns. The general incidence of cMM in Sweden is rising, interestingly we found no rise of incidence in AM during the researched periods[256]. ALM incidence trends can serve as a surrogate for AM incidence, and the results of our study align with studies on ALM in the US and East-Central Europe[257-259].

It is evident that incidence of AM differs from other types of melanomas. The causes for this are unknown. However, one proposed risk factor is mechanical stress, given that AM often appears on weight-bearing areas of the feet and is most commonly found on the thumb and great toenails[260,261].

There is a sharp contrast between the stable incidence of AM compared to cMM arising in other skin areas. A possible reason for the overall increase in melanoma incidence could be the earlier diagnosis of cutaneous melanomas, particularly SSM, due to better the advancement in diagnostic methods. Or could increasing public awareness of cMM influence incidence and overdiagnosis[261,262]. It appears either that early stages of AM are stabilising or that symptoms of early-stage AM do not prompt individuals to seek medical attention[255]. However, maybe the simplest answer is the most correct, that increase exposure to UVR do not constitute as much of a risk factor concerning AM as it does for cMM on other parts of the body in fair-skinned populations[263].

Furthermore, in this population we detect no change in the diagnostic delay or of the poor prognosis of AM. More than half of the AMs registered were tumours greater than Over half of the AMs were great than 2.0 mm in depth, compared to slightly over a fifth of all cMM[255]. Diagnostic delay could be attributed to their often hypopigmented appearance and the misdiagnosing as benign conditions [264]. Our study also found that female sex to be an independent favourable prognostic factor, aligning with previous studies on cMM[265-268]. Similar to our findings, previous research on both AM [269] and ALM[270,271] indicated a predominance of female cases and male sex as an independent adverse prognostic factor. AM is a more aggressive subtype of melanoma compared to those found in non-acral locations[272]. In this study, we show that the 5-year MSS rates

for males and females with AM were lower than the overall melanoma survival rates in Sweden during the same period[147].

Studying the subtypes on acral sites internationally, the ALM subtype has been reported to either have a comparable[272,273] or worse[274] prognosis than acral SSM. However, our study suggests that ALM tends to show better survival rates than SSM and NM in acral sites.

Main conclusions

Paper I

In this study, we conclude that phenotypic and environmental risk factors do play a role in the development of cSCC. This large, prospective study firmly establishes that the use of sunbeds is an independent risk factor for cSCC in Swedish women. Importantly, there is a dose dependant risk for sunbeds use and the risk of developing cSCC. The use of immunosuppressive medication and having freckles, red or light blond hair are also independent risk factors. Our findings support the need for implementing regular dermatological evaluation as a standard practice for patients who are immunosuppressed and consider a total ban of the use of sunbeds for cosmetic purposes.

Paper II

We have shown that the novel HSI device (MSI-03) has a high accuracy in detecting cMM in a fair skinned population consisting of with skin types I and II according to Fitzpatrick. Consequently, the technique of HSI and this specific HSI device have shown it might be a useful clinical tool for physicians managing patients and where further triage and examination of PSLs is important. We also conclude that the specificity of HSI must increase and that the device needs some practical improvements in the clinical setting to truly fulfil the potential of the technique.

Paper III

We found significant evidence of estrogen use for an increasing risk of skin cancers BCC, cSCC and cMM. Furthermore, we could see that the use of loop diuretics increases the risk of cSCC, and the use of thiazides increases the risk of BCC. Since these drugs are common and widely used, we suggest that physicians advise their female

patients who are treated with estrogen, thiazides, or loop diuretics to limit their sun exposure. We can also conclude that studies in the field of photosensitizing drugs and skin cancer risk often are conflicting. Hence, future well-designed prospective studies are warranted in order to further investigate the relationships between common photosensitizing drugs and risk of skin cancer.

Paper IV

The incidence and mortality of acral melanoma (AM) in Sweden have remained stable over the last 30 years. The proportion of AM is higher among females than males, although the prognosis remains less favourable for males. Furthermore, as in many other cancers, age matters. Individuals aged 70 years and older face the highest risk of developing and deceasing of AM. Since AM are rare to both patients and health care professionals, there is a pressing need for enhanced public and healthcare professional awareness and education concerning warning signs and improving early diagnostic efforts in order to reduce mortality rates associated with AM.

