A Scientific Review Addressing Occupational Skin Cancer

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Foreword

The present work was financed by a research grant received from the Danish Work Environment Fund. An international open call was issued in January 2013 with application deadline in February 2013. The draft report was prepared from August 15 – October 1 2013.

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After finishing of the draft report it was sent to external reviewers. The manuscript has been corrected according to the comments, and the comments are enclosed.

A one-day review meeting took place in Copenhagen 28 November. Professor Thomas Diepgen and Professor Åke Svensson participated, together with the working group.

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Prof. Dr. T.L. Diepgen, University Heidelberg, Dept. of Social Medicine, Occupational and Environmental Dermatology , Heidelberg, Germany.

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Abbreviations

AK: actinic keratosis

BCC: basal cell carcinoma

CMM: cutaneous malignant melanoma

NMSC : non-melanoma skin cancer

OR : Odds ratio

PDT: Photo Dynamic Therapy

SCC: squamous cell carcinoma

SED: standard erythema dose

UV: ultraviolet

WHO: World Health Organisation

Dansk Resume

Udredning af årsager til arbejdsbetinget hudkræft

Et videnskabeligt review af Tove Agner, Niels Ebbehøj, Hans Christian Wulf og Jens Peter Bonde. Bispebjerg Hospital

Arbejdet er blevet til i 2013 på baggrund af et opslag fra Arbejdsmiljøforskningsfonden.

Baggrund

Opgaven var at beskrive den videnskabelige baggrund for en sammenhæng mellem eksponeringer i arbejdsmiljøet og udvikling af hudkræft.

Indledningsvist gør vi opmærksom på, at hudkræft og forstadier hertil er en klinisk meget bred gruppe af sygdomme, som har forskellig epidemiologi, forskellig klinik og forskellige individuelle og miljømæssige årsagsfaktorer. Derfor bliver vurderingen af evidens for årsagssammenhænge baseret på epidemiologi som vanligt, men også en række andre videnskabelige resultater er inkluderet i arbejdet for at give et så komplet billede som muligt.

Over de sidste 10 år er anmeldt 7 tilfælde af hudkræft pr år i gennemsnit, med en stigende tendens. Over halvdelen bliver anerkendt. Det er formentlig en stor underrapportering pga. ringe tradition for at anse lidelserne for arbejdsbetingede.

Hudkræft og forstadier

Rapporten omhandler de former for hudkræft, der kan have en arbejdsmæssig årsag. Det drejer sig om basalcellekræft (BCC), spinocellulært karcinom (SCC), aktinisk keratose (AK), som er et forstadie til spinocellulært karcinom, og malignt melanom i huden (CMM) og. En række sjældne andre hudkræftformer har ingen kendt arbejdsmæssig årsag.

Basalcellekræft (BCC, basalcellecarcinom) er den hyppigste hudkræftform. Den dannes i de basale cellelag i huden og der registreres 11-12.000 tilfælde i Danmark om året, men formentlig er der mange flere. Tumor vokser langsomt, metastaserer stort set ikke, og prognosen er god.

Planocellulært carcinom (SCC, spinocellulært karcinom, pladecellekræft) diagnosticeres i knap 2000 tilfælde om året, lidt hyppigere for mænd end for kvinder. SCC metastaserer også relativt sjældent, men dog hyppigere end BCC, så udsigterne til helbredelse er dårligere.

Aktinisk keratose (AK) er en præmalign tilstand som kan udvikle sig til SCC, men ikke BCC.

Kutant malignt melanom (CMM, modermærkekræft) diagnosticeres godt 2000 gange årligt, lidt hyppigere hos kvinder end mænd, og også hyppigt i yngre aldersklasser. Prognosen for CMM kan

direkte relateres til den histologisk vurderede tumortykkelse. Af hudkræftformerne har CMM den højeste dødelighed, og behandlingen er ikke altid effektiv.

For tumorformerne BCC og SCC anvendes fællesbetegnelsen non-melanom hudkræft (NMSC)

UV stråling og hudkræft

Det skønnes at > 90 % af alle tilfælde af hudkræft og næsten alle tilfælde af AK forårsages af ultraviolet stråling fra solen. UVB stråling med en bølgelængde på 320-280 nm forårsager direkte skade på DNA og RNA ved at forårsage kemiske bindinger mellem nucleotider, mens UVA med en bølgelængde fra 400 til 320 nm forårsager indirekte skade ved en fotokemisk proces. Hudtyper er forskelligt modtagelige for UV stråling, ligesom tilvænning (solbrændthed) er en beskyttende faktor.. Den største individuelle variation i risiko for udvikling af hudkræft ligger dog i individuelle forskelle i risiko-adfærd i relation til UV eksponering. Adfærdsmæssige forskelle giver en stor variation i UV dosis, op til 50 gange.

Mønsteret i eksponeringen er en væsentlig risikofaktor såvel som modificerende faktor. Daglig moderat eksponering kan beskytte mod forbrændinger og er især relateret til udvikling af SCC og AK, hvor den totale UV-eksposition er den afgørende risikofaktor. Det samme gælder til dels for BCC. Intermitterende UV eksposition, som let kan lede til solforbrændinger, især er relateret til udvikling af CMM.

Arbejde og UV stråling

Strålingsdosis ved udendørsarbejde er direkte relateret til antallet af udendørs arbejdstimer. Herudover spiller breddegrad, højde over havet, tidspunkt på dagen og refleksion fra vandoverflader (dvs arbejde til søs) en rolle.

Tabel 1 viser eksempler på fag med forskellig udsættelse for UV stråling: Landmænd, bygningsarbejdere, udendørs vedligehold, brevbærere, fiskere, og tagdækkere m.fl. er eksempler på højt eksponerede. Udendørs maskinoperatører og reparatører, tømrere er moderat eksponerede, og lastvognschauffører og kurerer er lavt eksponerede.

Tabel 2 viser miljømæssige og individuelle faktorer af betydning for den dosis UV stråling der når huden, og dermed for risikoen for udvikling af hudkræft. Tabellen viser også forebyggelsesmuligheder, idet indendørs frokost mellem kl 12 og 15 signifikant mindsker dags-dosis.

Arbejde og BCC

På basis af 23 studier fra hele verden findes en samlet OR for udvikling af BCC hos udendørs arbejdende at være 1,43 (1,23-1,66). Studier af landmænd er de kvalitativt bedste, og studier der foretager justering for ikke-erhvervsmæssig soleksponering viser de højeste OR. Seks studier af BCC og udendørs eksponering er udført ved breddegraden mellem 49 0g 55, svarende til

Danmarks placering. I 3 af disse studier er risikoestimatet over 1 om end kun signifikant i det ene. Risikoestimatet er under 1 i 2 af studierne.

Arbejde og SCC

Kumulativ UV-dosis er den vigtigste årsag til SCC og risikoen er direkte relateret til den totale UV dosis. Baseret på 18 studier hvoraf de 12 viste en signifikant overhyppighed er risikoen for udvikling af SCC OR 1,77 (1,40-2,22). Risikoestimaterne var identiske i kohorte- og i case-control studier. På grund af misklassifikation af den erhvervsmæssige eksponering, manglende kontrol for privat eksponering og individuelle risikofaktorer er den reelle OR formentlig lidt højere. En OR på omkring 2 er foreslået.

Fem af de nævnte studier er udført ved breddegrader der ligner de danske, og her findes OR mellem 1,0 og 4,0. Højest OR findes i et studie med fokus på de seneste 10 års eksponering.

Arbejde og CMM

Udvikling af CMM er relateret til udsættelse for både UVA og UVB.

CMM relateres til solforbrændinger og intermitterende soleksponering, som typisk er ikke-erhvervsmæssig, og der er kun begrænset evidens for at erhvervsmæssig eksponering giver en øget risiko for udvikling af CMM,. For de højeste eksponeringsgrupper (erhvervsbetinget eksponering) er sammenhængen formentlig modsat, idet konstant UV eksponering har en beskyttende virkning overfor solforbrændinger, hvorimod intermitterende bestråling øger risikoen for forbrændinger og CMM.

Kunstig UV stråling

Svejsning, glaspustning, solarier og enkelte andre kunstige UV kilder giver en eksponering for UV stråling, men der er aktuelt kun evidens for solarier som årsag til øget forekomst af hudkræft.

Vinduesglas beskytter mod UV stråling i så høj grad at indendørs arbejde, herunder arbejde i drivhus mm, ikke er forbundet med udvikling af nogen form for hudkræft.

Eksponeringsvurdering

En række studier har målt UV eksponering i arbejdsmæssig og privat sammenhæng. Dosis angives i SED-enheder, som er et mål for hvor rød huden bliver ved en given dosis. Gennemsnits danskere udenfor arbejdsmarkedet modtager 168 SED pr år. Ved indendørs arbejde reduceres dosis til 132 SED pr år, ved udendørs arbejde øges dosis til 264 SED pr år. Desuden findes en række modificerende faktorer som kan indregnes i dosisestimatet, så det er muligt for en given eksponeringshistorie at angive den procentvise øgning i forhold til gennemsnittet. Rapporten angiver i bilag 4 med nogle eksempler hvordan dette kan gøres.

Konklusion

Naturlig UV stråling er en årsag til alle 3 beskrevne former for hudkræft, BCC, SCC og CMM, samt AK. Hvor evidensen for arbejdsbetinget UV eksponering og udvikling af SCC, AK , samt – om end

lidt svagere – af BCC foreligger, er evidensen for relationen mellem arbejdsbetinget UV eksponering og CMM svag. Særlige job med risiko for intermitterende UV eksposition og solforbrændinger kan dog være relateret til udvikling af CMM.

For kunstig UV stråling er evidensen svag og bygger hovedsagelig på eksperimentelle undersøgelser.

For en række andre eksponeringer som for eksempel kemi og visse erhverv er det kun udsættelse for sod og stenkulstjære, der med stor sandsynlighed kan lede til hudkræft. De andre eksponeringer mangler enten epidemiologiske data eller biologisk plausibilitet.

Fremtidig forskning

Der er behov for yderligere epidemiologisk forskning i sammenhæng mellem nutidig eksponering i forskellige erhverv og udvikling af hudkræft, i vurdering af eksponeringen i forskellige arbejdsmæssige situationer og endelig i betydningen af kunstig UV stråling både på dosis og på effektsiden. Desuden forskning i relationen mellem forskellige subgrupper af de omtalte hudcancertyper og arbejdsmæssig UV eksponering, samt forskning i tidsmæssige sammenhænge mellem eksponeringer og udvikling af hudcancer.

Introduction

Skin cancer predominantly includes the following types of malignant skin tumours; basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), generally called non-melanoma skin cancer (NMSC), and cutaneous malignant melanoma (CMM). These tumours all have different aetiology, pathology, clinical manifestations and consequences. Actinic keratosis (AK) is a premalignant change in the skin that may sometimes proceed to SCC.

Development of skin cancer is related to genetic factors, pheno-typical characteristics, and especially to exposures, of which UV radiation is considered the prevailing one. Some chemical exposures are also known to cause skin cancer. The incidence of skin cancer cases has increased significantly during the last decades, and a yearly increase in incidence of non-melanoma skin cancer has been reported since 1960 worldwide[1].

Until 2005 *The List of Occupational Diseases (Bekendtgørelse om fortegnelse over erhvervssygdomme)* in Denmark comprised *skin cancer or premalignant skin conditions caused by exposure to soot, tar, asphalt containing tar, pitch, anthracene, mineral oil, and paraffin*. From 1/1 2005, the list was extended to include solar radiation as well. Today the list includes skin cancer caused by the following exposures: *arsenic, anthracene, creosote, mineral oil, paraffin, shale oil, solar radiation, soot, coal tar and coal tar pitch.* In the period 01/01 2000- 31/12 2009 a total of 67 cases of occupational skin cancer were reported to *The Danish National Board of Industrial Injuries*, and a total of 36 cases were recognized as occupationally related malignant and premalignant skin conditions [2]. Of these recognised cases, 25 patients were diagnosed with BCC, 9 with SCC, 2 patients had both BCC and SCC, and 4 patients had premalignant changes only. The mean age at recognition was 61 years, the most frequent exposure was UV-radiation, and the most important single risk factor was sun exposure due to outdoor work. Although provided for by law, there is no well-established tradition for reporting occupational skin cancer in Denmark, but the number of notified cases more than doubled from the period 01/01 2000-31/12 2004 to 01/01 2005-31/12 2009[2]. Due to the lack of tradition for reporting skin cancer as an occupational disease it is anticipated that a significant underreporting may take place.

During the last years an increasing number of skin cancer cases related to UV exposure have been reported as occupational, and also internationally the attention to the association between UV skin cancer and occupational exposure has been increasing. The focus of this report will therefore be on UV induced skin cancer. Sun exposure is the most important risk factor for the development of all skin cancers, but while the relationship between cumulated sun exposure and SCC is well established, the link with BCC and CMM is more complex[3]. A great challenge with respect to occupational skin cancer is to differentiate between occupational and recreational exposures, in particular with respect to solar UV radiation. The main objective of the present report is to describe and evaluate risk factors for development of occupational skin cancer, and to discuss factors that modify the risk for skin cancer. Only limited epidemiological evidence exists within this research area, and due to this fact the conclusions in the present report are based on basic research as well as epidemiological studies.

Methods

A literature search was made in Pub Med and EmBase on work related/occupational skin cancer, including exposures studies, as described in Appendix 2. A total of 2250 papers were identified. From titles and abstracts 2030 papers were found not to meet the search criteria. From the 220 remaining papers 3 structured reviews/meta-analyses were found on NMSC, 5 on CMM and 3 on other exposures leading to skin cancer. Papers on which the meta-analyses were based were all identified in the literature search. This report is based on the structured reviews/meta-analysis as well as on the 220 papers identified in the literature search, of which the most recent and relevant papers are included in the reference list.

Objectives:

To review and analyse the medical documentation for a relationship between occupational exposure(s) and the development of skin cancer.

Background

Skin cancer and precursors of skin cancer: Causes, treatment and prognosis.

Skin cancer predominantly includes BCC, SCC and CMM. AK is a premalignant condition, which may sometimes proceed to SCC, and is therefore included in the report.

Cutaneous B- and T-cell lymphoma, Kaposi sarcoma, Merckel cell tumour and other rare malignant skin tumours, which are not associated with occupational exposures, are not covered by the present report.

A schematic structure of the skin is shown in Appendix 1.

Basal cell carcinoma (BCC)

(in Danish basalcellecarcinom, basalcellekræft, basaliom).

