Linköping University Medical Dissertation No. 1891

Understanding Skin Cancer Risk and Prevention

with Emphasis on Actinic Keratosis Patients

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To Mariana,
and Perla

"Learning is experience, everything else is just information"
Albert Einstein

CONTENTS

ABSTRACT

The rising incidence of skin cancer globally makes it important to emphasize preventive measures that promote sun protection, particularly among individuals with phenotypic predisposition and/or risky sun habits. Actinic keratosis (AK) is the predominant actinic lesion observed in fair-skinned populations, recognized as a sign of actinic skin damage and as an occasional precursor to squamous cell carcinoma (SCC).

The aim of this thesis was to explore, from a primary care perspective, how enhanced understanding of risk factors for skin cancer development can aid in identifying individuals for patient education on prevention and early detection of skin cancer.

Paper I suggests that personalized sun protection advice delivered in person by the GP can result in both short-term and long-lasting improvements in sun protective behaviour. Paper II demonstrated that individuals diagnosed with AK face a significantly elevated risk of developing SCC, basal cell carcinoma (BCC), or malignant melanoma (MM) in the following decade compared to sex- and age-matched controls. Paper III highlighted the fact that the presence of chronic lymphocytic leukaemia, and to a lesser degree hypertension and Parkinson's disease, independently raises the risk of skin cancer. This underscores the importance of providing tailored preventive guidance to individuals with these conditions. Paper IV showed that both age and male gender were factors found to be associated with an increased risk of developing skin cancer in AK patients while no risk increase was identified for any of the other variables studied.

In conclusion, personalized sun protection advice from general physicians (GPs) can bring about lasting improvements in sun protective behaviour. Reinforcing this advice during medical consultations, such as nevi checks, is important to sustain this effect over a long period. This is encouraging for the accepted practice of giving sun protection advice to patients with MM, SCC and BCC. A diagnosis of AK not only indicates an increased risk of skin cancer but also serves as a readily identifiable criterion for implementing personalized preventive measures. The presence of AK substantially increases the likelihood of developing future skin cancer, even more pronouncedly when combined with specific comorbidities such as chronic lymphocytic leukaemia, hypertension, and Parkinson's disease.

Future research should investigate how sun protection advice interacts with other behavioural counselling and evaluate its effectiveness over time. Additionally, exploring other factors influencing skin cancer risk in individuals with AK would facilitate the provision of comprehensive preventive interventions.

SVENSK SAMMANFATTNING

Den ökande förekomsten av hudcancer globalt gör det viktigt att betona förebyggande åtgärder som främjar solskydd, särskilt bland individer med solkänslig hudtyp och/eller riskfyllda solvanor. Aktinisk keratos är en mycket vanlig typ av hudförändring hos ljushyade personer, välkänd för att vara ett tecken på hudskada orsakad av långvarig solexponering, och som också kan utgöra ett förstadium till skivepitelcancer.

Syftet med denna avhandling var att utforska, ur ett primärvårdsperspektiv, hur ökad förståelse för riskfaktorer för utveckling av hudcancer kan hjälpa till att identifiera individer för patientutbildning om förebyggande och tidig upptäckt av hudcancer, med särskilt fokus på just individer med aktinisk keratos.

Artikel I föreslår att individuellt utformade solskyddsråd som ges personligen av allmänläkare kan resultera i både kortsiktiga och långvariga förbättringar av solskyddsbeteendet. Artikel II visade att individer som diagnostiserats med aktinisk keratos löper en signifikant ökad risk att utveckla någon av de tre viktigaste hudcancertyperna skivepitelcancer, basalcellscancer eller malignt melanom, under det följande decenniet jämfört med individer i en köns- och åldersmatchad kontrollergrupp. Artikel III påvisade att förekomsten av kronisk lymfatisk leukemi, och i mindre grad högt blodtryck och Parkinsons sjukdom, självständigt ökar risken för hudcancer. Detta understryker vikten av att ge skräddarsydd förebyggande vägledning till individer med dessa tillstånd. Artikel IV visade att både ålder och manligt kön var faktorer som visade sig vara associerade med en ökad risk att utveckla hudcancer hos patienter med aktinisk keratos, medan ingen riskökning identifierades för någon av de andra variablerna som studerades, såsom antal och storlek på förändringarna.

Sammanfattningsvis kan personliga solskyddsråd från allmänläkare leda till bestående förbättringar av solskyddsbeteendet. Att återupprepa sådana råd i samband med läkarbesök, såsom vid kontroller av hudförändringar, är sannolikt viktigt för att bibehålla denna effekt över tid. Detta ger stöd till den vedertagna strategin att ge solskyddsråd till patienter med hudcancer. Förekomst av aktinisk keratos indikerar inte bara en ökad risk för hudcancer utan kan också ses som ett enkelt identifierbart kriterium för att utforma individanpassade solråd med avseende på framtida hudcancerrisk, då detta avsevärt ökar sannolikheten för att utveckla framtida hudcancer. Risken tycks ännu mer uttalad i kombination med andra samtidiga

sjukdomar såsom kronisk lymfatisk leukemi, högt blodtryck och Parkinsons sjukdom.

Framtida forskning bör undersöka hur solskyddsråd samverkar med annan beteenderådgivning och utvärdera dess effektivitet över tid. Att utforska andra faktorer som påverkar risken för hudcancer hos individer med AK skulle dessutom underlätta tillhandahållandet av omfattande förebyggande insatser.

LIST OF PAPERS

I. Hedevik H, **Guorgis G**, Anderson CD, Falk M: Sustainable effect of individualised sun protection advice on sun protection behaviour: a 10-year follow-up of a randomised controlled study in primary care.
BJGP Open. 2019 Oct 29;3(3):bjgpopen19X101653. doi: 10.3399/bjgpopen19X101653. PMID: 31344682; PMCID: PMC6970591.

II. **Guorgis G**, Anderson CD, Lyth J, Falk M: Actinic Keratosis Diagnosis and Increased Risk of Developing Skin Cancer: A 10-year Cohort Study of 17,651 Patients in Sweden.
Acta Derm Venereol. 2020 Apr 29;100(8):adv00128. doi: 10.2340/00015555-3486. PMID: 32314794; PMCID: PMC9128984.

III. **Guorgis G**, Anderson CD, Lyth J, Falk M: Associations with comorbidities in the development of skin cancer in patients with actinic keratosis.
Submitted.

IV. **Guorgis G**, Anderson CD, Falk M: Predictive Factors in Skin Cancer Development in Actinic Keratosis Patients: Insights from a Retrospective Chart Review.
Manuscript.

ABBREVIATIONS

AK	Actinic keratosis
BCC	Basal cell carcinoma
CDWÖ	Care Data Warehouse in Östergötland
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
GP	General physician
HR	Hazard ratio
Is-SCC	*In-situ* squamous cell carcinoma
KSC	Keratinocyte skin cancer
MM	Malignant melanoma
MS	Multiple sclerosis
NMSC	Nonmelanoma skin cancer
OR	Odds ratio
PDT	Photodynamic therapy
PHC	Primary health care
SEPI	Sun Exposure and Protection Index
SCC	Squamous cell carcinoma
SOTRs	Solid organ transplant recipients
TBP	Total body photography
TTM	Transtheoretical Model
UV	Ultraviolet

ACKNOWLEDGEMENTS

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You made this possible.