Future perspectives

Looking towards the future, I will here take a wider perspective on my research path. Firstly, will the studies that we have done have any meaning for the future? Well, none of our findings in these for papers will lead to a Noble Prize. None the less, that does not mean that our results cannot be used and utilized. All new knowledge is important, specifically when it comes to knowledge about factors that can influence risks that are constantly all around us. In this regard, my fellow researchers and I have made some valuable scientific insights and helped to expand knowledge as a whole, specifically regarding skin cancer in fair-skinned populations.

We have confirmed that the use of sunbeds can indeed have negative health effects and is a risk factor for developing a skin cancer. Maybe even more important that our study only had female participants, since women use sunbeds more. There is sufficient proof of the damaging effect of indoor tanning for cosmetic purposes that new legislative measures of a total ban can be made in our country. Having that said, and keeping in mind that smoking is not yet forbidden, it is not likely that such a total ban will see the light of day any time soon. If not legislation, what about information? Several other countries such as Australia and Denmark, have large health campaigns focused on the risks of UVR and skin cancer. A lot can be learned from these campaigns. A problem in our country is that it is the Swedish Radiation Safety Authority, mainly dealing with issues concerning nuclear radiation, that is responsible for the public health matters concerning UVR. This should be under the umbrella of the National Board of Health and Welfare. Furthermore, if successful large public campaigns can be designed, this could in turn lead to behavioural change and perhaps change our thoughts of what is cosmetically desirable. In this context, it is vastly important that we continuously scientifically follow the behavioural trends concerning UVR exposure and its effects on public health.

Turning to our novel Japanese hyperspectral imaging device, our contribution can be a small step in an ongoing process to fulfil the quest for a new and reliable non-invasive diagnostic technique. The research in this field is very interesting and I am confident that we will have diagnostic techniques that by far will surpass us dermatologists in both specificity and sensitivity. The promise of AI will most definitely play an increasing role

in this aspect. This is also true in many fields of medicine, not only dermatology. As a clinician it will be a journey to look out for, both with joy and with hesitation. Firstly, it is very important that the road ahead must follow a scientific route. Secondly, legislation must follow the developments, preferably somewhat ahead. So far, we are not ready for a machine to make the decision in full if a suspicious skin lesion should be excised or not. There are several diagnostic techniques on the market and none of them have all the boxes ticked. Many are early in their developments and still have a long way to go to be an easy-to-use, cheap and trustworthy adjunct tool in the clinical setting, wherever that may be in the future.

Concerning photosensitizing drugs and the association with skin cancer, it is truly difficult to show cause and effect because of many confounding variables are hard to exclude. There is a lot of scientific debate in this field. Therefore, it is paramount that more well-designed prospective studies with long study periods are made. For now, I will leave that for other researchers to investigate. However, this is a very important field, since more knowledge can change the way we inform our patients about certain drugs and their UVR effect. Consequently, it can also change the way photosensitizing dugs are prescribed by physicians. Immunosuppressive medication and the association with skin cancer is important to follow. Several immunosuppressive drugs are used in OTR to battle transplant rejection. Depending on OTR and specific organ, the immunosuppressive therapies are used in diverse amounts and regiments which change over time, offering an avenue of scientific research for the future. Can new and improved immunosuppressive therapies lead to decreasing trends of skin cancer in OTRs, specifically cSCC? This is something I will follow in the future.

The melanomas that arise on acral sites are both difficult-to-find and therefore difficult-to-treat. The more the public and fellow physicians know about skin cancer in general and cMM and its subtypes in particular, the better it is. Overall, the underlying statistics of cMM in Sweden is concentrated and upheld in SweMR. In the future, it will continue to contribute to valuable research on all subtypes of cMM in the Swedish population. National information campaigns on skin cancer is one way to go in enhancing patient awareness. From a public health perspective, this is warranted and desired.

There are many interesting fields of research in dermatology. For me, my interests both clinically and scientific is concentrated to skin cancer. I hope to continue this in the future. For now, I do not know on which scientific path it will take me. But I am in the right place, being part of a university dermatological department and in translational group of fantastic clinicians and researchers at a university hospital pouring out new and interesting scientific projects and plans. The road I have travelled the last 10 years have given me very much on several levels. 10 years is a long time, and

lot of things have happened during the years, both in my workplace and in life outside of work. I have without a doubt learned very much about the scientific process from start to finish. My intention is to put that to good use in the future as well. Soon going on 10 years, I have had the privilege of being the Head of the Department of Dermatology and Venereology at Skåne University Hospital. Here, I have had the fortune of seeing research from a different angle concerning financing and facilitation of projects so my esteemed colleagues can fulfil their scientific goals in order to expand knowledge. This, if anything has made this journey worth it.

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