The tumour is caused by malignant change in cells in the basal layer of the epidermis. It is the most frequent subtype of skin cancer, more than 6 times more frequent than SCC. In 2011, 11463 new cases were registered in DK[4]. It is generally anticipated that the disease is largely underreported by a factor 2-3 in cancer registers, due to its benign course in most cases. The prevalence is increasing with increasing age, and for NMSC as such 80 % of all cases occurs in people aged 60 years or older[1]. The annual age-adjusted incidencerate (incidence per 100.000 persons) was 194 for men and 187 for women in 2011 in Denmark[4]. The risk for BCC is dependent on geographical factors (higher at lower latitudes)[1]. The tumour is slowly growing (years), the morphology is quite typical and the diagnosis is based on medical history (slow growth), morphology and histological examination.
Risk is increased in individuals with light skin, eye, and hair colour, with an inability to tan, and those with benign sun-related skin disordersieg, actinic keratoses and solar lentigines[1]. It mainly occurs on sunexposed areas provides indirect evidence for the role of ambient solar radiation.

Subtypes of BCCs

- Superficial BCC: Superficial element that may grow to a size of several centimetres. Often confused with eczema or psoriasis, mostly localised on the trunk.

- Nodular and ulcerating BCC (*ulcus rodens*): mother of pearl-shine, infiltrated, ulcerating tumour
- Sclerosing and infiltrating BCC: Diffusely bounded white/yellowish element
- Pigmented BCC: Rare subtype that may be confused with CMM.

BCC can be treated effectively either by surgery (excision or curettage), X-ray treatment, photodynamic therapy (PDT), kryo-therapy or pharmacological treatment [5]. The choice of treatment depends on the sub-type, since superficial and nodular tumours need different treatments, and the infiltrating type, in particular, is challenging to treat. Also the localisation of the tumour and the age of the patient are important factors for the choice of treatment. Except for when PDT- and pharmacological treatment is used, the tumour will leave a scar on the skin.

The prognosis for BBC is generally very good. BCCs have very low metastatic potential and are associated with low mortality. Most tumours grow slowly, and metastasis from the tumour is an exception. Relapses of the disease are not rare, as the cosmetic result is weighed up against completeness of the therapy. 95-99% of patients are cured 5 years after onset, although re-treatment may sometimes be necessary. Conversely, a BCC left untreated will not heal spontaneously, but will continue to grow locally, gradually also destroying muscles and bones in the region.

New tumours may often arise in patients who have had BCC. A 3-year cumulative risk of development of new tumours is reported to be 44 %[6]. BCC-patients are reported to have a slightly increased risk of other cancers (CMM, lung cancer, thyroid cancer, mamma-cancer, cervix-cancer and non-Hodgkin lymphoma)[7].

Squamous cell carcinoma (SCC)

(in Danish planocellulært carcinoma, spinocellulært carcinoma, pladecellecancer).

SCCs arise in the squamous epithelium, and in most cases from actinic keratosis (estimated 60 %)[8]. SCC is the second-most frequent type of skin cancer constituting 20% of non-melanoma skin cancer. In 2011 1810 new cases were registered in Denmark, probably also underreported as for

BCC. , The annual age-adjusted incidencerate (incidence per 100.000 persons) was 75 for men and 62 for women in 2011 in Denmark[4]The tumour incidence increase with age (Fig 1).

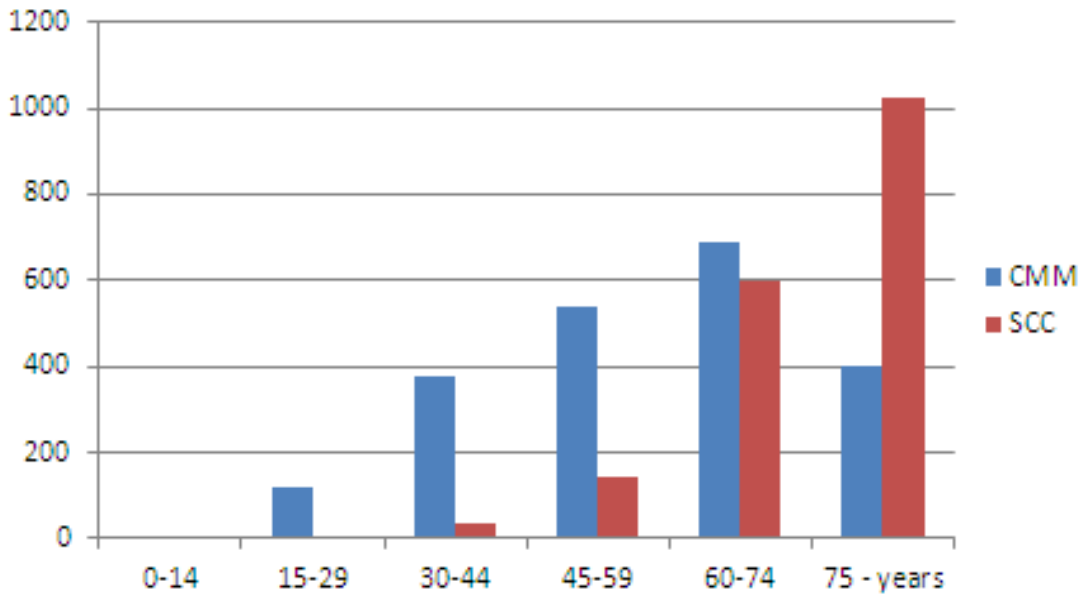

Fig 1. Data from the Danish Cancer Register 2011, showing the age distribution for CMM and SCC. Data comprises numbers of CMM and "other skin cancers except BCC" only, and the latter is here interpreted as SCC. Data on BCC is not available, but is anticipated to be similarly distributed as SCC with respect to age.

Risk of SCC is increased in individuals with light skin, eye, and hair colour, with an inability to tan, and those with benign sun-related skin disorders—eg, actinic keratosis (AK) and solar lentigines[1]. Organ transplanted patients are in special risk for development of SCC[1]. Unlike BCC, SCC may develop from premalignant skin disorders (AK and Bowens disease). It mainly occurs on sun exposed areas provides indirect evidence for the role of ambient solar radiation. SCCs grow more quickly than BCCs. They present as firm, infiltrated, sometimes verruca-like and rarely ulcerated tumours, varying in size from millimetres to centimetres. Diagnosis of the tumour is based on medical history, morphology and histological examination. Local lymph nodes should be examined to rule out metastases.

Surgery is the treatment of choice for SCC, but X-ray is also an effective treatment and often used in elderly people[5;6]. Scar(s) on the skin will result from treatment.

The prognosis for SCC is good, although not as good as for BCC, and metastasis may take place. Host factors are of importance and the prognosis is more severe in immunoincompetent patients[1,9]. The frequency of metastasis depends on localisation of the tumor. For most localisations metastasis is expected in up to 5% of cases, however when localised on ears or lips the frequency of metastasis may increase up to 11 and 15%, respectively[10]. New tumours may often arise in the patients who have had SCC. 3-year cumulative risk for development of new tumours is reported to be 18 %[6].

Actinic keratosis (AK)

(In Danish: aktinisk keratose, solar keratose)

AK is skin condition that is not skin cancer but sometimes develop into skin cancer. AK is considered as an early step in the continuum of transformation from normal skin to invasive SCC[11]. The transition rate from AK into SCC is reported to be 1-10 % in a 10 year period[1]. The presence of certain clinical features of AK, such as large size, ulceration, or bleeding, suggests an increased risk of disease progression[11]. Also host factors (immunosuppressed patients), the presence of numerous AKs, as well as ongoing risk exposure may increase the transition rate[1]. AKs are extremely common, the etiology of the disease is sun exposure, prevalence is strongly related to age, and an increased risk is present in countries at low latitudes and in fair-skinned individuals. In an English population the prevalence was reported to be 34.1% and 18.2% in men and women aged 70 years and above, respectively[12]. The morphology is a yellow-red, scaly lesion, 1 millimetre to 2 centimetres in size, with a rough surface, located almost entirely on sun-exposed areas of the body, i.e. the head- and neck region together with forearms and hands. Multiple AKs are often present, and may then sometimes cover larger areas of sun-exposed skin. This is sometimes called field cancerization, and is a phenomenon in which multiple cancers easily occur on a specific area due to UV exposure[11].
AK is treated by curettage, cryo-therapy, pharmacological therapy or by photodynamic therapy (PDT). While the two latter treatments in most cases leave no scar, scars or depigmentation of the skin will follow other treatments. Consequent use of sun-protection and/or avoidance of solar

radiation will stop the appearance of new AKs, and lead to the regression of some of those already developed.
AKs may undergo malignant transformation into SCC. The rate of progression of individual actinic keratoses to invasive squamous-cell carcinoma has been estimated as 0.1 over 1 year[8], however the risk may be considerably higher in patients with more than 5 AKs[1]. AKs do not transform into BCC or CMM.

A *subtype of SCC* is morbus Bowen, an in-situ variant of SCC, which may, over years, develop into a regular SCC. Clinically it presents as a scaly lesion which may be mistaken for eczema, psoriasis or superficial BCC.

Cutaneous malignant melanoma (CMM)

(In Danish: malignt melanom i huden, modermærkekræft)

The tumour arises from pigmented cells in the basal layer of the epidermis, either from a pre-existing nevus or from previously normal skin. Clinically CMM typically presents as a pigmented lesion, which may often be asymmetric, have an uneven border, and spotted or deep black pigmentation. It is often – but not always – more than 6 mm in diameter, and the lesion undergoes changes. 5 % of all CMM appear as amelanotic, pink- or flesh coloured tumours, which may be difficult to recognise as CMM. After malignant transformation the tumour penetrates into the dermis. The diagnosis is based on medical history, clinical morphology and histological examination. Dermoscopy is an investigation that may improve the clinical decision-making.

The incidence of CMM is increasing and has almost doubled within the last ten years[5]. In 2011 a total of 2134 new cases were diagnosed in Denmark (Fig1), 982 men and 1152 women, and the number has further increased in 2012 up to 2300 cases. In contrast to BCC and SCC, the incidence of CMM is also high in younger age groups (Fig 1). Location of CMM is not limited to sun-exposed skin, but may also appear on non-exposed sites. With respect to location on body sites, 40% are localised on the trunk and 40% on arms and legs. The location is gender-dependent, since CMM is mostly localised on the trunk in men, and mostly on thearms/legs in women. The present report

addresses CMM only, but malignant melanoma may also arise in mucous membranes, eyes and lymph nodes. However, CMM comprises 90 % of all cases of malignant melanoma.

Subtypes of CMM

- Superficially spreading CMM comprises more than 70 % of CMM cases. It is a slightly elevated pigmented lesion that spreads horizontally for a longer period (years), before invasive growth is initiated. The significant increase in CMM over recent years comprises mostly this group.
- Nodular CMM comprises 10-15% of CMM cases. It is a pigmented nodule that spreads invasively, and proceeds to metastatic phase early.
- Acral, lentiginous CMM comprises 5-10 % of CMM cases. It appears on the hand and feet and spreads invasively. The diagnosis is often delayed since the changes may not appear "dangerous" to either the patient or the doctor.
- Lentigo maligna melanoma comprises 5% of CMM cases. It arises in a previous lentigo maligna lesion (i.e. a pigmented lesion in sun-damaged skin in elderly people, most often localised on the face). It presents as a pigmented slowly growing lesion. While the growth for lentigo maligna is horizontal, it is renamed lentigo maligna melanoma when the growth becomes invasive and infiltrates the deeper layers of the skin.
- Amelanotic CMM comprises 5% of CMM cases. It presents as a non-pigmented flesh-coloured or reddish tumour that spreads invasively. It may often cause diagnostic difficulties due to the lack of pigmentation.

CMM is treated by surgery, and the prognosis relies on an early diagnosis and treatment. Pharmacological treatment is added only when metastases are present. Approximately 10 % of patients with CMM die from the disease. This percentage is, however, decreasing due to earlier diagnosis than was previously the case, and also due to the fact that it is the superficially spreading CMM that increases in frequency, and this subtype has a better prognosis than other subtypes. With respect to prognosis, early diagnosis and treatment is essential. The prognosis is directly related to the thickness of the tumour measured on the histological preparation. A

thickness less than 1 mm indicates a trusty prognosis. Tumour thickness > 1 mm indicates a more severe diagnosis, and in case of regional or systemic metastases the prognosis is poor.

UV radiation and skin cancer. Risk factors, modifying factors and possible bias.

Biological plausibility for UV radiation causing skin cancer

Skin cancers (BCC, SCC and CMM) are caused by UV radiation mainly from sun exposure in > 90 % of all cases, and AKs are caused by UV radiation in almost all cases. The effect of UV radiation on human health is however, far from simple, since it can act as a tumour initiator or promoter, a (co)-carcinogen and an immune-suppressor, and at the same time has the ability to stimulate processes that prevent skin cancer.

UV-radiation is in clinical studies divided into:

- **UVA**: 400 nm – 320 nm
- **UVB**: 320 nm – 280 nm
- **UVC**: 280 nm – 200 nm

Solar UV radiation is generally 95 % UVA and 5 % UVB, but the UVB contingent may vary from 0 – 10%. UVB has significant adverse health effects, and is very likely to cause sunburns, and DNA damage. UVB radiation causes direct damage to DNA and RNA by inducing covalent bond formation between adjacent pyrimidines, leading to generation of mutagenic photoproducts. UVA is less mutagenic than is UVB, and causes indirect DNA damage via a photo-oxidative-stress-mediated mechanism, resulting in formation of reactive oxygen species, which interact with lipids, proteins, and DNA to generate intermediates that combine with DNA to form adducts, and several complex DNA repair systems are needed to prevent the harmful effects of these pre-mutagenic adducts[1], [13].

Clearly any sun exposure will contribute to DNA mutations, especially on naive skin. UVB is mainly absorbed in the epidermis and all the mentioned skin cancers occur in this part of the skin. UVA probably also plays a role mainly via the formation of free oxygen radicals that can result in mutations if they are formed very close to the DNA. Epidemiological data indicate, that while UVB radiation is the most important factor for development of SCC and BCC, UVA may play an important role for the development of CMM [14]. Studies have supported a link between sunbed use and CMM, as well as for NMSC, and this further indicates that UVA could be a factor in the genesis of CMM [15]. It is, however, in most epidemiological studies difficult to measure the effect of UVA and UVB separately, and therefore UV radiation is typically treated as a whole, and has, as such, been classified by WHO as a Group 1 carcinogen[16].

While the link between UV radiation exposure and SCC seems to be simply related to cumulative amount throughout a person´s lifetime, the association for BCC and CMM is more complex. For BCC and CMM UV radiation exposure in childhood or early adulthood, sunburn and intermittent- as opposed to continuous- exposure are reported as important risk factors.