THANK YOU ALL!

PROLOGUE

As a family medicine specialist actively involved in primary care, I encounter a diverse array of individuals seeking with various medical challenges. Some patients exhibit more pronounced effects of a multitude of diseases, disorders, and symptoms, occasionally leaving me with a sense of professional self-doubt.

My interest in dermatological diseases, particularly skin cancer, dates back to my early years as a physician. During my specialization training, I conducted a small study on Actinic Keratosis at the dermatology clinic in Kalmar hospital, under the supervision of Esben Jörgensen and Katarina Holmdahl Källèn. I did not realize that this exploration would mark the beginning of my journey toward a PhD thesis.

Returning to Mantorp Health Care Centre in 2013, I encountered Karin Rådholm, who enthusiastically encouraged me to embark on a PhD study. Her guidance illuminated the path for me, and Magnus Falk played a pivotal role in opening the door to an extraordinary journey through my own PhD trajectory, always leading toward expanded knowledge and enriched experiences.

INTRODUCTION

Background

The increasing incidence of skin cancer in Sweden has become a major concern within healthcare and for those affected. In 2022, more than 5,200 individuals were diagnosed with malignant melanoma (MM), the most serious form of skin cancer, a figure which has steadily increased over the past several decades (1). Additionally, approximately 9,000 new cases of squamous cell carcinoma (SCC) are now diagnosed annually, nearly double the number from ten years ago (2).

In addition, at least 50,000–70,000 cases of basal cell carcinoma (BCC) are detected in Sweden each year (3), along with an innumerable number of potential precursors to skin cancer in the form of actinic keratoses (AK).

With this increase in incidence and heightened awareness among the population about the risk of developing skin cancer, it is not surprising that the number of patients seeking primary care for assessment of skin lesions has also significantly increased. Consequently, the number of referrals to dermatology clinics has naturally increased at a similar rate. Skin cancer constitutes a significant burden of care for our health care system, a burden which shows no signs of decreasing (4).

Skin cancer

Malignant melanoma (MM) is the most serious form of skin cancer, where early detection is crucial to prevent metastasis and advanced disease. The most common location is the trunk for men and the extremities for women (5). The prognosis has improved over the years, likely due to increased awareness leading to earlier detection. More recently significant improvements in the prognosis of metastatic disease have been made thanks to new oncological therapies (6).

Treatment for MM is always surgical, with possible subsequent wide excision depending on histopathological thickness (Breslow). For the more slowly developing and less aggressive in situ form, lentigo maligna, alternative treatments may be considered such as Bucky/Grenz rays (7).

Squamous cell carcinoma (SCC) is another form of skin cancer that can metastasize, but it is usually less aggressive in that regard compared to

MM. However, poorly differentiated forms can metastasize more rapidly, particularly in certain locations such as the lips. Transplant patients, for whom the use of systemic immunosuppression is necessary, often experience an increasing frequency of SCC in the skin after a few years (8,9).

Survival rates for SCC are good, although worse in immunosuppressed subjects. Treatment is usually surgical, however, for the condition's in situ form (is-SCC or Bowen's disease), there are various alternative treatment options depending on the location and size (10). SCC often arises in sun-damaged areas of the skin, where multiple AKs are simultaneously present. Areas of pronounced sun damage are termed "field cancerization" (11).

Basal cell carcinoma (BCC) is the most common form of skin cancer. It is locally destructive but typically does not metastasize. In Sweden, BCCs are registered since 2003 in the Swedish BCC Registry. BCC is a tumour type that often lends itself to treatments other than conventional excisional surgery (3).

Risk Factors for Skin Cancer

The sun plays a major role in the development of MM, SCC, and BCC. Hereditary factors steer individual susceptibility, particularly through variable sensitivity to erythema and ability to form pigment (the factors behind the classical Fitzpatrick skin type). The sun's ultraviolet (UV) radiation causes damage to the cells' genetic material in the process of carcinogenesis which can eventually result in cancer (12,13). It is known that the risk of MM increases in people who have been exposed to many sunburns (14). Cumulative UV is important for SCC and BCC (15,16).

It is considered particularly risky to get UV exposure and particularly sunburns as a child and young person, since the skin of a growing person is considered more vulnerable than that of an adult (17).

Tanning in tanning beds can also contribute to an increased risk of skin cancer. The Swedish Radiation Safety Authority generally advises against tanning beds, and since September 2018 there has in Sweden been a law prohibiting use under the age of 18 (18).

Most people have moles, also known as nevi, in their skin. People with unusually many or large moles are at increased risk of developing MM (19). They should therefore be extra careful to monitor changes and protect their skin in the sun. UV overexposure during childhood is known to increase the number of naevi which develop(17).

Over and above the mentioned factors influencing risk for skin cancer, impaired immune function, particularly through use of immunomodulating therapy, e.g. for inflammatory disease or solid organ transplantation, increases risk markedly (20,21). Solid-organ transplanted patients, such as those with heart, lung and kidney transplants, are at specifically increased risk of developing malignancies, including skin cancer and, especially, SCC, due to immunosuppression (22-27).

Actinic Keratosis (AK)

AK is a common skin condition caused by long-term exposure to the sun in susceptible individuals. It typically develops on sun-exposed areas, such as the face, neck, balding scalp, chest, shoulders, and the backs of the arms and hands, mainly in caucasian adults (27-33), presenting as a rough, dry, scaly or crusted lesion which can be skin-coloured or tanned, sometimes with an erythematous base. Clinically, AK is sometimes difficult to differentiate from other benign skin conditions, such as lichenoid keratosis and other benign keratotic lesions (34,35). AKs are often asymptomatic but can sometimes be sore or itchy (30,36).

The diagnosis of AK is, in practice, often set clinically, based on its typical appearances, without histopathological confirmation, and the condition is therefore not systematically recorded in pathology databases to allow for reliable interpretation (29,36). Data about the prevalence of AK are thus relatively sparse, and originate mostly from Australia and the USA, with only a few studies available from Europe and Asia and no information from Africa and South America (37,38).

On the one hand, as is the case for most lesions, a single AK lesion may be completely harmless, with only cosmetic consequences for patients. On the other hand, however, the potential for malignant transformation is well documented, AKs are the most common precursor of invasive SCC (39). Any single AK lesion may have 1 of 3 possible outcomes: it can enter spontaneous remission; remain stable without further progression; or transform over time into in situ or invasive SCC (28,30,40).

The reported risk of malignant progression of AK is widely variable. A systematic review found that the estimated risk of a single AK lesion becoming malignant ranged between 0.075% and 0.096% per year, or approximately 1% over 10 years, with some estimates as high as 10% over 10 years (28). In another review, the risk of progression of AK to invasive SCC varied between 0.025% and 16% per year (40). AK, and non-melanoma skin cancer (NMSC), are both also risk factors for the development of MM; a

study in Italy (41) has shown that more than 40% of patients with a previous diagnosis of multiple AKs developed a NMSC or a MM during a follow-up period of 5–11 years.

The risk of SCC has been found to increase for those with more than 5 AKs, and the majority of SCCs arise from AKs (28). AKs on sun-exposed body surfaces indicate previous chronic exposure to UV radiation, and may, together with other factors, such as age, duration, and skin type, be sufficient to facilitate malignant reformation. Just as for BCC and SCC, the prevalence of AK is typically higher in sun-intense geographical regions, but the specific pathogenic factors associated with the progression of AK to SCC are not clear (42).

Although the most common reason for treatment of AK is prevention of malignancy, lesions are also treated for cosmetic purposes and to provide relief from symptoms, such as tenderness or itch (29), and can either be lesion directed, such as curettage and cryotherapy, or field directed, using a variety of topical, pharmacological treatments and photodynamic therapy (PDT) (30,36,43). Some national guidelines or consensus reports recommend treatment of AK, and subsequent clinical follow-up of treated patients, due to its malignant potential (44,45), whereas others are less dogmatic (46). Routine obligatory treatment of AK would entail a substantial burden on general practitioners and on dermatological specialist care, which, in many cases, is already strained by the diagnostic process and care of an increasing number of cutaneous malignancies (29).

Skin cancer prevention

Increasing skin cancer incidence is associated with substantial patient suffering and healthcare costs worldwide (47-51), emphasising the necessity of preventive measures directed towards the disease. The role and effectiveness of interventions to promote sun avoidance and protection in order to prevent skin cancer have been studied and debated during recent decades. Studied interventions range from local educational or informational efforts directed at defined target groups to broad, national government initiated campaigns, and include a variety of methodological and informational approaches (ranging from brief, written information sheets to personalised face-to-face mediated advice).

Interventions have been reported to have had varying success (52-55), but based on systematic reviews, there is a consensus that educational measures to increase sun protection are both effective and worthwhile, at

least when directed at younger individuals who are at the highest risk of establishing a future lifetime risk for skin cancer (53-55).

A complicating factor in this respect is the difficulty of demonstrating not only the effect of interventions to reduce UV exposure but also, in the longer term, the effect on skin cancer incidence (52-54). Instead, present knowledge relies on the reasoning that if sun protection advice is proven to lead to increased sun protection, and increased sun protection per se is known to be associated with a reduction in risk for developing skin cancer (56-58), it is likely that measures efficient in promoting sun protection will also reduce the likelihood of developing skin cancer in the future. In most studies, however, follow-up intervals are short (52-55), making conclusions on sustainability of any observed behavioural change difficult to draw. Additionally, since the main negative effects of UV radiation (such as skin cancer) derive from long-term exposure, any behaviour change in a favourable direction would need to be maintained over a longer period of time to have effect.

Another issue is the balance between beneficial and harmful effects of UV radiation. Lately, increasing attention has been directed towards vitamin-D deficiency, and since UV exposure (in moderation) may also have other beneficial effects, with regard to the individual's whole health perspective, not all individuals would necessarily gain from reducing sun exposure (20-22). Variations in intensity of UV radiation, according to geographic location and latitude, and fluctuation between seasons need to be considered. Therefore, if undertaken by healthcare providers, there is a reliance on the performing physician to balance the content of the advice given and to direct it towards those most likely to gain from it. This demands adequate consideration of the patient's integrated health state and history, a task often undertaken by the GP.

The objective of prevention and control is to minimize disease-related mortality and morbidity by lowering incidence, enhancing early detection, delaying onset and disability, and/or enhancing health-related quality of life.

Decreasing the burden of skin cancer through prevention and control strategies necessitates an understanding of its natural progression and risk factors. Health promotion and primary prevention strategies are viable when risk factors are well-established. These strategies primarily target modifiable risk factors, such as minimizing UV radiation exposure through physical, topical, or systemic protection. Interventions may include educational, behavioural, environmental and/or multicomponent approaches (58).

Secondary prevention involves screening for skin cancer and chemoprevention. However, there is a lack of consensus on skin cancer screening

recommendations. Noninvasive imaging modalities, such as dermoscopy and total body photography (TBP), are advised for selectively screening high-risk patients. Recommendations regarding the chemoprevention of skin cancer are limited, with acitretin being favoured in solid organ transplant recipients (SOTRs)(60-61). Nicotinamide has given mixed results in studies on patients with varying risk for skin cancer (62,63).

It is essential to identify predictive factors that can help determine the likelihood of AKs developing into skin cancer (28). Male gender, older age, light skin pigmentation status, severe baldness, skin wrinkling and a high tendency for sunburn were significantly associated with extensive actinic damage, especially, bald males who were at an increased risk of severe actinic skin damage on the head. The prevalence of AK is very high, especially among elderly bald males (29).

A broadened understanding of predictive or enhancing factors for skin cancer development can be of value for clinical management and medical decisions in AK patients. High-risk patients may require closer surveillance, more aggressive treatment, or targeted therapies to prevent or detect skin cancer at an early stage. Additionally, these predictive factors can support and individualize patient education, promoting sun-protective behaviours and regular skin examinations.

How this fits in

The principle "prevention is better than cure" emphasizes the effectiveness of stopping problems before they arise, particularly in primary healthcare (PHC). This concept is fundamental in PHC practice, where treatment of an actual medical condition must not be allowed to overshadow the provision of preventive care. Effective strategies such as vaccinations, screenings, health education and lifestyle interventions are utilized to prevent diseases and promote overall health. Ultimately, this principle guides PHC efforts to improve population health, enhance quality of life, and reduce healthcare costs associated with treating preventable diseases.

However, it is essential that the actual effects of preventive measures, on disease outcomes, are sufficiently evaluated, so that healthcare resources are not used for purposes originating from good intention, but in practice making no or little difference. Considering the increasing incidence of skin cancer, research on prevention and early detection measures to counteract the increase, or health effects of the increase, is important, not least

from a PHC perspective, where the great majority of patients are primarily managed. This includes the identification of individuals who are at particular risk of developing skin cancer, among whom patients with AK emerge as an identifiable and potentially important category.

AIMS OF THE THESIS

General aim

The overall aim of this thesis was to investigate factors of importance for the performance of individualised skin cancer prevention, with specific emphasis on actinic keratosis as a risk factor, and from a primary care perspective.

Specific aims

The main aims of the individual papers of the thesis were the following:

I. To study the long-term effect of individualised sun protection advice given in primary health care (PHC), on sun habits and sun protection behaviour **(Paper I)**.

II. To investigate, in a cohort of patients with a diagnosis of AK the relative risk of developing skin cancer during a follow-up period of 10 years **(Paper II)**.

III. To explore possible associations between other sun related conditions and common comorbidities, and the risk of developing skin cancer, in individuals with AK, during ten years of follow-up **(Paper III)**.

IV. To explore possible clinical characteristics in individuals diagnosed with AK, and association with an increased risk of developing skin cancer later in life. **(Paper IV)**.

METHOD

Paper I:

The study commenced in 2005 as a randomized controlled trial (**Figure 1**) (64,65), with all patients aged 18 years and above visiting a PHC centre in Linkoping, Sweden, during three weeks in February considered as the baseline. At this time, patients received written study information, consent forms, and questionnaires, regardless of the purpose of their visit. Exclusion criteria included abnormal UV sensitivity, use of UV-sensitizing medication, and cognitive impairment/inability to provide informed consent.

Following inclusion, participants were randomly allocated to one of three study groups. Group 1 received individualized sun protection advice via letter, including personalized risk assessment and advice based on questionnaire responses. Groups 2 and 3 received verbal advice through a personal GP consultation, with Group 3 also undergoing a phototest to assess UV sensitivity (66,67). Phototest results were reported by participants, and adjusted sun protection advice was provided based on the outcomes (68-71). The sample size for each group aimed for was n = 100, considering possible dropouts, based on previous studies with similar measures.