Occupational and intermittent UV radiation

Occupational solar UV radiation exposure is directly related to time spent outdoor during working hours. Based on a Canadian study[17], using data from registries worldwide, an estimate of risk for different occupations is given in Table 1 . High risk jobs are here defined as jobs with outdoor work > or =75% of the workday. Intermittent UV radiation exposure does not have a specific definition, but is generally related to recreational exposure, such as time spent on the beach or sunbathing.

Occupation	**Risk group**
Farmers, farm managers, farm workers	High
Construction trade helpers and labourers	High
Landscaping and grounds maintenance labourers	High
Letter carriers (postal workers)	High
Fishing vessel skippers and fishermen	High
Roofers and shinglers	High
Nursery and greenhouse workers	High
Bricklayers	High
Heavy equipment operators (except crane)	Moderate
Heavy-duty equipment mechanics	Moderate
Carpenters	Moderate
Public works and maintenance labourers	Moderate

Couriers, messengers and door-to-door distributors	Moderate
Delivery and courier service drivers	Low
Truck drivers	Low

Table 1. Prevalence of exposure to solar ultraviolet radiation by occupation. **High risk:** outdoors > or =75% of the workday. **Moderate**: Either all workers in that job perform similar mixed indoor and outdoor tasks; or different workers in the job may have very different amounts of time spent indoors and outdoors. **Low risk**: Almost never exposed. *Data is derived from a Canadian surveillance project estimating exposure to carcinogens in Canada, and is partly based on Australian data on outdoor jobs*[17]

UV radiation- modifying factors

Environmentally related modifying factors

Factors modifying UV radiation on the skin are summarised in Table 1. Variation in UV radiation related to latitude is important. At low latitudes (closer to the Equator) there is a higher ambient UV-emission as can be measured in standard erythema doses (SED), since there is a greater proportion of shorter wavelengths, related to the small angle of the incoming radiation. The ambient SED varies significantly from countries with low latitudes to countries with high latitudes, and levels of total annual UV radiation vary approximately by a factor 4 across from high to low latitudes [18]. Total ambient UVR/year was reported to be 3757 SED in Denmark (latitude 56 N), 6193 in Northern USA (latitude 42-46 N), and 8710 in Southern USA (latitude 33-34 N)[19]. Even within minor differences in latitudes a difference in incidence of skin cancer has been reported. In a Swedish study[20] significantly higher incidence of SCC was found at lower latitudes than at higher latitudes within Sweden (varying from 55 – 69 degrees). For most subjects, UVR exposures vary from between 5% to 15% of total ambient UVR, with the exception of outdoor workers whose exposures can reach 20-30% of ambient UVR [18].

Environmental:
- latitude
- variation related to time of day
- ozone layer
- weather condition
- altitude
- reflection from ground/sea

Individual:
- sun behaviour

- holiday to sunny areas
- continuous or intermittent exposure

Other factors influencing UV-related risk of skin cancer

- individual susceptibility (skin type)
- defective DNA repair system due to disease or impaired immune system,
- skin pigmentation variation from summer-winter
- individual naevi count
- age
- gender
- behaviour (cloths, sunscreen use, sun seeking behaviour)

Table 2. The table comprises environmental and individually related factors that influence the amount of UV radiation reaching the skin, as well as other individually related factors modifying the risk of skin cancer.

Altitude is also a factor that influences UV radiation[21-23], Table 2. Increasing altitude increases UVR intensity by decreasing the air mass through which solar radiation must pass. Working at the seashore, where light is reflected from the sea, may increase ambient UV radiation significantly , and subsequently increase incidence of skin cancer[24] , as may working in snow where downwards directed areas of the skin that are usually protected are now exposed[18;25], (Table 2).

UV radiation has different intensity during the day, being at its strongest between 12-noon and 3 pm, when 50 % of the daily UV radiation is transmitted[26]. Planning of outdoor work might reduce UV exposure dose, e.g. by having lunch indoors during these hours as shown in a study of Danish and Irish gardeners[25] . UV-exposure also varies significantly during the year, and in Denmark the UV radiation exposure during winter is negligible (Fig 2).

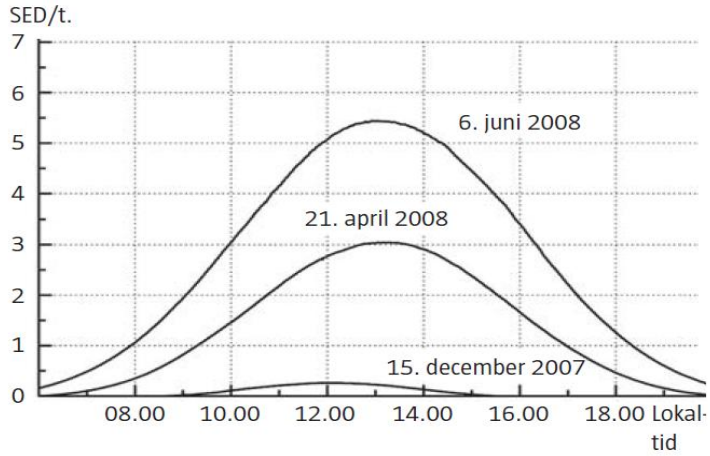

Fig 2. Illustrates the variation in ambient UV radiation during the day an during the year in Denmark.
(From Wulf and Erichsen[27])

Other factors that may influence the intensity of UVR reaching the skin are weather conditions, where cloudy weather will reduce UV radiation.

Individually related modifying factors

The transcription-coupled DNA-repair systems are very important and, if defective, the risk of skin cancer may increase by up to 2000 times[28]. The repair system is defective in some inborn diseases, and in patients with compromised efficacy of the immune system, caused either by disease or by medication. Non-melanoma skin cancer is the most frequent cancer observed in solid organ transplant recipients, tumours are mostly located on sun-exposed areas, and the prognosis in this group of patients is more severe than in immune-competent patients[1].

Constitutive or facultative pigmentation plays a part in absorbing UVB and diminishing the penetration to cellular DNA. The Fitzpatrick skin pigmentation scale is often used to characterizse UV sensitivity in individuals[29] (Table 3). In individuals with fair skin UV radiation penetrates deeper, and they are therefore more prone to develop skin cancer than those with intermediate or deeply pigmented skin. For the average Dane the protection by pigment will be 3-4 times higher in summer than in winter[19]. The incidence of SCC, BCC and CMM is higher in fairer skinned, sun-sensitive people than in darker-skinned less sun-sensitive people [3;30]. High individual number of naevi was found to be a risk factor for CMM but not for BCC[31;32]. High-dose UV radiation exposure after a period of sun avoidance will be received on skin with relatively low melanin content, and present a high risk of DNA damage.

I.	**Always burn, never tan**
II.	**Usually burn, tan less than average, with difficulty**
III.	**Sometimes mild burn, tan about avarage**
IV.	**Rarely burn, tan more than average (with ease)**

Table 3. Fitzpatrick skin pigmentation scale[29]

Understanding the UV radiation exposure for an individual under a particular level of ambient UV radiation is not straightforward, since behavioural aspects are also highly important. The individual variability related to sun protection behaviour in yearly risk dose shows up to about a 50 times difference [26]. Thus, even in areas of relatively low ambient UV radiation, it is possible to have high personal exposure[18]. UV radiation during leisure hours and holidays contributes significantly to the total UV-dose. In particular, travelling to sunny holiday destinations, may increase the yearly dose by 50 %[33]. In some individuals much of the annual exposure to UV radiation may be concentrated in a brief annual summer holiday[33].

Occupational UV radiation exposure and risk of BCC

Along with genetic factors and other environmental factors UV radiation exposure is considered the most important risk factor for BCC. The relevant UV-exposure pattern, cumulative versus intermittent exposure, however, probably differs between SCC and BCC. While the development of SCC is strongly associated with cumulative and lifelong UV radiation exposure, the development of BBC seem to depend on prolonged cumulative as well as intermittent exposure of UV radiation [3 34 35].

In our literature search on the subject of occupational UV radiation exposure and risk of BCC one meta-analysis with focus on BCC only[36], and one structured review with focus on non-melanoma skin cancer[37] were identified, both studies by the same author group.

In the meta-analysis it was concluded that individuals with outdoor UV exposure at work are significantly at higher risk of developing BCC (pooled OR 1.43 (1.23-1.66)[36]. The analysis was based on 24 studies, of which only 23 studies had sufficient data to be included in the analysis. 11 studies found a statistically increased risk of BCC in individuals with occupational UV exposure, 6 studies found a non-statistically significant increase (OR 1.2-1.7), 2 studies found no link, and 5 studies found a non-significant inverse relationship (OR 0.74-0.9)[36]. The results are illustrated in Fig 3.

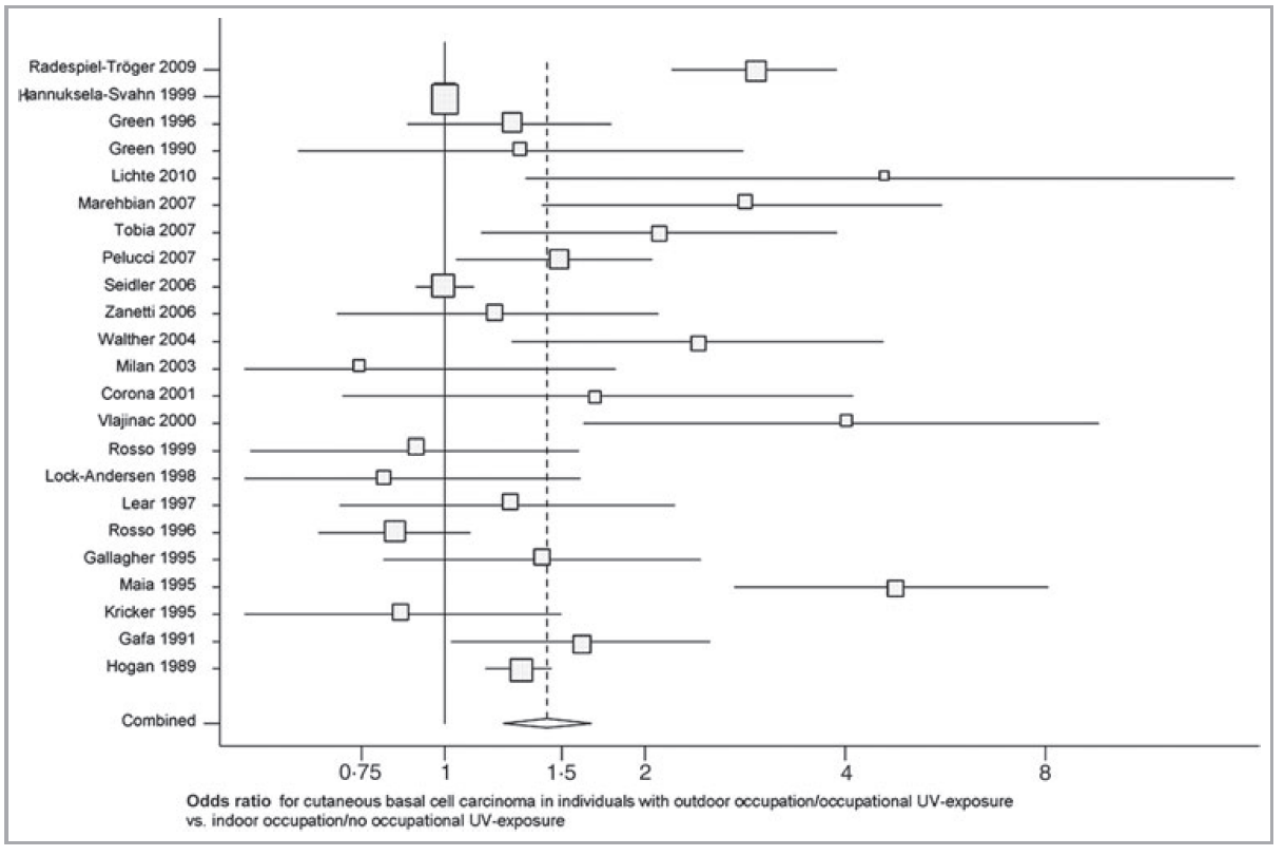

Fig 3. Result of meta-analysis shows the OR values for BCC in individuals with outdoor versus indoor occupations. From Bauer et al[36]

The reported ORs were almost identical in cohort studies and in case-control studies, however, ORs for cohort studies did not reach statistical significance (1.48 (0.83-2.66)). Studies adjusting for non-occupational exposure showed a stronger link than those that did not adjust[38;39]. Data from agricultural workers are in particular convincing [40;41]. As also reported for SCC, effect modification was reported with a significant risk for individuals > 55 years of age only [42], and it was reported that individual sensitivity/skin type modified the risk of BCC, with an increased association for individuals with a medium skin complexion/well tanning as compared to those with fair skin complexion/tanning poorly. This could be a result of self-selection of workers in outdoor occupations, indicating a trend in workers who do not tolerate the sun very well to seek indoor jobs.

Non-differential misclassification of occupational UV radiation exposure occurs in many studies and will lead to under-estimation of the risk of skin cancer. Over- or under-estimation of the risk in the meta-analysis may be due to a lack of controlling of relevant confounding factors (age, gender, and individual UV sensitivity)[36] in most studies. A possible dose-response effect was investigated in 9 studies, of which 2 found a significant dose-response relationship between BCC and occupational UV radiation exposure, and 4 found a significant relationship between BCC and non-occupational UV radiation exposure[36].

An important issue with respect to risk of BCC is intermittent versus continuous UV exposure. This was explored in an Australian study, where the risk of BCC was reported to increase substantially with increasing intermittency in poor tanners, but not at all in good tanners[43]. In a recent "in depth review" – not a systematic review – Young concluded that a clear link between BCC and UV radiation exists, and that the risk can be attributed to both occupational and recreational exposure [16]. The author emphasises recreational childhood exposure as an important risk factor, but an increase in lifetime occupational exposure is also acknowledged [44]. UV exposure before the age of 30 may play an important role for the development of BCC. In a recent high quality-study including patients with prior BCC tumours and monitoring them over a period of 6 years with respect to development of new BBCs in the head and ear-region, data shows that UV exposure under 30 years of age is strongly linked with BCC risk[45]. Occupational exposure before age 30 was significantly linked with incidence of BCC after controlling for exposure after age 30 or overall occupational exposure OR 1.31 (1.04-1.64)[45].