The questionnaire

The questionnaire comprised three main sections:

a) Sun habits and sun protection behaviour assessed using 5-point Likert scales (e.g., never/seldom/sometimes/often/always).

b) Propensity to increase sun protection, based on the Transtheoretical Model of Behavior Change (TTM), which categorizes individuals into one of five stages: pre-contemplation, contemplation, preparation, action, or maintenance. Four behavioural items were explored: giving up sunbathing, using clothes for sun protection, applying sunscreen, and seeking shade during midday. Stage-of-change scores ranged from 1 to 5, reflecting a declining propensity to increase protection.

c) Attitudes towards sunbathing, also measured using Likert scales. Likert scale responses, previously validated for sun habits and attitudes towards sunbathing, were scored from 1 to 5, indicating increasingly risky behaviour or attitude (e.g., positive attitude towards sun exposure) (72,73).

Demographic data collected included age, sex, educational level, skin type according to Fitzpatrick's classification (74), and personal or family history of skin cancer.

Sun Exposure and Protection Index (SEPI)

SEPI is a validated scoring instrument for the assessment of sun habits and sun protection behaviour. It consists of two parts; part I addressing the present behaviour, and part II addressing propensity to increase sun protection.

Eight of the questions in the questionnaire that the study participants filled in, which are related to sun habits and sun protection behaviour, were very similar to those later included in the SEPI questionnaire (75), covering intentional tanning, vacationing at sunny resorts, sunscreen use, wearing long-sleeved shirts or sweaters, using sun hats, experiencing sunburn, spending time in midday sun, and staying in the shade. The SEPI scores sun exposure habits from 0 to 32 points, indicating increasing UV risk exposure. During analysis, responses to these eight questions were combined into a cumulative score closely identical to the SEPI score.

Follow-up

The intervention's effects, measured in terms of changes in self-reported sun protection behaviour, propensity to increase sun protection (primary outcome), and attitudes towards sunbathing (secondary outcome), were evaluated at 6 months and 3 years after baseline using repeated postal questionnaires, as reported in previous studies (64,65). In the present study, the questionnaire was repeated 10 years after baseline, also via post. Additionally, responses were assessed with regard to SEPI scores at both the 3- and 10-year follow-up points.

Statistical analyses

Changes in questionnaire responses between baseline, 3 years, and 10 years were evaluated using a linear model of longitudinal data. Restricted maximum likelihood estimation of variance components was employed to handle the unbalanced data. Response outcomes in four domains (sun habits, propensity to increase sun protection, attitudes towards sun exposure, and SEPI) were analyzed separately. Each model included time

(baseline, 3 years, and 10 years), intervention group (Groups 1, 2, and 3), and the interaction between time and intervention group as fixed factors.

The covariance parameters of the repeated effects (time) were estimated using an unstructured method based on the information criteria of the models. Additional contrast analyses on change between time points were conducted to assess differences in change between the intervention groups. Statistical significance was set at $p < 0.05$, and Šidak correction was applied to control for familywise error rates in multiple comparisons. IBM SPSS Statistics for Windows (version 23.0) was used for all analyses.

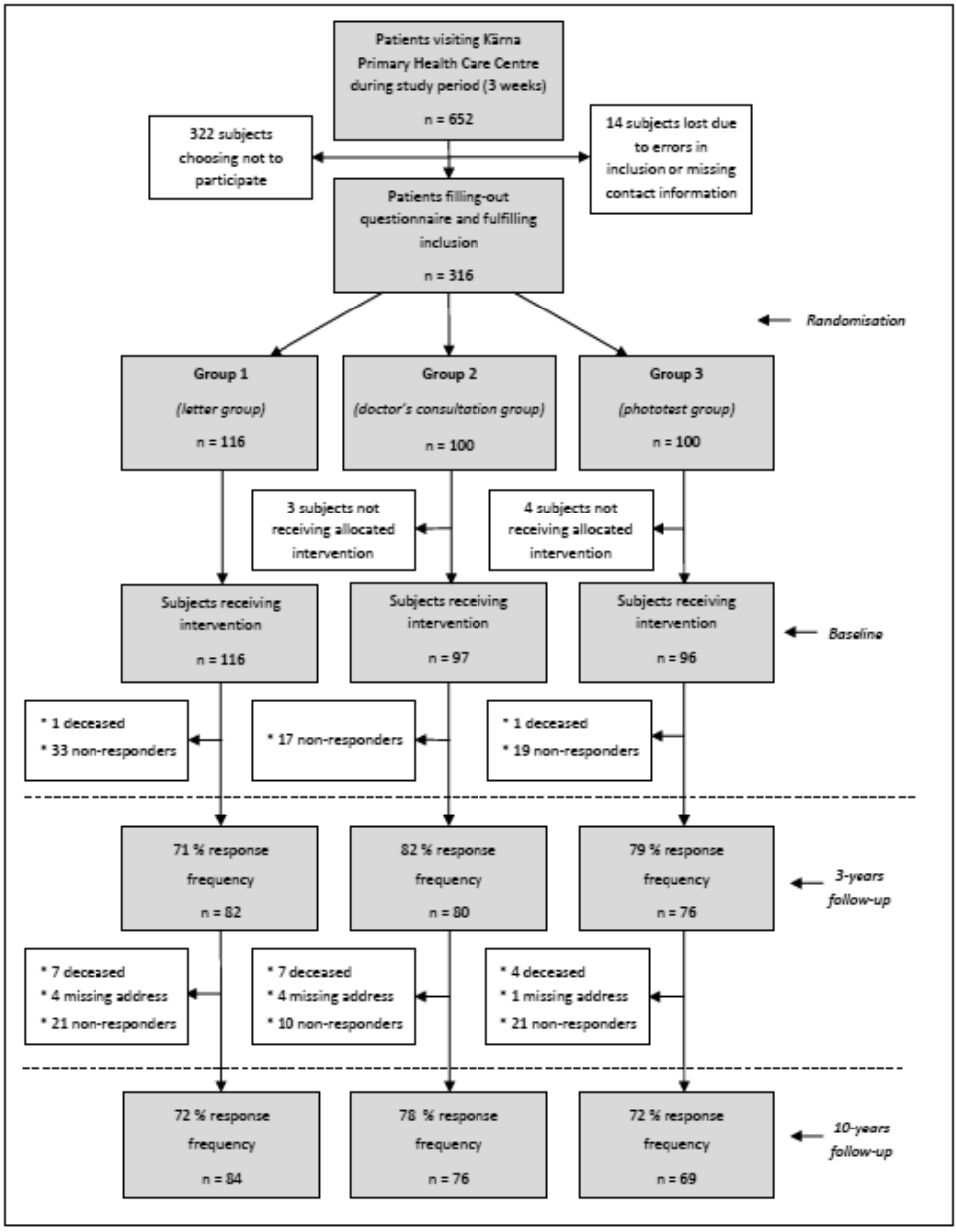

Figure 1. Distribution of study participants in the three intervention groups, and response frequencies at baseline, at 3-year, and at 10-year follow-up. The percentages given at 3 and 10 years describe the proportional response rate with regard to baseline.

Paper II:

The study was conducted as a registry-based cohort study in Östergötland County, southeastern Sweden, with a population of approximately 453,600 inhabitants in 2017. Utilizing the Care Data Warehouse in Östergötland (CDWÖ), an administrative healthcare registry capturing over 95% of healthcare utilization since 1998, patients aged 18 years or older diagnosed with AK between January 2000 and December 2004 were identified. The date of AK diagnosis marked the index date. Exclusions were made for patients with prior skin cancer diagnoses (melanoma, SCC, or BCC) recorded in the National Swedish Cancer Register. A control cohort, consisting of up to 5 individuals without AK during the same period, was matched by age, sex, and index year. Follow-up extended from baseline to 2014, using data from the Cancer Register to identify subsequent diagnoses of MM, SCC, or BCC. Participants were monitored from their index date until cancer diagnosis, loss to follow-up, death, or the study's end in 2014, with events of skin cancer recorded for each cohort (see **Figure 2**).

Eligible study individuals consisted of 3,422 individuals in the AK cohort and 17,110 individuals in the non-AK control cohort. A history of prior skin cancer was an exclusion criterion. In the AK cohort, 439 individuals (12.8%) were excluded, whereas only 332 (1%) individuals were excluded from the control cohort. After the exclusion of individuals with a previous history of skin cancer the AK cohort comprised 2,983 patients and the control cohort comprised 16,778 individuals. If an AK patient was excluded due to previous skin cancer, its identified matched controls were also excluded, unless they matched another AK patient with fewer than 5 identified controls (85 of 2,110 excluded controls were re-matched to the AK cohort). In the analysable material, 2,983 individuals remained in the AK group and 14,668 in the control group (see **Figure 2**).

Statistical analysis

Categorical data were analyzed using a $\chi 2$ test, while continuous data were analyzed using an independent t-test. The Kaplan–Meier method was employed to estimate cumulative incidence rates for different endpoints (1: all skin cancers; 2: SCC; 3: BCC and 4: MM) in both patients and controls. Multivariable Cox regression was conducted to determine HR and corresponding 95% confidence intervals (95% CI) for the listed endpoints, adjusting for age and sex. Additionally, sex- and age-specific HRs were calculated to examine potential variations in HRs between patients and controls

based on sex and age, with p-values for the interaction presented. All Cox models were adjusted for age and sex.

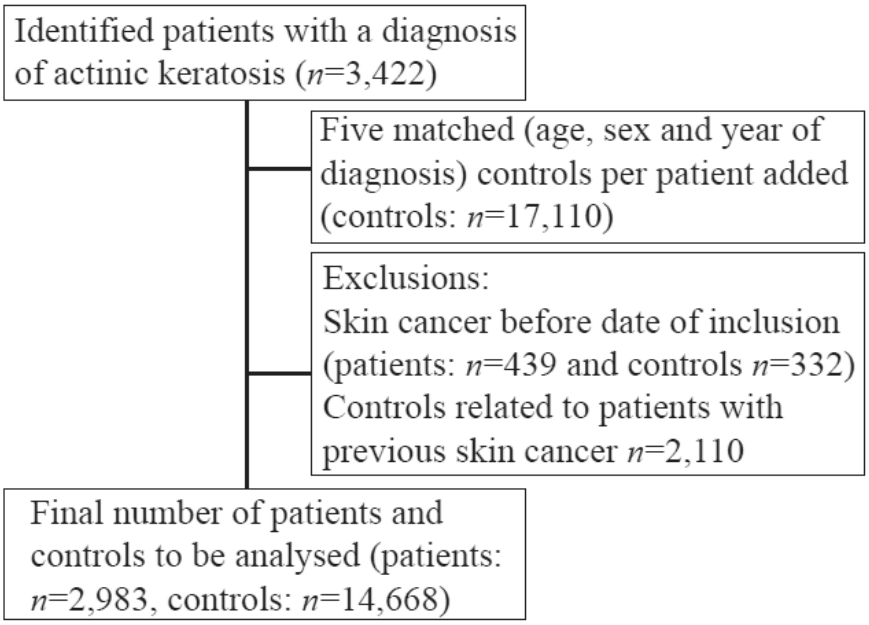

Figure 2. Flow chart of the distribution of study participants, by means of patients with actinic keratosis and matched controls.

Paper III

In this registry-based cohort study, we utilized the same cohorts analyzed in paperII (see **Figure 2**). However, in addition to AK and skin cancer diagnoses, we also extracted information on a selection of various, relevant comorbidities potentially associated with sunlight exposure and/or skin cancer risk. For example, conditions with a known aetiological association with UV exposure such as cataract, age-related diseases such as macular degeneration, and those in some way influenced by sun exposure such as eczema. Other disease groups studied encompassed autoimmune, neurological, endocrine, respiratory, deficiency, and immune system impairment conditions. Solid organ transplantation-related diagnoses were excluded due to coding complexities and the established association with subsequent skin cancer risk. Cases recorded before or after the follow-up period were not considered in the analysis.

Statistical analysis

Since it is important to acknowledge that comorbidities may arise at various points during the follow-up period, we employed a Cox model with time-varying covariates. This method considers individuals as unexposed until they receive a specific diagnosis, at which point they are considered exposed in the analysis. By doing so, we account for when patients received their diagnoses in our analyses. The follow-up period for assessing outcomes such as death, skin cancer, and comorbidities was consistent for both case and control groups, extending until December 31, 2014.

In the model, the exposure to a specific comorbidity was set to "0" at the index date and changed to "1" if a diagnosis occurred within the follow-up period. HRs with 95% CIs were utilized as risk measures. We examined three different outcomes/events: 1) all skin cancers, 2) keratinocyte skin cancers (KSC), and 3) MM. Separate models were applied for patients and controls, with censoring applied in the event of patient death or at the end of follow-up.

Paper IV

The study employed a case-control design, utilizing the AK cohort from paper II but excluding individuals diagnosed with AK before the year 2000. This resulted in 2,357 patients diagnosed with AK between 2000 and 2004. Follow-up data until 2014, obtained from the CDWÖ, was used to identify skin cancer diagnoses (MM, SCC, or BCC). Each participant was observed from the index date until the occurrence of skin cancer, loss to follow-up, death, or the study's end in 2014.

Of the 2,357 patients, 810 developed skin cancer during follow-up, with 1,547 remaining skin cancer-free. After excluding those diagnosed with skin cancer within five years of AK diagnosis, 297 patients developed skin cancer, leaving 1,313 without skin cancer. From this cohort, 200 cases and 200 controls were randomly selected, Dropouts due to missing charts or incorrect diagnoses occurred in 5 cases and 18 controls, resulting in 195 patients eligible for chart review in the case cohort and 182 in the control cohort. The total follow-up interval for each person in both cohorts ranged from 5 to 14 years.

Retrospective chart reviews were conducted for each individual's healthcare visit when AK was diagnosed. Data extracted included age at diagnosis, gender, AK locations, number and size of lesions, and clinical

management decisions. Adjustments were made for lesion categorizations, such as grouping multiple lesions as five and defining small lesion size as 3 mm in diameter. For lesions described in coin sizes, the known diameter of the specific coin mentioned was applied as lesion diameter. Medical records were pseudonymized during the review to protect participant privacy.

Statistical analysis

We conducted binary logistic regression analysis to compute Odds ratios for the various lesion characteristics, and for the different lesion managements decided on by the physician.