The association between AKs and BCC reported in several studies strongly support the hypothesis that the accumulated amount of UV radiation plays an important role in the development of BCC. Occurrence of AK was reported to be significantly associated with BCC localised on the head (histologically of the nodular type)[46], and another study reported presence of AKs as a risk factor for the development of BCC[47].

Latitude has been reported significantly to influence the risk of occupational BCC, and an inverse relationship between latitude and risk of BCC is reported in the literature[1]. We therefore decided to look more closely at studies made of latitudes similar to Denmark, i.e. 50 – 60 degrees. The results of this are presented in Table 4. A total of 6 studies were identified, out of which a positive

link between occupational UV radiation exposure and incidence of BCC was found in three studies although only statistically significant in one[41], which included agricultural workers with controls recruited from the same residential area. The other two studies reported a decreased risk for outdoor workers[48;49]. Limitations related to some of the other studies are: in one study the participants considered were 25-58 years of age, which is problematic,as there are indications that the link between occupational UV exposure and NMSC is present only in individuals older than 55 years of age [42]. Two studies were register studies based on job titles, where bias may more easily be introduced in relation to exposure[48;50].

Reference	**Lati-tude**	**OR (95% CI)**	**N**	**Study**	**Source**	**Exposure time**
Lock Andersen [49], 1999	55	0.8 (0.4-1.6)	320	Case control	Outpatient clinics	From 20 years -
Lear[51], 1989	51-53	1.24 (0.69-2.20)	906	Case control	Outpatient clinics	Lifelong
Gallagher [44]	53	1.4 (0.8-2.4)	632	Case control	Interview	Lifelong
*Hogan[41]	49-54	1.29 (1.13-1.42**)**	1276	Case control	Questionn-aire	Lifelong
Kenborg[48]	55	0.86 (0.78-0.95)	34276	Case-control	Several registers	> 10 years out-door work

Table 4. Association between occupational UV radiation exposure and incidence of BCC in meta-analyses with data based on population residing at latitudes 50-60 degrees only. *Agricultural occupation and controls matched to the residence of cases. The table is based on data from Bauer et al[36].

An effect of social class on occurrence of BCC was reported[51] with an increased incidence of BCC being associated with high social class. In general it is anticipated that higher social class is associated with highly paid occupations and that the increased risk of BCC may be due to more frequent overseas travel with resultant increased intermittent sun exposure. However, higher social class may also be associated with more frequent visits to physicians and an increased reporting of BCC. In a recent study including BCC in the head and ear-region only the association to

high social class could not be confirmed, and low educational level was found to be statistically associated with BCC[45].

Important key factors for the link between occupational UV radiation and the development of BCC are histological sub-type of BCC and the location of tumour on body sites. Histological type was explored in one study only [52], which reported a significantly positive association between occupational UV radiation exposure and nodular BCC. With respect to the location of the tumour, the same study reported a significant positive association between occupational UV radiation exposure and BCC located on the head and neck, but not for superficial BCC or tumours located on the trunk[52]. This finding was not supported by the Kenborg study [48], which, however, had severe limitations due to the age group studied being only up to 58 years. These potentially very interesting factors are currently not sufficiently evaluated in the literature.

Occupational UV radiation exposure and risk of SCC

Cumulative UV radiation is the most common and important cause of SCC[3], and the incidence of SCC is positively associated with sun-damaged skin.

In our literature search on the subject of occupational UV radiation exposure and risk of SCC one meta-analysis with focus on SCC only[53], and one structured review with focus on non-melanoma skin cancer[37] were identified, both studies by the same author group.

In the meta-analysis it was concluded, that individuals with outdoor UV exposure at work are significantly at risk of developing SCC (pooled OR 1.77 (1.40-2.22) [53]. The meta-analysis was based on 18 studies of which 12 studies found a statistically significantly increased risk for SCC in individuals with occupational UV exposure, 4 studies found an increased risk that was not statistically significant, 2 studies found no link, and no studies found an inverse relationship (Fig 4).

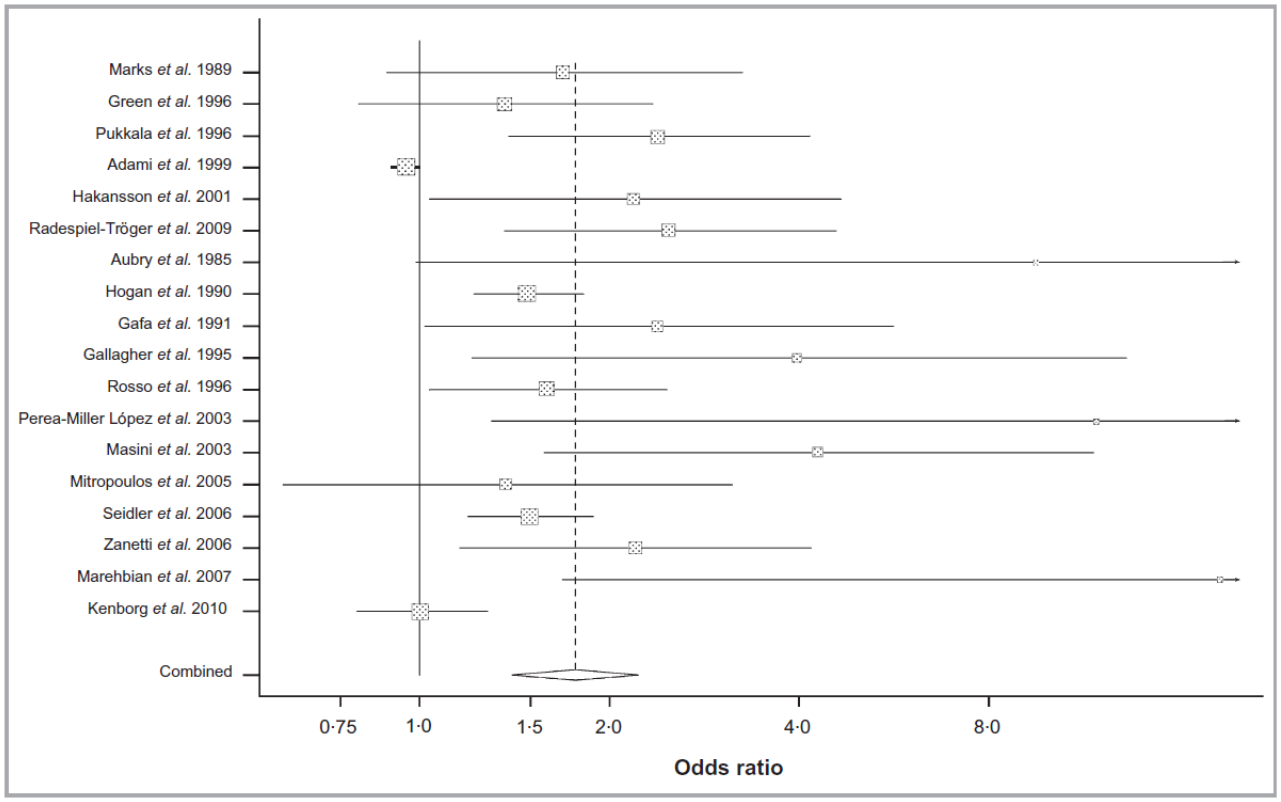

Fig 4. Result of meta-analysis shows the OR values for SCC in individuals with outdoor versus indoor occupations. From Schmitt et al[53]

The reported OR was almost identical in cohort studies and in case-control studies, further supporting the result. The most important confounders were age, gender, individual UV sensitivity and non-occupational UV exposure, and these were all only considered in 3 studies, of which the OR in two of the three studies was > 10. This indicates that the pooled OR may be under-estimated[53]. Another bias that may probably induce under-estimation is that controls were not truly unexposed in most studies. With respect to individual factors modifying the risk of skin cancer, an effect of age was reported [42], indicating that the increased risk for outdoor workers was present for workers > 55 years old only. The systematic review[37] is based on the same data as the meta-analysis and concludes that the association between occupational UV exposure and SCC is well documented and that the increased risk related to occupational UV radiation is approximately two-fold. In a recent "in depth review" – not a systematic review – Young [16] concluded that there

is a clear link between total UV radiation and SCC, and that the risk is due to both occupational and recreational exposure.

Latitude has been reported significantly to influence the risk of occupational SCC with higher risk at decreasing latitude. The relationship between latitude and strength of link to development of SCC can be seen in Fig.5.

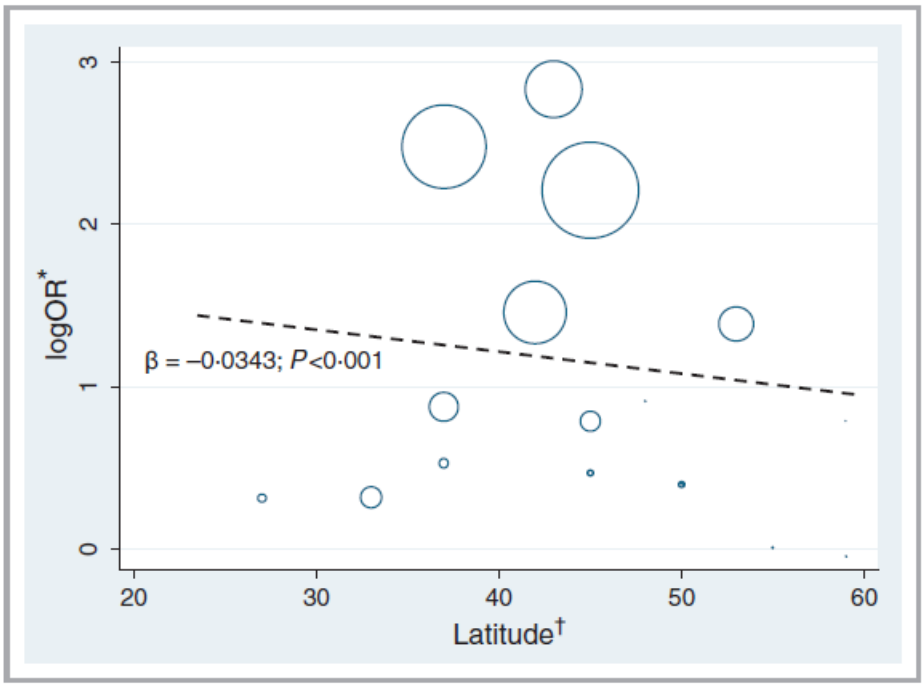

Figure 5. Relationship between latitude and strength of association between occupational ultraviolet (UV) exposure and SCC. The circle corresponding to each study has an area inversely proportional to the variance of the log-odds ratio. The superimposed line is obtained by weighted regression using a restricted maximum likelihood (REML) estimate of residual heterogeneity variance.41 *Log-odds ratio (OR) of the relationship between occupational UV light exposure and squamous cell carcinoma of the skin. The figure is taken from Schmitt et al[53].

We therefore decided to look more closely at studies made on latitudes close to Denmark, i.e. 50 – 60 degrees. The results of this are presented in Table 5. A total of 5 studies were identified, of which 4 found a positive link between occupational UV radiation exposure and incidence of SCC [20;50;54;55], although in one of the studies the link was significantly positive for women only[20]. In one study the association was not confirmed[48]. However, this study has some limitations with respect to exposure assessment, being a register study, where job titles were used as a proxy for occupational UV exposure. Additionally, the participants considered were 25-58 years of age,

which is problematic, as there are indications that the link between occupational UV exposure and SCC is present only in individuals older than 55 years of age [42]. Although included in the meta-analysis [53] a study by Haakonsson et al[56] is not included here, as no differentiation was made between SCC and BCC in that study.

Reference	Lati-tude	OR (95% CI)	N	Study	Source	Exposure time
Adami[20], 1999	59	Men 1.0 (0.9-1.0) Women: 1.3 (1.1-1.6)	4171175	cohort	Cancer-register	Lifelong
Hogan[55], 1989	50	Men: 1.5 (1.2-1.8) Women: 1.8 (1.2-2.7)	462	Case-control*	Questionn-aire	Lifelong
Gallagher[54],	53	4.0 (1.2-13.1)	586	Case-control	Interview**	Lifelong
Seidler[50]	50	1.5 (1.2-1.9)	109230	Case-control	Cancer register	-
Kenborg[48] 2010	55	1.0 (0.8-1.3)	5826	Case-control	Registers	> 10 years out-door work

Table 5. Association between occupational UV radiation exposure and incidence of SCC in meta-analyses with data based on population residing at latitudes 50-60 degrees only. * agricultural occupation and controls matched to the residence of cases. **increased risk for exposure last ten years before diagnosis. The table is based on data from Schmitt et al[53].

Occupational UV radiation exposure and AK

AK is considered to be a premalignant disease and an in-situ version of SCC. AKs are caused by cumulated UV radiation exposure, and the prevalence is therefore strongly related to age[12], and lesions are often found together with sun-damaged skin. A link between AK and SCC is identified at the histological level, since the same atypical cells are present in both lesions. The percentage of malignant transformation of AK into SCC is not known, and is reported as a rate varying from 0.025% and up to 10-20% per year/per lesion[69]. AK is thus an early manifestation of a potential malignant disease, however, if UV radiation exposure is discontinued, the lesions may regress and new lesions will not appear.

In the UK population the number of AKs is high, reported to be 34% for men and 18% for women over the age of 70[12]. Multiple AKs are often found, either scattered over sun-exposed skin areas or as confluent lesions in highly sun-exposed areas of the skin, and multiple AKs increases the risk of development of SCC.

Occupational UV radiation exposure and risk of CMM

UV radiation is the predominant environmental risk factor for CMM. However, the relationship between sun exposure and CMM is not straight forward. While UVB radiation is associated with the genesis of SCC and BCC, the genesis of CMM is probably related to UVA as well as UVB exposure[57 58]. Development of CMM has been related to sunburn and intermittent exposure [58], and is not limited to sun-exposure but is also related to artificial light from sunbeds. The intermittent sunlight hypothesis is based on studies finding a higher incidence of CMM in indoor workers than outdoor workers, and finding CMM not predominantly occurring on body sites frequently exposed to the sun. It is generally accepted that short bursts of intensive exposure to sunlight increase the risk of melanoma, while more chronic, regular exposure seems to have a neutral or inverse effect. In particular intermittent exposure in childhood has been looked upon as a risk[59].

In our literature search on occupational UV radiation exposure and risk of CMM, we identified a total of 5 systemic reviews/metaanalyses[59-63]. Pooled ORs for continuous occupational UV radiation exposure were reported as 0.85 – 0.95[62;63]. In a review from 1995[59] an OR was given for 15 studies, as illustrated in Table 6 for all studies and for studies from latitude 50-60 degrees only.

Occupational UV exposure and CMM	All studies (n=15)	Studies on latitude 50-60 degrees only (n=7)
positive association p<0.05	1	1
Positive association n.s.	5	1
Negative association p<0.05	4	2
Negative association n.s.	5	3

Table 6. Association between occupational UV radiation exposure and incidence of CMM in meta-analyses with data based on population residing at all latitudes and at latitudes 50-60 degrees only. The numbers indicate number of studies with positive and negative associations between

occupational UV radiation exposure and incidence of CMM. The table is based on data from Nelemans et al[59] .

Important issues discussed in the 5 reviews/meta-analyses were:

- A statistically significant link between intermittent non-occupational UV exposure, including sunburn, and development of CMM was supported in all studies.
- Careful interpretation of data indicates that there is a significantly decreased risk for maximum occupational exposure categories, while moderate occupational sun-exposure, which is often seasonal or short-term exposure, seems to increase the risk[60].
- A significant link with latitude was found, with a statistically significant link between CMM and chronic exposure at lower latitudes, and a statistically greater link between CMM and sunburn at high latitudes.[62] It is concluded that the seemingly protective effect of occupational UV exposure should be interpreted carefully, since the risk is not compared to no UV at all, but to a lifestyle with low continuous UV exposure combined with intermittent UV exposure (e.g.: white collar workers having intermittent exposure and sunburns during holidays)[62].
- The link between CMM and continuous sun exposure was statistically significantly higher for CMM localised on usually sun-exposed skin than on occasionally exposed skin.[64]
- Presence of actinic damaged skin was more strongly linked with CMM on occupationally exposed skin areas. Different aetiologies for CMM on different body sites are suggested[64].
- When CMM on UV exposed skin areas were examined separately, an increased risk for all outdoor workers was reported[16;65].
- Nevus count (high number of nevi) is known to be significantly associated with increased risk for melanoma. However this association is significant for nevi on the trunk only, but not related to CMM on the head and neck[32].

As for BCC a link with high social class has been reported for CMM, and in a recent study this was related to having a home garden[66]. However, the link may, as for BCC, also be explained by being able to afford holidays in the sun, or on the other hand, it could be explained by the fact that higher social class is associated with increased visits to physicians and better registration of disease.

Different subtypes of CMM exist (see above), and the aetiology is assumed to differ between these. Superficially spreading CMM and nodular CMM (accounting for > 85 % of all melanoma), are the histological types relevant for the intermittent sun exposure hypothesis, while lentigo maligna melanoma and acral lentiginous melanoma are considered to have separate aetiologies. Lentigo malignant melanoma generally occurs in elderly people, and chronically sun-exposed skin is a prerequisite for lentigo maligna melanoma [59]. However, a recent study, comparing lentigo maligna melanoma to ordinary CMM, reported no link with continuous or occupational UV radiation exposure for either of the tumours[64]. Some epidemiological cohort and case-control studies include lentigo maligna melanoma together with ordinary CMM, which could introduce a methodological pitfall, while these are excluded in other studies. However, in a Danish population-based case-control study from 1988, excluding lentigo maligna melanoma types [67], where data for chronic exposure was based on the question "working outside in the summer", the OR for occupational exposure and development of CMM was 0.70 (0.52-0-93).

Acral lentiginous melanoma often occurs in black skinned individuals, and is not assumed to be related to sun exposure, but to dependent on certain genetic alterations[68].

Artificial UV radiation

In some occupations exposure to UV radiation from artificial sources may occur. Artificial UV radiation differs from solar UV radiation with respect to intensity and spectrum, and an EU-regulation on health Effects of Artificial Light exists. In general, the probability is low that artificial lighting for visibility purposes induces pathologic conditions, since expected exposure levels are much lower than typical daylight exposures. Lamps/bulbs used to illuminate buildings have from a biological point of view no potential to cause skin cancer[70]. Window glass is protecting from UVB exposure to a degree that development of skin cancer from natural UV exposure through glass is unlikely to occur[71] Examples of use of artificial UV radiation are UV-treatment of skin diseases, sunbeds, use in dental clinics and in nail studios, and for UV-disinfection of water. Other occupational activities with UV radiation include welding and glassblowing etc. UV exposure from welding may from a biological point of view have the capacity to cause skin cancer, if protective

equipment is not consequently used, or if unprotective bystanders are exposed. However, on the basis of existing studies of welders and studies regarding occupations with "open flames" (using the example of the glassblower) it is evident that so far no reliable data exist regarding the chronic photo-damage or the occurrence of UV-typical skin cancers[72].

Sunbeds

UV radiation from use of sunbeds may further contribute to the total amount of SED (Fig 6), and thus significantly increase the risk of both CMM and NMSC[73]. Indirect epidemiological data have supported this particularly for CMM and SCC[73], and in a recent meta-analysis sunbed use was confirmed to be significantly associated with risk of melanoma, and the association increases with number of sunbed sessions and with onset of use at a young age (<35 years)[74;75].

Assessment of UV radiation

Direct assessment

The dose of UV radiation causing erythema in the skin is measured in units called Standard Erythema Dose (SED). The number of SEDs expresses the emission of ambient solar UV radiation, or how much UV radiation an individual has received, over a period of time[76], and SED is a way of measuring actual UV radiation exposure. The SED has been developed as an erythemally weighted measure of radiant exposure, equivalent to 100 J/m^2 [27]. The SED is independent of skin type and a particular exposure dose in SED may cause erythema in fair skin but none in darker skin. However, skin type can be quantified as the number of SEDs needed to provoke erythema, called pigment protection factor (PPF).

The SED received by an individual is estimated to be around 5-10 % of ambient SED. It is estimated by Godar[77] that an indoor worker receives around 3% and an outdoor worker around 10% of ambient UV radiation. Direct measurement of UV radiation exposure can be done by use of exact dosimeters that measures the actual SED for which an individual is exposed[26;78;79]. Frequently used dosimeters are electronic, and the magnitude of the change is related to the effective UVR dose[26]. They accumulate the dose over a certain time and data is subsequently analysed[78].

Since occurrence of all varieties of skin cancer is generally accepted to take place over a longer period of time (years), no such direct SED observations can be related to development of skin

cancer. However, dosimetry-results for individuals during various circumstances, such as work and recreational periods, are essential for our understanding of UV radiation exposure in relation to the development of skin cancer. Well-conducted studies are of importance to understand how and when UV radiation is received, and data is available from a number of Danish studies performed by use of personal dosimeters[19;25;26;80;81]. Data from these studies gives a differentiated picture of UV radiation obtained for different gender and age-groups, indoor and outdoor workers, and the additional UV radiation that can be obtained during sun-holidays. Some key data is given in Fig 6. The average Dane receives around 168 SED/year (additionally 5 SED/year for individuals < 20 years of age). In Denmark the UV light in the period November-February is negligibly, and all UV radiation is received during the summer months (Fig 2)[27]. UV radiation also varies during the day (Fig 2)[27], and is most intense from 12 noon until 3 pm. Ambient UV is related to latitude, altitude and reflection from sea or sand. Indoor workers receive significantly less UV radiation than outdoor workers (Fig 6). A sunny holiday is considered as an intermittent exposre as compared to outdoor work which is continuous exposure. Sun-behavioural aspects seem to be of utmost importance. Individual variability in yearly risk dose (SED) varies considerably from as low as 20 SED to as high as 1100 SED [26;33], corresponding to about a 50 times difference between extremes.

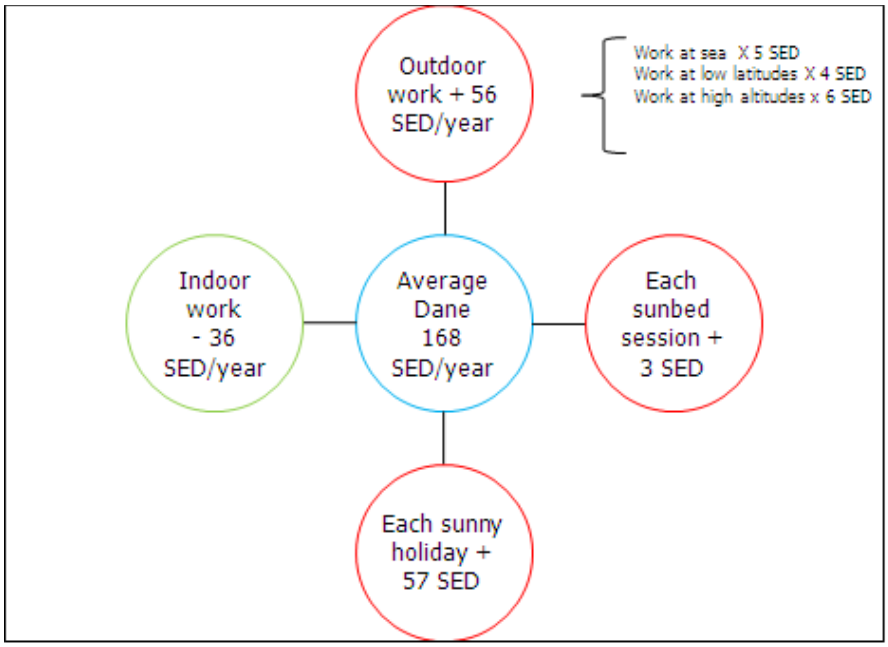

Figure 6. The figure estimates the average yearly SED for Danes, for indoor and outdoor workers, and also gives an estimate of factors that may add to or multiply the received SED. The individual range is very huge. A sunny holiday is considered as an intermittent exposre as compared to outdoor work which is continuous exposure. Data is based on Thieden et al[19;26;33;80;82], and values are dependent on where on the body the measurements are made.

As can be seen from Fig 6the difference in SED/year between an indoor and an outdoor worker, based on the Danish data, is approximately 100 SED (a precise calculation is 92 SED). However, another study based on international data, estimates a bigger difference between indoor and outdoor workers, reporting that UV radiation received is 3 times higher in outdoor workers[77]. Individual range is very huge (up to 50 X) with respect to UV exposure. The difference between the Danish and the internationally based data may partly be due to difference in latitude, to different methods used for exposure assessment, and also to from which body site the measurements are taken. In conclusion, it can be assumed that an outdoor worker will receive almost double the UV-amount as an indoor worker in Denmark, on a monthly base. It is important to consider that the occupational part of the totally received UV exposure over a lifetime will decrease after retirement.

In a recent German regulation[83] the SED for indoor and outdoor UV radiation exposure is calculated somewhat different from Fig 6. Data in Fig 6 is based on Danish studies with direct assessment of UV radiation by electronic dosimeters, as opposed to the German regulation which is based on German measurements of UV radiation by film dosimeters[78].
In this regulation it is argued that an additional 40 % UV radiation (caused by occupational exposure) increase the risk of SCC by 100 %[83]. This argumentation is based on data from studies by Armstrong and Kricker[3;84].

Occupational risk factors/behaviour	**Individual risk factors/behaviour**
Indoor/outdoor job	Immunosuppresive drugs
Working hours, indoor/outdoor, number of years	Sun risk behaviour (sun holidays, sailing as hobby etc)
Altitude at work	Use of sunbeds

Reflection at work Intermittent occupational exposure	Young age at exposure Residence in low-latitude region (current or previous)

Table 7. Important occupational and individual risk factors to be determined

In Table 7 some occupational and individual risk factors are given, which are important to assess.

Assessment in epidemiological studies

Measurement of sun exposure in epidemiological studies represents a challenge, and methods of recording vary considerably between epidemiological studies. The challenges are related to

- Use of data obtained directly from the individual, versus data taken from a register (i.e. use of job description as a proxy for occupational UV exposure). Accurate classification of occupations may also be a challenge. Register studies found significantly weaker association than studies using primary data [53].
- Difficulties in remembering risk behaviour, in particular difficulties in remembering childhood data. In epidemiological studies this recall bias may tend to over-estimate the association between exposure and risk.
- Difficulties in distinguishing between occupational and recreational exposure. This bias may in epidemiological studies often lead to an underestimation of occupational risk.
- Distinguishing between intermittent and continuous exposure. Intermittent exposure is generally associated with recreational UV exposure, as is sunburn, but intermittent work-related exposure, as well as work-related sunburn should also be considered.
- Estimating the quantity – in sun exposure – retrospectively is difficult. Questions related to sun protection, exposure during lunch hours etc [25], are generally not included in questionnaires used.
- Assessment of dose from ambient SED is often used, however, individual factors are important and may significantly influence the individual SED received.

Prevention of occupational skin cancer related to UV exposure

There is sufficient evidence to conclude that outdoor workers bear an increased risk of experiencing adverse health effects caused by solar UV exposure. Furthermore, outdoor workers' sun-protective behaviours are often inadequate and sunburn rates are high[85]. There is growing evidence that sun-safety programmes in the working environment can bring up favourable sun-protection habits among outdoor workers[85]. Sun safety education should ideally lead to an increased knowledge in workers about health adverse effects caused by the sun (immediate sun burn as well as long term risk of skin cancer), a change of workers' sun-protective behaviours in direction of a more favourable life style, and decrease number of sun burns and development of skin cancer.

Prevention strategies are summarised in Table 8. Primary prevention strategies should include recommendations about choosing to work and take breaks in the shade, particularly between 12-noon and 3 pm. Providing shelters for the sun can substantially reduce the daily UV dose [80]. UV-protective clothing made from clothes made of light, breathable materials ensuring an agreeable body climate, should be used. UV-protective headgear as part of the clothing is essential, since most NMSC develop in the face and head region. Sunscreens should be used, and this should particularly be addressed to male workers, who are traditionally less inclined to use of sunscreen products[86]. . Use of sunglasses should also be recommended. To initiate damage-control at an early point, regular skin examination of outdoor workers should be considered, either as self-examination or by a medical professional.

Sun-safety programmes have the potential for reducing the burden of skin cancer for outdoor workers in the future. In addition to targeting individual workers, it is crucial also to encourage employers to develop sun-safety policies for their companies, including ideally the provision of sun-protective gear free of charge at workplaces. Increased focus on the subject, as well as support from healthcare authorities, cancer foundations, unions, occupational physicians and dermatologists may help the implementation-process of sun safety-education programmes.

Tabel 8

Preventive strategy for outdoor workers to avoid adverse health effects from UV exposure

Primary prevention stratgies	Secondary prevention stratgies
Shade	Skin examination, self-examination
UV-protective clothing	Skin examination by a medical professional
UV-protective head gear	
Sunscreens	
Sun glasses	

Other exposures and skin cancer

Other exposures than UV radiation may lead to skin cancer, although less frequently. The following chapter is based on systematic reviews or meta-analyses [25;87-89], as well as the papers identified from the literature search mentioned above. The exposures mentioned in the Danish list of recognized occupational diseases are addressed, together with other exposures which occurred in the literature search as possible risk factors for skin cancers.