Ethical considerations (Paper I-IV)

Paper I is an intervention study, aiming to explore possible differences in intervention effect between the different study groups. As such, a fundamental risk in all intervention studies is that the intervention does more harm than good. In our study, we considered the risk of potential harm (e.g. participants with a high skin cancer risk profile would become less precautious in the sun), and the potential benefits in terms of increased scientific knowledge to outweigh this risk. The study was approved by the Regional Ethical Review Board in Linkoping (Dnr. 2014/468-31), and all participants filled in a consent form and were clearly informed that they could withdraw from the study at any time.

Papers II, III were purely registry-based studies, for which informed consent was not asked for from the participants. All research data were at outtake pseudonymized to the researchers to minimize infringement of personal integrity, as approved by the Regional Ethics Review Board in Linköping, Sweden (no. 2015/182-31).

Paper IV was based on a random selection of participants in the study cohorts in paper II. Since it comprises a review of individual charts from the patient records, although pseudonymized, there is a natural higher level of intrusion in personal integrity. In the original ethical application (the same as for papers II-III), the intention was to obtain written informed consent from the participants. However, since we reconsidered there to be a significant risk of selection bias and unwanted drop-outs, we applied for a change of procedure, in which we did not inform the participants. This change was approved by the Regional Ethics Review Board in Linköping (Dnr 2022-00959-02) prior to study start.

RESULTS

Paper I

Of the 316 participants included at baseline, 238 (77%) and 229 (74%) responded to the follow-up questionnaire at 3 and 10 years, respectively (see **Figure 1***)*

Sun habits and sun protection Behaviour

In **Figure 3**, the predicted mean response outcomes with 95% CI, for the questions regarding sun habits and sun protection behaviour, at baseline and follow-up, are presented.

For all questions, a declining mean score, corresponding to decreasing UV risk exposure, over time could be seen, independent of the group.

The most salient between-group differences at follow-up were seen for 'sunscreen use' and 'use of clothes for protection ', where the doctor's consultation group (Group 2) responses were on average lower (implying less risk) compared to the letter group (Group 1).

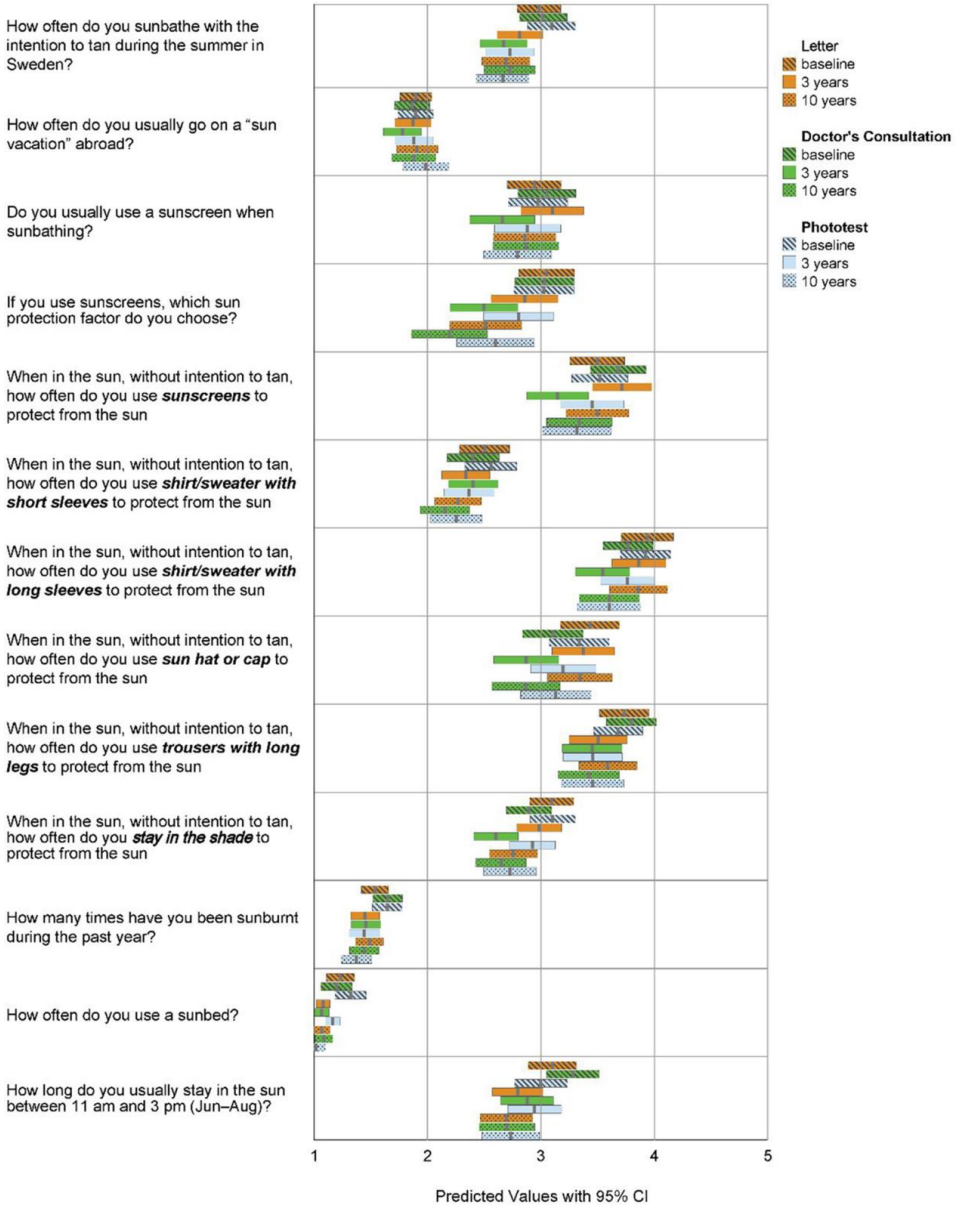

Figure 3: Predicted mean response values with 95% CI on each of the questions regarding sun habits and sun protection behaviour, at baseline and at 3- and 10-year follow-up, in each of the three intervention groups

To further explore the reported change of behaviour from baseline to follow-up, ***Table 1*** shows the mean changes of score between the three measurement occasions, and the P value according to the overall effect of time, group and a combination of both. Statistically significant decreases in sun exposure score were observed within several behaviour aspects, such as intentional tanning and sunscreen use, both at 3 and 10 years compared to baseline. However, none of these changes was found to be group dependent, rather indicating an effect of time.