Arsenic

One study systematically reviews issues related to arsenic in drinking water at or below the limit of 50 micrograms[87]. It is concluded that there is clear evidence that inorganic arsenic at concentrations of at least several hundred micrograms per litre drinking water may cause skin cancer. However, there is inadequate epidemiological evidence to support the hypothesis that arsenic in drinking water at or below 50 micrograms may cause adverse health effects. The effect of arsenic on human health has been studied for centuries, and the link between prevalence of non-melanoma skin cancer and ingested arsenic is well known[90]. Occupational effects are not discussed in any depth in the study, but a recent study examined a potential link between arsenic exposure at work and skin cancer[91] among Slovenian metal workers. In this new case-control study, the lifetime prevalence of work-related exposure to arsenic dust was 23.9% for cases and 15.5% for controls, and the OR reported was 1.94 (0.76–4.95). However, co-exposure to sunlight may further increase the ratio. Doses of arsenic exposure could not be quantified in detail in this study.

Oil refining industry

Five studies from 1984 to 2007 measure the risk of CMM in oil refinery workers with contradicting, but mainly negative results[88;92-95].

Significantly increased incidences of CMM were reported in refinery workers in Canada and the UK, but studies from the US and Finland found no excess risk incidences for skin cancer of any type. A critical review of cancer incidences in cohort studies of petroleum workers[88] concluded that there was no evidence of an increased risk of skin cancer in refinery workers. Several studies evaluate crude mineral oils for carcinogenicity in experimental settings, and decreasing carcinogenicity is reported with higher degree of refining of the oils[96].

Anthracene and creosot

Anthracene is a polyaromatic hydrocarbon generated during combustion processes. Unlike many other PAHs it is not classified by IARC, and no epidemiological studies are found on the carcinogenicity. Creosote is a mixture of PAHs, some of which have carcinogenic properties. The carcinogenetic effect of creosote was assessed in one study of 922 wood-workers exposed in the 1950ties to -70ties. The relative risk of any type of skin cancer was 2.37 (95% CI 1.08-4.50)[97]. No other studies were identified.

Soot

Soot is the classic carcinogen containing PAHs, and causing skin cancer In the 1750s scrotal cancer was first observed in chimney sweeps identifying soot as an occupational carcinogen. The carcinogenicity is well established, but no epidemiology supports the effect.

Metal working fluids

Metal working fluids have undergone a marked change in composition since the 1970s [78] now containing almost entirely aliphatic hydrocarbons and less aromatic hydrocarbons and impurities. This is expected to minimise the carcinogenicity.

A systemic review from 1998 of cancer risks among workers exposed to metal working fluids was identified[89]. With respect to skin cancer one cohort study (and a follow-up of that study) and one population-based study were included. In the cohort study[89] a 5-fold increased risk of SCC (one facial and 5 scrotal cases) was found in workers exposed to metal working fluids. One population study was included which showed that individuals ever employed in an occupation with a

potential metal working fluid exposure had an increased risk of SCC located to the scrotum, OR10.5 (4.0-36.9)[98]. In a 1987-published cohort study of workers exposed to aliphatic metal working fluids only, however, there were no observed cases of SCC (scrotal or not scrotal) [99] and it is discussed that changes in refinery methods since the 1950s have reduced the content of polycyclic aromatic hydrocarbons, which have been suggested as the causative agent for SCC[89]. In a recent cohort study of auto-workers following > 14000 workers for 20 years, increased incidence of CMM was reported, OR 1.99 (1.00-3.96), particularly with aliphatic mineral oils[100]. Apart from this, it should be mentioned that in a study of patients treated with coal tar on the skin for various skin diseases, no increased risk of any skin cancer was reported[101].

Flight personnel

A total of 4 studies (structured reviews or meta-analyses) on cancer incidence in flight personnel were identified [102-105]. Two of these are authored by the same group and include the same data [103;104].

One meta-analysis is based on 7 cohort studies and 1 case-control study including female flight attendants from civilian airlines[102]. An increased risk of CMM was found (RR 2.13 (1.58-2.88). It is concluded that the risk is increased for this specific working group. However, the aetiology is controversial, as the risk could be related to cosmic radiation during flight or to non-occupational leisure-time solar UV radiation exposure[102]. Another meta-analysis focused on the incidence rate in 6 included studies with focus on male pilots and female flight attendants, and found a statistically significantly increased mortality rate from CMM in male pilots (OR 1.97) , and an increased incidence (OR 1.54) of CMM in female attendants, although not statistically significant[105]. In a study including Scandinavian airline pilots only, an increased risk of CMM (2.3 (1.7-3.0)), but also of SCC (2.1 (1.7-2.8)) and BCC (2.5 (1.9-3.2)) was reported[106].

The overall problem with the meta-analysis and the Scandinavian study of data from flight personnel, is the difficultyof distinguishing between occupational exposure to cosmic radiation when airborne, and leisure-time exposure to UV radiation at destinations. Studies which correct for season and latitude of destination are neither identified in the literature search nor in the two reviews. There is not sufficient evidence for CMM as a result of cosmic radiation.

Pesticides

In a recent study including a total of 62960 Britain agricultural pesticide users [107], an increased link between pesticide use and cancer incidence rate for SCC was reported (1.11 (1.00-1.23)), while an increased risk of CMM was not found 0.94 (0.73-1.21). Data was not corrected for UV radiation exposure. In another study from Iowa[108] a significant link between CMM and some pesticides was reported when exposed for more than 55 days: maneb/mancozeb: OR = 2.4 (1.2-4.9), parathion: OR 2.4 (1.3-4.4), and carbaryl OR1.7 (1.1-2.5). Also in this study data was not corrected for UV exposure. In an Italian study from 2007 with focus on residential pesticide exposure, an increased risk of CMM was found in individuals exposed for > 10 years as compared to individuals exposed for < 10 years, OR 2.46(1.23-4.94), and a positive dose-response relationship for frequency of exposure was found[109]. Results from this study reinforce the hypothesis of an occupational risk of CMM in pesticide-exposed workers.There is not sufficient evidence for any of the tumour forms.

Polyvinyl chloride (PVC) and vinyl chloride monomer (VCM)

In a study from 2000 a reported excess of melanomas in a cohort of workers exposed in relation to work in manufacture of PVC, an increased occurrence of CMM as well as SCC was reported[110]. The RR was 3.5 (1,36-6,96 95%CI) for CMM and 2,99 (0,97-6,98 95%CI) for SCC. The risk of CMM, however decreased from 1st to 3rd follow-up of the cohort in the period 1953 to 1993. The authors conclude that the amount of excess monomer in the production has declined, thus minimising the exposure to a suspected carcinogen. However, data from future studies from other cohorts is not yet available.

Polychlorinated biphenyls (PCB)

In a follow-up study of workers on an electrical capacitor manufacturing plant in Indiana with exposure to PCB, an overall increased mortality risk of CMM was reported[111]. In a recent update of this cohort as well as workers from two additional capacitor manufacturing plants elsewhere in USA, an increased risk of CMM was found in long-term workers (OR = 1.41 (1.01–1.91), but not in short term workers[112]. One earlier study from 1992 found a case SMR on 3.5, 95% CI 1.4-3.7 from CMM based on 3 cases [113].

Fire-fighters

A systematic review of cancer in fire-fighters arrived at a summary risk of NMSC cancer of 1.39 (95% CI 1.10-1.73) based upon nine studies but considering the applied study designs the authors

consider the likelihood of a real increased risk due to workplace exposure ‘possible’ rather than ‘probable’[114]. For instance, some studies indicating a link were proportional mortality studies. Fire-fighting is by IARC classified in group 2B, indicating a possible carcinogenic exposure. Fire-fighters are exposed to a number of suspected carcinogens, but the effect of protective equipment is thought to be good. The real exposure to carcinogens is not evaluated. A meta-analysis from 2006 based on 32 studies found a RR of CMM at 1.3 (1,1-1,6 95% CI) based on 8 of the 32 studies[114].

Conclusions

In the following the epidemiological criteria are rated according to Appendix 3.

point	**Statements**	Rating according to appendix 3[1] The rating is however modified to also include biological evidence where no epidemiological is available
1	UV radiation is positively linked with development of BCC. Epidemiological data indicate that both accumulated and intermittent exposures are important.	**+++**
2	Occupational UV radiation is positively associated with development of BCC on exposed skin	**++**
3	Occupational UV radiation exposure in Denmark is positively associated with development of BCC on exposed skin (based on biological evidence on UV and BCC)	**++**
4	Accumulated, long-term exposure to UV radiation is associated with development of SCC. The association is confirmed from animal studies, the biological background is well understood, and epidemiological data is convincing	**+++**
5	Occupational exposure can cause SCC on exposed skin areas	**+++**
6	Occupational exposure in Denmark can cause SCC on exposed skin areas	**+++**
7	UV radiation is linked with development of CMM.	**+++**
8	Occupational exposure can cause CMM on exposed skin areas	**+**
9	Occupational exposure in Denmark can cause CMM on exposed skin areas (based on biological evidence on UV and CMM)	**+**
10	Accumulated, long-term exposure to UV radiation is linked with development of AK. AK is understood as precursors of SCC. This association is confirmed from gene studies, the biological background is well	**+++**

	understood	
11	Occupational exposure can cause AK on exposed skin areas (based on biological evidence on UV and AK)	**+++**
12	Occupational exposure in Denmark can cause AK on exposed skin areas (based on biological evidence on UV and BCC)	**+++**
13	Occupational artificial UV radiation may lead to NMSC or CMM	**(+)**
14	Other occupational exposures than UV radiation:	
	Arsenic may lead to NMSC	++
	Metal working fluids may lead to NMSC	(+)
	Tar, soot may lead to NMSC	+++
	Pesticides may lead to CMM	(+)
	Polyvinyl chloride (PVC) may lead to CMM	(+)
	Polychlorinated biphenyls (PCB) may lead to CMM	(+)
	Air crew work may lead to CMM	+
	Refinery workers work may lead to skin cancer of any type	(+)
	Work as firefighter may lead to NMSC	+

Comments:

Point 1, 2 and 3: With respect to development of BCC the link with UV exposure cannot be doubted. Recreational, intermittent exposure seems to be more important than occupational exposure when looking at BCC as such. However, there are indications that different etiological pathways for development of BCC exist for different exposure patterns on different body areas. Occurrence of AKs, indicating sun-damaged skin and chronic sun exposure, is related to BCC localised on the head and neck, histologically being of the nodular type. Thus, the link between occupational UV exposure and nodular BCC localized on skin exposed during working hours, may well be related to occupational UV exposure. In particular, occupational UV exposure before the age of 30 may be a risk factor.

Point 4-6: Many epidemiological cohort- and case-control studies support the link between accumulated, occupational UV exposure and development of SCC. AKs are found to be related to the presence of CMM, confirming the importance of total UV radiation exposure. The UV dose-response curve for

development of skin cancer is not known. In a recent German regulation additional 40 % UV radiation from occupational exposure was suggested as a criterioin for occupational disease[83].

Point 7-9: With respect to development of CMM the link to UV exposure cannot be doubted. Recreational, intermittent exposure seems to be more important than occupational exposure when looking at CMM as such. However, there are indications that different etiological pathways for development of CMM exist for different anatomic locations. CMM localizsd in the head- and neck region may be more strongly associated with occupational exposure than CMM on the trunk.

Point 10-12: While development of skin cancer takes place over years, the development of AKs may more easily be monitored, since continued exposure may often cause development of new AKs within a shorter period of time (i.e. one year), while end of exposure may partly cause regression within a shorter period (i.e. one year). In a recent German study a link between AK and occupational exposure may be accepted only when there are more than 5 AKs, or confluent AKs covering an area of 4 x 4 centimetres, present on sun exposed skin ares[83].

All points:

- It should be considered that AKs and NMSCs are extremely common diseases with increasing age, due to an increased cumulative total UV radiation dose received over years.
- In epidemiological studies continuous exposure and occupational exposure are interpreted as being the same. It should, however, be considered that occupational exposure may sometimes also be intermittent (e.g.: seasonal work, berry picking etc.).

Future studies

From the present report is clear that the epidemiological evidence available at the moment for development of occupational skin cancer is limited, and to make conclusions it is therefore needed to include also biological evidence. More large-scale epidemiological studies evaluating incidence of skin cancer within different occupations, and with exposures comparable to our national latitude, and relevant for our national work sites, would be welcomed. Epidemiological studies however, also have their limitations, as discussed above, and exposure assessment is a critical point in all epidemiological studies.

Future studies aiming at UV exposure assessment are necessary to more precisely determine the amount of UV received in different occupations. UV exposure after retirement is also an important aspect to focus at, since many of the skin cancers develop and appear after retirement where the percentage of occupationally related UV exposure gradually decline.

Future studies should attempt to divide different skin cancers into subtypes. There is today data indicating that nodular BCCs may be more related to continuous UV exposure, while the superficial BCCs are more related to intermittent UV exposure, however, these data should be further substantiated. Future epidemiological studies distinguishing between lentigo malignant melanoma and CMM would add information if lentigo malignant melanoma is more related to continuous UV exposure, and not to intermittent exposure as is CMM.

With respect to artificial UV exposure, this area also needs to be studied in more detail, and one place to start could be workers occupied with welding (and bystanders), since the exposure in this group is assumed to be high.