	Model results											
	Change in estimated marginal means									Tests of fixed effects, *P* value		
	Letter			Doctor's consultation			Phototest					
	A	B	C	A	B	C	A	B	C	Time	Group	Time x Group
Sun habits/sun protection behaviour												
How often do you sunbathe with the intention to tan during the summer in Sweden?	-0.17	-0.12	-0.29[a]	-0.35[b]	0.06	-0.30[a]	-0.37[b]	-0.06	-0.43[b]	<0.001	0.979	0.402
How often do you usually go on a 'sun vacation' abroad?	-0.02	0.04	0.01	-0.09	0.10	0.01	-0.01	0.10	0.09	0.220	0.748	0.897
Do you usually use a sunscreen when sunbathing?	0.16	-0.24	-0.08	-0.39[a]	0.21	-0.18	-0.09	-0.09	-0.18	0.125	0.787	0.032
If you use sunscreens, which sun protection factor do you choose?	-0.19	-0.34	-0.54[a]	-0.54[a]	-0.30	-0.84[b]	-0.23	-0.20	-0.43	<0.001	0.281	0.371
When in the sun, without intention to tan, how often do you use any of the following ways to protect from the sun:												
(a) sunscreens	0.22	-0.22	0.00	-0.53[b]	0.19	-0.34	-0.07	-0.14	-0.20	0.093	0.457	0.004
(b) shirt or sweater with short sleeves	-0.16	-0.07	-0.23	0.00	-0.25	-0.25	-0.19	-0.12	-0.31	0.009	0.805	0.708
(c) shirt or sweater with long sleeves	-0.08	-0.00	-0.08	-0.22	0.06	-0.17	-0.16	-0.16	-0.32	0.018	0.199	0.654
(d) sun hat or cap	-0.06	-0.03	-0.09	-0.24	-0.00	-0.24	-0.14	-0.06	-0.21	0.068	0.038	0.890
(e) trousers with long legs	-0.23	0.09	-0.14	-0.35[a]	-0.03	-0.38[a]	-0.22	-0.00	-0.23	<0.001	0.864	0.677
(f) staying in the shade	-0.11	-0.23	-0.34[a]	-0.29[c]	0.04	-0.25	-0.18	-0.20	-0.38[a]	<0.001	0.111	0.384
How many times have you been sunburnt during the past year?	-0.09	0.04	-0.05	-0.19[c]	-0.02	-0.21	-0.20[c]	-0.07	-0.27[a]	<0.001	0.907	0.291
How often do you use a sunbed?	-0.15[c]	-0.01	-0.17	-0.13	0.02	-0.11	-0.16[c]	-0.15[a]	-0.31[b]	<0.001	0.542	0.109
How long do you usually stay in the sun between 11am and 3pm (Jun–Aug)?	-0.30[c]	-0.10	-0.40[a]	-0.40[a]	-0.18	-0.58[b]	-0.06	-0.21	-0.27	<0.001	0.791	0.222
Propensity to increase sun protection												
Giving up sunbathing	-0.47[a]	-0.17	-0.65[b]	-0.63[b]	-0.03	-0.66[b]	-0.49[a]	-0.24	-0.76[b]	<0.001	0.510	0.909
Using clothes for sun protection	-0.22	0.04	-0.17	-0.26	0.08	-0.18	-0.29	-0.07	-0.35	0.006	0.199	0.925
Using sunscreens	-0.07	0.03	-0.05	-0.32	0.28	-0.04	-0.09	0.04	-0.05	0.131	0.557	0.658
Staying in the shade	-0.34[c]	0.76[b]	0.42[a]	-0.74[b]	0.93[b]	0.19	-0.22	0.82[b]	0.60[b]	<0.001	0.626	0.073
Attitudes towards sun exposure												
How do you like sunbathing?	-0.11	-0.18	-0.29[a]	-0.10	-0.00	-0.10	0.03	-0.11	-0.08	0.015	0.279	0.333
Do you think that the advantages of sunbathing outweigh the disadvantages?	-0.29[c]	-0.15	-0.44[b]	-0.29	0.14	-0.15	-0.04	-0.22	-0.26	<0.001	0.885	0.139
How extensive do you consider the health risks of sunbathing?	-0.06	-0.14	-0.20	-0.35[a]	0.19	-0.16	0.08	-0.05	-0.03	0.079	0.895	0.028
How extensive do you consider the risk for you to develop skin cancer?	-0.11	-0.02	-0.14	-0.07	0.00	-0.06	0.00	-0.19	-0.19	0.034	0.329	0.531
How important is it for you to get tanned during the summer?	-0.08	-0.11	-0.18[c]	0.01	-0.14	-0.13	-0.15	-0.13	-0.28[a]	<0.001	0.077	0.542
SEPI score	-0.45	-0.37	-0.82	-2.20[b]	0.15	-2.04[b]	-1.20[a]	-0.83	-2.04[b]	<0.001	0.312	0.005

[a]*P*<0.01. [b]*P*<0.001. [c]*P*<0.05.
A – change baseline to 3 years. B – change 3 to 10 years. C – change baseline to 10 years.
A negative value indicates change towards lowered risk behaviour, increased propensity to change behaviour, and lowered risk attitude, respectively.
Sidák adjustment for multiple comparisons.

Table 1. Mean changes of score between the three follow-up occasions (baseline, 3 years, and 10 years), regarding sun habits and sun protection behaviour, and the statistical significance according to the overall effect of time, group, and a combination of both

Propensity to increase sun protection

Figure 4 A shows the predicted mean response outcome with its 95% CI for each of the four questions regarding readiness to increase sun protection. The time-dependent pattern of declining mean score observed in **Figure 3**, for sun habits, was not as obvious in this case, except for the 'giving up sunbathing' item. Again, however, a difference especially between the doctor's consultation group (Group 2) and the letter group (Group 1) responses at follow-up were seen for all four questions. As seen in ***Table 1***, all statistically significant changes in the propensity-to-change score noted appeared to be dependent on time, with no significant group-dependent changes found.

Attitudes towards sun exposure

Figure 4B shows the predicted mean response outcome with its 95% CI for the questions concerning attitudes towards sun exposure. A slight tendency towards a less positive attitude to sun exposure could be seen over time, but between-group differences were smaller. As illustrated in ***Table 1***, observed changes in attitude were shown to be time dependent.