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Ref Type: Report

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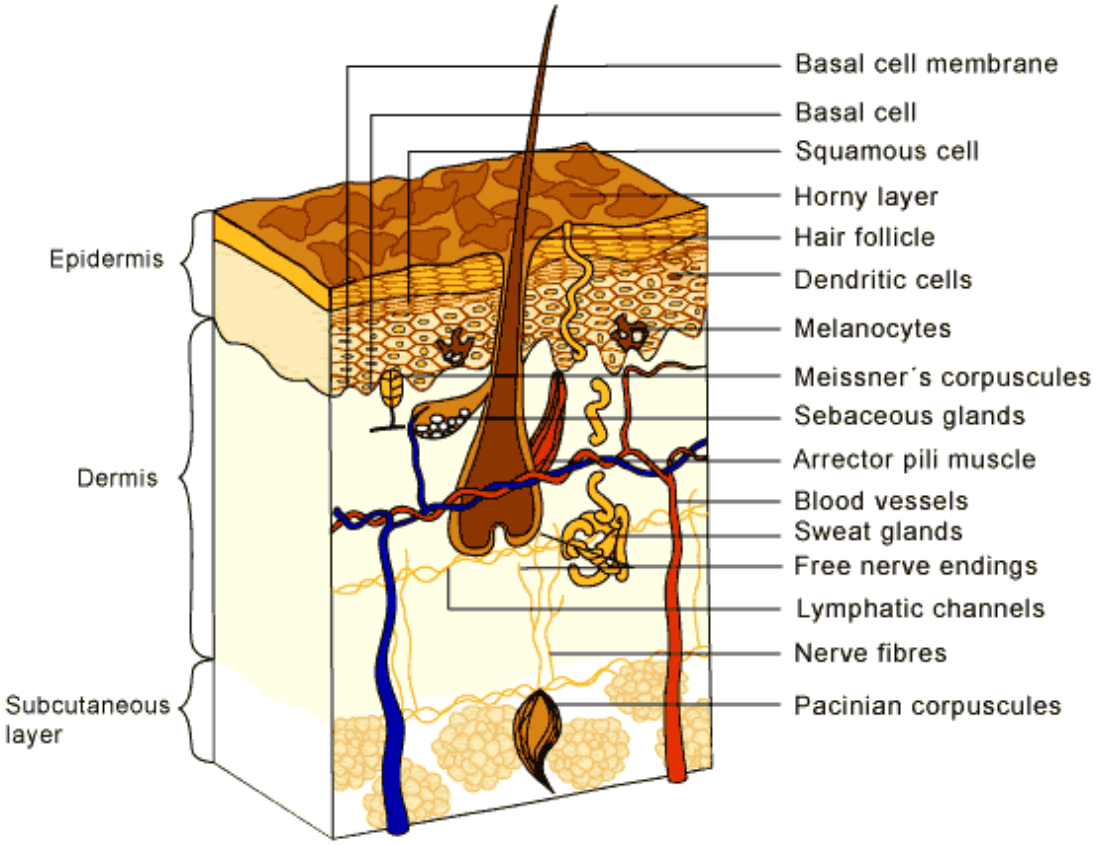
Appendix 1

Reference: http://skincancer.dermis.net



Appendix 2

The literature searches were performed in PubMed and Embase. These bibliographic databases were selected because they index the relevant part of the biomedical and health science periodical literature as to coverage of the literature and to the scientific peer reviewed contents. The contents of the Cochrane Database of Systematic Reviews is also indexed in the PubMed and EmBase databases.

Search strategies in PubMed 1996-

Strategy A

((ethnology OR morbidity OR epidemiology OR epidemiological OR incidence OR occurrence OR mortality OR frequency OR frequencies OR prevalence OR follow up studies OR longitudinal studies OR cohort studies) AND humans)) AND ((((((indoor tanning OR artificial tanning OR solarium OR solar beds OR welding OR welders OR occupational diseases OR occupational OR work OR industrial OR work related OR occupations OR occupational exposure)) AND (lentigo maligna OR keratoacanthoma OR skin cancer OR skin neoplasms OR basal cell carcinoma OR melanoma OR squamous cell carcinoma OR actinic keratosis OR actinic keratoses))) OR ((chemically induced AND ((tars OR hydrocarbons OR polyaromatic hydrocarbons OR mineral oil OR occupational diseases OR occupational OR work OR industrial OR work related OR occupations OR occupational exposure)) AND (lentigo maligna OR keratoacanthoma OR skin cancer OR skin neoplasms OR basal cell carcinoma OR melanoma OR squamous cell carcinoma OR actinic keratosis OR actinic keratoses)) AND humans)) Filters: Publication date from 1996/01/01; Humans

Strategy B

((ethnology OR morbidity OR epidemiology OR epidemiological OR incidence OR occurrence OR mortality OR frequency OR frequencies OR prevalence OR follow up studies OR longitudinal studies OR cohort studies)) AND (((actinic keratosis OR actinic keratoses) AND (exposure OR environmental exposure OR pigmentation OR skin type OR pigment protection OR ultraviolet rays OR intermittent OR cumulative OR dose response)) Filters: Publication date from 1996/01/01 to 2014/12/31; Humans

Strategy C

((((((((((ethnology OR morbidity OR epidemiology OR epidemiological OR incidence OR occurrence OR mortality OR frequency OR frequencies OR prevalence OR follow up studies OR longitudinal studies OR cohort studies) AND (indoor tanning OR artificial tanning OR solarium OR solar beds OR welding OR welders OR occupational diseases OR occupational OR work OR industrial OR work related OR occupations OR occupational exposure) AND (lentigo maligna OR keratoacanthoma OR skin cancer OR skin neoplasms OR basal cell carcinoma OR melanoma OR squamous cell carcinoma OR actinic keratosis OR actinic keratoses))) OR (chemically induced AND (tars OR hydrocarbons OR polyaromatic hydrocarbons OR mineral oil OR occupational diseases OR occupational OR work OR industrial OR work related OR occupations OR occupational exposure) AND (lentigo maligna OR keratoacanthoma OR skin cancer OR skin neoplasms OR basal cell carcinoma OR melanoma OR squamous cell carcinoma OR actinic keratosis OR actinic keratoses))) OR ((ethnology OR morbidity OR epidemiology OR epidemiological OR incidence OR occurrence OR mortality OR frequency OR frequencies OR prevalence OR follow up studies OR longitudinal studies OR cohort studies) AND (actinic keratosis OR actinic keratoses) AND (exposure OR environmental exposure OR pigmentation OR skin type OR pigment protection OR ultraviolet rays OR intermittent OR cumulative OR dose response))) OR (ultraviolet rays AND (sun OR sunlight) AND (geography OR circadian variation OR geographic variation OR diurnal variation)))) OR ((sunburning OR lentigo maligna OR keratoacanthoma OR skin cancer OR skin neoplasms OR basal cell carcinoma OR melanoma OR squamous cell carcinoma OR actinic keratosis OR actinic keratoses) AND (sun light OR sunlight OR solar radiation OR environmental exposure OR ultraviolet rays) AND (pigmentation OR skin color OR skin type OR pigment protection OR healthy skin) AND (estimation OR dosimeter OR dosimeters OR intermittent OR cumulative OR dose response))) AND ((Meta-Analysis[ptyp] OR systematic[sb]) AND ("1995/01/01"[PDat] : "3000/12/31"[PDat])))) OR (((((((((ethnology OR morbidity OR epidemiology OR epidemiological OR incidence OR occurrence OR mortality OR frequency OR frequencies OR prevalence OR follow up studies OR longitudinal studies OR cohort studies) AND (indoor tanning OR artificial tanning OR solarium OR solar beds OR welding OR welders OR occupational diseases OR occupational OR work OR industrial OR work related OR occupations OR occupational exposure) AND (lentigo maligna OR keratoacanthoma OR skin cancer OR skin neoplasms OR basal cell carcinoma OR melanoma OR squamous cell carcinoma OR actinic keratosis OR actinic keratoses))) OR (chemically induced AND (tars OR hydrocarbons OR polyaromatic hydrocarbons OR mineral oil OR occupational diseases OR occupational OR work OR industrial OR work related OR occupations OR occupational exposure) AND (lentigo maligna OR keratoacanthoma OR skin cancer OR skin neoplasms OR basal cell carcinoma OR melanoma OR squamous cell carcinoma OR actinic keratosis OR actinic keratoses))) OR ((ethnology OR morbidity OR epidemiology OR epidemiological OR incidence OR occurrence OR mortality OR frequency OR frequencies OR prevalence OR follow up studies OR longitudinal studies OR cohort studies) AND (actinic keratosis OR actinic keratoses) AND (exposure OR environmental exposure OR pigmentation OR skin type OR pigment protection OR ultraviolet rays OR intermittent OR cumulative OR dose response))) OR (ultraviolet rays AND (sun OR sunlight) AND (geography OR circadian variation OR geographic variation OR diurnal variation)))) OR ((sunburning OR lentigo maligna OR keratoacanthoma OR skin cancer OR skin neoplasms OR

basal cell carcinoma OR melanoma OR squamous cell carcinoma OR actinic keratosis OR actinic keratoses) AND (sun light OR sunlight OR solar radiation OR environmental exposure OR ultraviolet rays) AND (pigmentation OR skin color OR skin type OR pigment protection OR healthy skin) AND (estimation OR dosimeter OR dosimeters OR intermittent OR cumulative OR dose response))) Filters: Meta-Analysis; Systematic Reviews; Publication date from 1995/01/01

Search strategies in EmBase 1996-

Strategy D

((sunburning or lentigo maligna or keratoacanthoma or skin cancer or skin neoplasms or basal cell carcinoma or melanoma or squamous cell carcinoma or actinic keratosis or actinic keratoses) and (sun light or sunlight or solar radiation or environmental exposure or ultraviolet rays) and (pigmentation or skin color or skin type or pigment protection or healthy skin) and (estimation or dosimeter or dosimeters or intermittent or cumulative or dose response)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

Strategy E

1 (ethnology or morbidity or epidemiology or epidemiological or incidence or occurrence or mortality or frequency or frequencies or prevalence or follow up studies or longitudinal studies or cohort studies).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

2 (indoor tanning or artificial tanning or solarium or solar beds or welding or welders or occupational diseases or occupational or work or industrial or work related or occupations or occupational exposure).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

3 (lentigo maligna or keratoacanthoma or skin cancer or skin neoplasms or basal cell carcinoma or melanoma or squamous cell carcinoma or actinic keratosis or actinic keratoses).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

4 (tars or hydrocarbons or polyaromatic hydrocarbons or mineral oil).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

5 1 and 2 and 3

6 3 and 4

7 ((actinic keratosis or actinic keratoses) and (exposure or environmental exposure or pigmentation or skin type or pigment protection or ultraviolet rays or intermittent or cumulative or dose response)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

8 (ultraviolet rays and (sun or sunlight) and (geography or circadian variation or geographic variation or diurnal variation)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

9 1 and 7

10 5 or 6 or 9

Appendix 3

Criteria for rating Epidemiological Evidence for Causal Inference proposed by the Danish Society of Occupational and Environmental Medicine.

Degree of evidence of a causal association between an exposure to a specific risk factor and a specific outcome

The following categories are used:

+++ strong evidence of a causal association
++ moderate evidence of a causal association
+ limited evidence of a causal association
0 insufficient evidence of a causal association
- evidence suggesting lack of a causal association

Description of categories:

Strong evidence of a causal association (+++):

A causal relationship is very likely. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It can be ruled out with reasonable confidence that this relationship is explained by chance, bias or confounding.

Moderate evidence of a causal association (++):

A causal relationship is likely. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It cannot be ruled out with reasonable confidence that this relationship can be explained by chance, bias or confounding, although this is not a very likely explanation.

Limited evidence of a causal association (+):

A causal relationship is possible. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It is not unlikely that this relationship can be explained by chance, bias or confounding.

Insufficient evidence of a causal association (0):

The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of a causal association (-):

Several studies of sufficient quality, consistency and statistical power indicate that the specific risk factor is not causally related to the specific outcome.

Comments:

The classification does not include a category for which a causal relation is considered as established beyond any doubt. The key criterion is the epidemiological evidence.

The likelihood that chance, bias and confounding may explain observed associations are criteria that encompass criteria such as consistency, number of 'high quality' studies, types of design etc.

Biological plausibility and contributory information may add to the evidence of a causal association.

Appendix 4

Examples of UV exposure in out-door and in-door workers on exposed skin

When calculating the total UV exposure during life time the UV radiation received during childhood and after retirement should be included. In childhood and after retirement the the annual UV dose is estimated as 168 SED (Fig 6).

For indoor workers the annual UV dose is estimated to be 132 SED (Fig 6). Outdoor work is estimated to double the received UV dose, i.e. annual dose 264 SED*.

With respect to division into indoor and outdoor occupations see Table 1.

Example 1:

70 year old man/woman with 30 years of outdoor work and 40 years out of work.

Total UV dose: UV dose received during years out of work (168x40) + UV dose received during years with outdoor work: (264x30) = total dose 14640 SED.

Additional UV dose as compared to indoor worker (264x30) – (132x30) = 3960 SED

Additional work-related UV dose in percentage: (3960x100/14640) = **27%**

Example 2:

50 year old man/woman with 30 years of outdoor work and 20 years out of work (childhood).

Total UV dose: UV dose received during years with outdoor work: (264x30) + UV dose received during years out of work (168x20) = total dose 11280 SED.

Additional UV dose as compared to indoor worker (264x30) – (132x30) = 3960 SED

Additional work-related UV dose in percentage: (3960x100/11280) = **35%**

Example 3:

75 year old man/woman with 25 years of outdoor work, 20 years of indoor work and 30 years not working.

Total UV dose: UV dose received during years with outdoor work: (264x25) + UV dose received during years with indoor work (132x20) + UV dose received during years not working (168x30) = total dose 14280 SED.

Additional UV dose as compared to indoor worker (264x20) – (132x20) = 2640 SED

Additional work-related UV dose in percentage: (2640x100/11280) = **23%**

Important factors that will further increase the occupational exposure are working abroad on different latitudes, working at different altitudes, and working at sea.

Working hours exposed to:	**The UV dose is increased by factor:**
Low latitudes	4 (annual dose 4 x 264 SED)
Sailing/seashore	5 (annual dose 5 x 264 SED)
High altitudes	6 (annual dose 6 x 264 SED)

Important personal risk factors increasing risk of skin cancer and non-occupational UV exposure are:

- Immune suppression/ use of immunosuppressive drugs
- Sun risk behavior

With respect to immune-suppressive drugs the influence on skin cancer may differ between different drugs. For most drugs used in organ-transplanted patients the increased risk for NMSC is significant.

With respect to sun risk behavior: Each sunbed session is estimated to contribute with 3 SED. Regular use of sunbeds once weekly will add an extra of 156 SED per year. The contribution from "sunny holidays" is more difficult to estimate, since behavior during such holidays may differ significantly (for more detailed information see page 32). The variation in SED between individuals may be as high as 50 times due to differences in sun risk behavior.

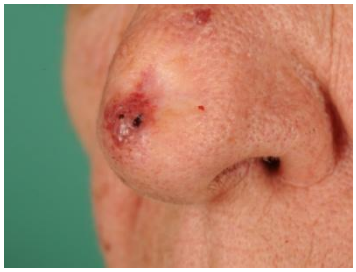
For comparison, in the recent German regulation[83] skin cancer (SCC) can be recognized after an additional 30% work-related UV exposure.

* *In Fig 6 the annual dose for outdoor workers is reported as 224 SED, however, the exact figure may depend on where on the body the measurement is taken, as well as other factors. Data from the literature estimates 2-3 times higher SED for outdoor workers, and an estimate of double UV dose for outdoor workers as compared to indoor workers in Denmark seems to be a rational compromise). The dose is received on exposed skin.*

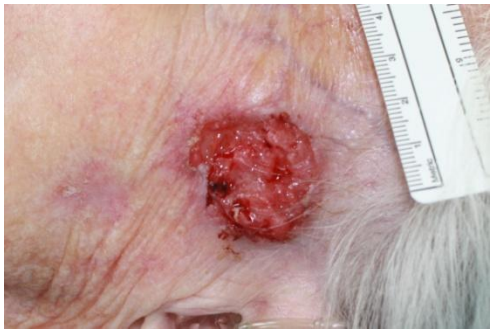
Appendix 5

Photos of skin tumors

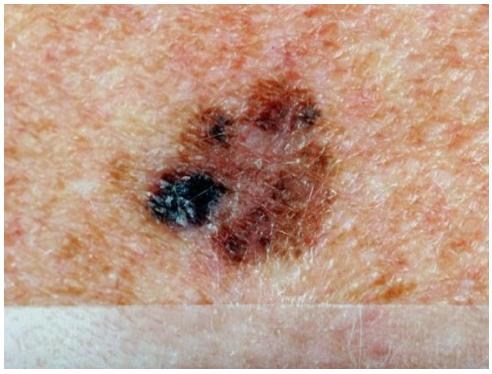
BCC Carcinoma Basocellulare



SCC Carcinoma Spinocellulare



CMM Cutaneous Malignant Melanoma



Appendix 6

Review comments and comments to reviews

Minutes from review meeting

Review meeting November 22.nd 2013 at Bispebjerg Hospital.

Participants: Tove Agner (TA), Thomas Diepgen (TD), Åke Svensson (AS), Hans Christian Wulf (HCW), Jens Peter Bonde (JPB), Niels Ebbehøj (NE)

Agenda:

9.00: Niels Ebbehøj. Welcome and background.

9.30: Åke Svensson: Review comments to be discussed.

10.30: Thomas Diepgen: Review comments to be discussed.

11.30: Tove Agner discusses the review comments from Rosemary Nixon

12.00: Lunch break

13.00: Discussion of the conclusions part.

14.00: End of meeting.

Minutes

NE: The background for the meeting was the review process of the report to the Danish Occupational Environment Fond about Occupational exposures and the Development of Skin Cancer.

TD, AS and Rosemary Nixon have sent review comments to be discussed at the meeting. The comments will be attached to the report together with a statement from the authors how the comments have been included in the final report. The final report and attachments will be sent to reviewers for information.

General comments:

TD: UV radiation is by far the most important environmental cause of skin cancer, and should be stressed in the report. Artificial UV radiation should be highlighted, and the paragraph on artificial UV should be extended.

AS missed a chapter about prevention, and in general a better structure of the report. Also definitions of UV radiation, – occupational exposure – private exposure how and methods for measurement of exposure should be included. TA went through the comments from Rosemary Nixon. They are mainly related to specific paragraphs in the text, and they will be considered page by page.

Add photos to illustrate and clarify.

Suggestions page by page:

Note in the foreword, that the evidence in this field is hard to assess in epidemiological terms as the DASAM criteria describes. A large amount of clinical and experimental evidence need to be taken into consideration in addition to the epidemiological evidence.

It was discussed if AKs are carcinoma in situ. It was decided that the important thing for this specific report is that AKs are generally accepted as precursors of SCC.

TD emphasised that nodular BCC is more likely to be occupationally related than superficial BCC

It was generally agreed that continous UV radiation is more related to work, while intermittent sun exposure is related to recreational exposure. Seasonal workers may comprise an exception as well as travelling engineers going south for short time jobs.

Intermittent exposure is equivalent to being sunburned.

It was generally agreed that the assumption that outdoor workers recieve approximately double the UV dose as compared to indoor/non-outdoor workers workers is ok.. The exposure is approximately. linear over a life-span

End of the meeting

NE thanked the reviewers for their valuable contribution to the work, and wished everybody a safe trip home.

Ref

Niels Ebbehøj

Review from Rosemary Nixon:

Review of occupational skin cancer report November 2013

Overall comments

This is a sound, well structured and comprehensive review and I commend the authors for their diligence. Well done! I have no problems with the design and structure of the report.

Major comments

Page 12

I strongly disagree with the assertion that actinic keratosis is an in situ SCC. Bowen's disease is, however. Perhaps you mean to say that AK is a precursor of SCC. This is also referred to on page 28 and in Conclusion point 10

Comments from the authors: This was discussed during the review meeting, please see comments there.

Page 14

The paragraph beginning : While the association.... needs a reference

Page 32

Assessment in epidemiological studies. As mentioned, assessment of exposure is a real challenge. Somehow I thought this issue, and the associated descriptions, which are all very valid, needed more emphasis.

Specific comments

Page 6

Skin cancer **predominantly** comprises BCC,SCC,CMM (because of other cancers eg Merkel cell etc), same comment under Background page 7

English suggestions (sorry these are included for whole document here rather than by page)

I am sure that the English will be corrected now but there are a few issues

Page 6: 'due to the lacking tradition for reporting skin cancer...' suggest rephrase

cumulative not cumulated, (page7); also **page** 20, cumulative not accumulated; page 27 cumulative not chronic exposure (line2), Conclusions point 1: cumulative not accumulated, also point 4,10; also page 39 cumulative not accumulated

mamma-cancer (page 9) (presume this is breast cancer?!) , 'trusty' prognosis (page 12); regression not regress (page12) UV component not contingent (page 14) postal workers not letter carriers (page 15) latitudes not attitudes (page 15); working in snow where down directed areas of skin....is a bit clums; page 22

Cumulative radiation is the most ....important **cause not course;** also **Same spelling in Conclusions points 5,6,8,9,11,12**

1950s not 1950ties page 34, similar 1750s etc

Page 8

Sub-types of BCC: under nodular, I would include 'nodular' not infiltrated; for sclerosing and infiltrated I would include poorly defined border rather than 'diffusely bounded'. **Often** white/yellowish element

Page 10

In our experience, SCCs are rarely not sometimes ulcerated. I would say they present as firm, scaly, infiltrated nodules on sun-exposed areas

I would say: Surgical removal of SCC will be associated with scarring

Page 11 Subtypes of **CMM**

Nodular CMM: I would note that these are far more likely to be amelanotic than superficial CMM, so would revise use of **pigmented nodule**

Page 12

Second sentence in top paragraph is a little clumsily worded

Major disagreement re AK and in situ SCC as noted above

I don't think I would describe AK as yellow-red, just red scaly..

....scars or depigmentation of the skin **may (not will)** follow other treatments (cryotherapy in experienced hands does not scar or depigment)

Page 13

We use the term Bowen's disease not morbus Bowen

Page 15

Legend to Table 1: data is taken from Canadian and Australian studies, then this should have two references?

Ref 16. Is this correctly cited? There is a much greater difference between high to low latitudes than 4x: I suppose it is how you define low latitudes! They get a lot lower than 33-34.....

Page 16 need to clarify Table 2. Under Individual, maybe say sun-seeking behaviour while under Other factors, maybe put sun-protective behaviour eg clothing, sunscreen use. Perhaps this could also go under Individual. What about sunbed (solarium) use?

Page 17

Under Individually related modifying factors, I would note that the increased skin cancers in transplant (Her indsættes Åke Svenssonrecipients is predominantly comprised of SCC

Page 18

I meant to check: I have always used the Fitzpatrick scale with 6 categories- should I and II be combined?

Page 22

In 2nd para, 4th sentence begins 'this finding'....which finding were you referring to?

Page 27

Nevus count....the sentence beginning 'however this association... ' is not that clear.

Page 28

Regarding AKs regressing, no reference is provided

The end! I am happy with the conclusions and the assignment of the evidence base.

Comments to review from Rosemary Nixon

We are grateful to the reviewer for some important comments.

Authors comment: Suggestions from Rosemary Nixon have been followed and are included in the new text. More references are added. The text clarified and language checked.

Skåne University Hospital

November 15, 2013

Department of
Dermatology and Venereology
Åke Svensson, Head of Department
Mail:ake.svensson@skane.se

Dear Professor Tove Agner!
Tove.Agner@regionh.dk

I have ,as an international reviewer, read the scientific review addressing occupational skin cancer by Agner T et al.
Initially the authors give a clinical summary of especially the most common types of skin cancer and actinic keratosis. The authors present relevant epidemiological data as well as which treatments that are recommended for the different types of lesions.
After this background there is a report about UV radiation and skin cancer. The authors start the chapter with a short summary in which they try to explain biological plausibility for UV radiation causing skin cancer. The text in this part is not easy to follow and it could be an idea to try to explain details in a way that would be more understandable for a reader not very involved in the field.
After this short text about biological plausibility they describe UV radiation and risk factors, modifying factors and different types of bias. This part is presented in an easily comprehensible way though these things are very complicated. The text is updated with adequate references to the most reliable international journals. When all these things are mentioned the authors continue and present data about occupational exposure for UV radiation and risk for basal cell carcinoma, squamous cell carcinoma, cutaneous malignant melanoma and actinic keratosis.The text is short but stringent and I can not find that there is any important data in literature that is not presented.
After the presentations mentioned there is a very short summary about artificial UV radiation and risk for skin cancer from use of sunbeds.
Assessment of UV radiation is described in detail. The authors have been involved in several international high ranked studies regarding direct assessments of UV radiation and that chapter give an excellent overview.
The challenges of measurement of sun exposure in epidemiological studies is also presented clearly. This knowledge is very important when risk assessments are made.

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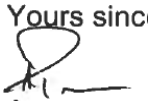
At the end of the document the authors present data about other exposures and skin cancers. The content seems to be up to date regarding relevant literature.
In the authors conclusions there are very valuable estimations of evidence regarding statements of exposure and association of skin cancer based on existing knowledge.
Beside the minor critic in the text mentioned I would suggest the authors to already in introduction report on that there are also several rare skin tumours. This fact is now mentioned in background but should be mentioned earlier in introduction. The text "skin cancer includes BCC, SCC and CMM " should be more nuanced. On page 8 is a sentence about treatment of BCC. Kryo-therapy should also be listed .Look for example at Lindemalm-Lundstam B, Dalenbäck J Prospective follow-up after curettage-cryosurgery for scalp and face skin cancers.Br J Dermatol 2009
At page 12 is if I am right low altitudes mentioned for the first time. The explanation about that is mentioned but not until page 15. In Table 3 there are missing parts on line 1 and 2.
On page 36 line 5 is a sentence that is not complete
On page 39 about comments to point IV-VI is a sentence that need a reference. "AKs are found to be related to presence of CMM, etc"
In the text as well at the reference list are some flaws that need corrections before the review is completed.
In Summary
This is an adequate and updated review of what is internationally known about occupational skin cancer. For more rare skin tumours there is not evidens for an association with occupation but that can in part depend on lack of investigations. In this document should favourably a chapter be included about what is known about prevention on occupational skin cancer. Skin cancer increase and it would be valuable to think about prevention both at and outside working places.

Yours sincerely



Åke Svensson

Comments to review from Åke Svensson

We are grateful to the reviewer for some important comments.

It has now been mentioned in the text that more skin tumours than those included in the report exist. We have also mentioned cryo-therapy as a frequently used treatment for BCC.

With respect to many of specific comments we have included most of these in the manuscript

Review from Thomas Diepgen

Heidelberg, 18. Nov. 2013

A scientific review addressing occupational skin cancer

Agner T, Ebbehøj Niels E, Wulf HC, Bonde JP

Review:

This is an excellent review describing and evaluating risk factors for occupational skin cancer with a special focus on occupational UV exposure.

The authors performed a literature search in Pub Med and EmBase on work related/occupational skin cancer, including exposures studies, and identified a total of 2250 papers. The relevant papers including 3 structured reviews/meta-analyses on NMSC, 5 on CMM and 3 on other exposures leading to skin cancer were included in this review. The final report is based on the structured reviews/meta-analysis as well as on the 220 papers identified in the literature search, of which the most recent and relevant papers are included in the reference list. The methods used in this review are sufficient and the most relevant references are given.

The text is well written, however quite often statements are made without a corresponding reference. I did some comments where references should be added (in the original report). I strongly recommend to add some additional references.

Comment from authors: references have been added.

This review is very helpful and answers the questions raised in the "project notice". It clearly demonstrates that there is an increased risk for squamous cell carcinoma (SCC) and their precursors (actinic keratosis) in workers exposed to natural UV irradiation at work. There is also an increasing risk for basal cell carcinomas (BCC). For cutaneous malignant melanomas (CMM) the situation is

more complex. However lentigo maligna melanoma, a subtype of CMM are also associated to occupational UV exposure.

Comment from authors: This issue is addressed at page 29.

On page 38 and 39 a summary is given. The conclusions are supported by the data.

In the background section I would discuss Actinic Keratosis after SCC instead of after CMM. Comment from authors: This has been changed. I would also recommend to report more details about the pathogenesis of the different skin tumors in this section. A good overview about Non-melanoma skin cancer is given in a paper by Madan (Lancet 2010: 375: 673-85). Comments from authors: This is now included. In this paper there is also an excellent paragraph about prognostic factors especially for SCC. On page 10 other prognostic factors for SCC should be given. The increased risk of organ transplant patients and immunosuppression should be also mentioned in this paragraph.

Comment from authors: This has been added.

The most important section is on UV radiation and skin cancer and later the relationship between occupational UV radiation and occupational skin cancer (pages 13 to 32. For me it seems more logical to start with the biological effects of UV radiation, and to describe the modifying factors. Thereafter I would describe how to assess UV exposure and thereafter what we know about the different occupational UV exposures (intermittent, chronic, artificial). After that the associations between occupational UV exposure and different skin cancers should be discussed.

Otherwise the ranking of the different sections and paragraphs are sometimes a bit confusing. As an example the term SED is mentioned but will be introduced later in the text.

Comment from authors: We thank the reviewer for this comment. We have made some minor changes in the disposition of the report.

The role of artificial UV radiation in the occupational setting has to be described in more details and more references should be given.

Comment from the authors: This paragraph has been re-written.

Other exposures and skin cancer are reported very well and are highlightening new interesting results (e.g. on flight personal). In the conclusion (point 13) well known substances like tar, soot, pitch should be also mentioned and the corresponding skin cancer risk given.

Comment from the authors: These risk factors are now included.

In summary this is an excellent review.

Prof. Dr. T. L. Diepgen

Comments to review from Thomas Diepgen

Comment from authors: We thank the reviewer for his comments. The suggested changes are included in the manuscript.