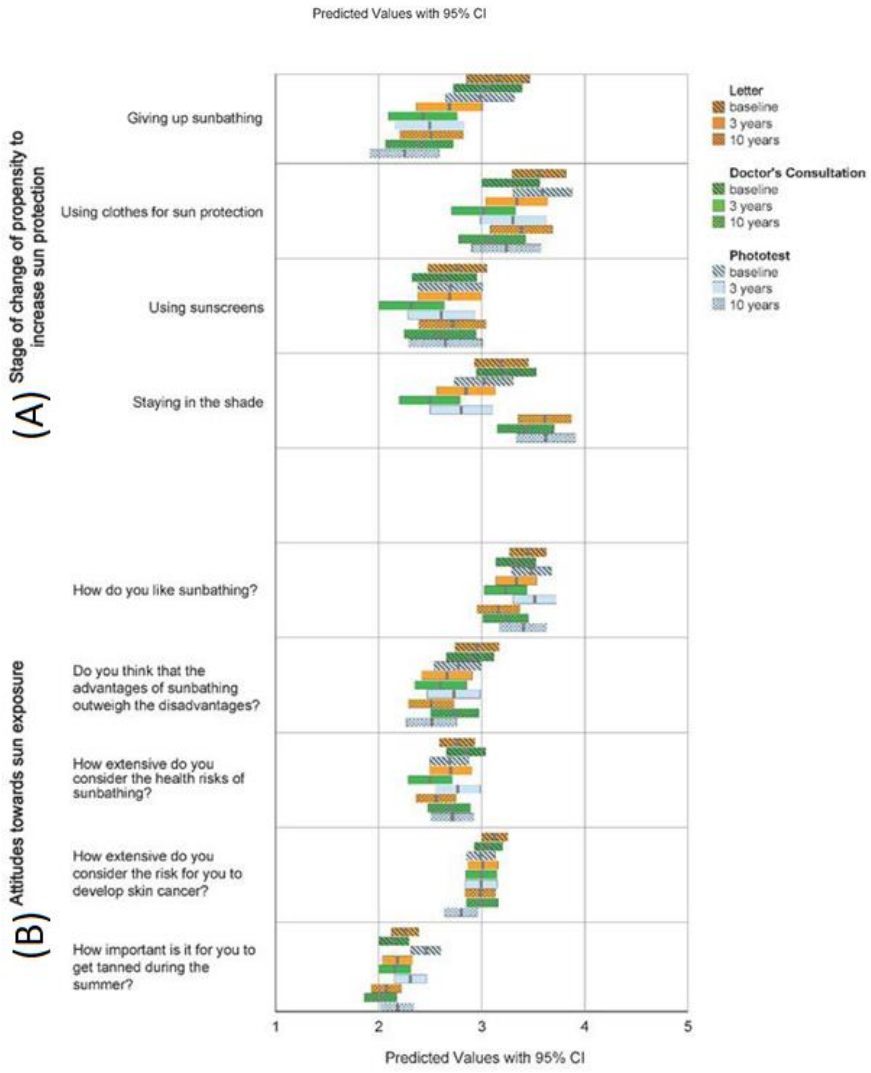

Figure 4: Predicted mean response values with 95% CI for each of the questions addressing stage of change of propensity to increase sun protection **(A),** and the questions regarding attitudes towards sun exposure **(B),** at baseline and at 3 and 10 years follow-up, in each of the three intervention groups.

SEPI

The results of accumulated question responses added together in a comprehensive score, following the contents of SEPI, are shown in **Figure 5**. A greater decrease in score for Groups 2 and 3 was seen at both 3 and 10 years. Whereas no significant change in SEPI score could be detected in Group 1, the scores in Groups 2 and 3 decreased by around 2.0 in mean score (***Table 1***). Even after accounting for the effect of time, a significant group-dependent effect could be demonstrated.

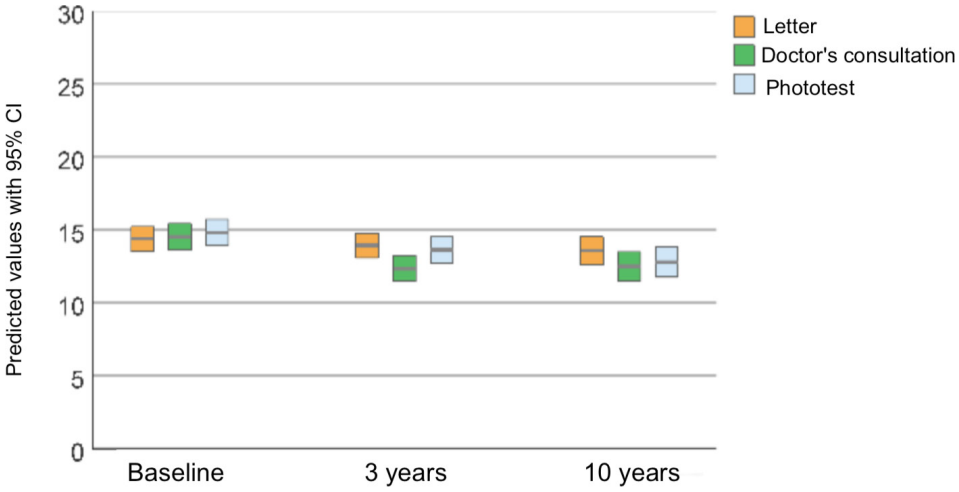

Figure 5: Predicted mean Sun Exposure and Protection Index (SEPI) score with 95% CI, at baseline and at 3- and 10-year follow-up, in each of the three intervention groups

Paper II

The median follow-up time in the study cohort was 10.6 years (range 0.1–14.99 years). Follow-up was stopped if the person had an event. Consequently, if there were fewer events in a group, then the follow-up time would be longer in that group. Patients in the AK cohort were thus followed for a shorter time compared with the control cohort; 9.6 (0.1–14.99) and 10.7 (0.1–14.99) years, respectively.

The characteristics of the study cohort of patients with AK and the matched controls are shown in ***Table 2***. There was a somewhat greater proportion of women (56.3%), and a higher representation of individuals within the age interval 70–79 years, representing 55.9% of our population.

The lack of statistically significant differences between the 2 groups regarding sex, age and year of inclusion confirmed that the controls were successfully matched to the patients.

	Patients	Controls	*p*-value
All patients, *n* (%)	2,983 (100)	14,668 (100)	
Sex, *n* (%)			0.97
Men	1,304 (43.7)	6,417 (43.7)	
Women	1,679 (56.3)	8,251 (56.3)	
Age, *n* (%)			0.95
< 60 years	618 (20.7)	3,071 (20.9)	
60–69 years	697 (23.4)	3,449 (23.5)	
70–79 years	926 (31.0)	4,576 (31.2)	
≥ 80 years	742 (24.9)	3,572 (24.4)	
Age, mean (SD)	70.0 (12.5)	69.8 (12.4)	0.55
Year of inclusion, *n* (%)			1.00
2000	731 (24.5)	3,607 (24.6)	
2001	715 (24.0)	3,527 (24.0)	
2002	529 (17.7)	2,592 (17.7)	
2003	516 (17.3)	2,517 (17.2)	
2004	492 (16.5)	2,425 (16.5)	
Controls per patient, *n* (%)			–
≤ 3	101 (1.3)	–	
4	160 (5.4)	–	
5	2785 (93.4)	–	
Number of controls, mean (SD)	4.92 (0.34)	–	–

SD: standard deviation.

Table 2. Characteristics of the patients in the actinic keratosis cohort and the control cohort.

Table 3 shows the cumulative incidences of SCC, BCC and CMM in the 2 cohorts, and also the HR for each diagnosis. As seen, the AK cohort had a higher risk for all 3 cancer forms than did the control cohort. Patients with AK had 5.1 (95% CI: 4.7–5.6) times higher risk of developing some form of skin cancer within 10 years compared with the control group, i.e. individuals without AK. The difference was significant for all types of skin cancer, but most pronounced for SCC.

	Patients/controls *n*	Events *n* (%)	Hazard ratio (95% CI)	*p*-value	Cumulative incidence (95% CI) 5-year	10-year
Skin cancer[a]*						
Patients	2,983	1,007 (33.8)	5.1 (4.7–5.6)	<0.0001	19 (18–21)	33 (31–35)
Controls	14,668	1,062 (7.2)	1.0 (ref)		3.1 (2.8–3.4)	7.6 (7.1–8.0)
Squamous cell carcinoma						
Patients	2,983	561 (18.8)	7.7 (6.7–8.8)	<0.0001	9.5 (8.5–11)	17 (16–19)
Controls	14,668	355 (2.4)	1.0 (ref)		0.9 (0.8–1.1)	2.4 (2.1–2.7)
Basal cell carcinoma						
Patients	2,983	626 (21.0)	4.4 (4.1–5.0)	<0.0001	11 (10–12)	21 (20–23)
Controls	14,668	692 (4.7)	1.0 (ref)		2.0 (1.8–2.2)	5.1 (4.7–5.5)
Cutaneous malignant melanoma						
Patients	2,983	86 (2.9)	2.7 (2.1–3.6)	<0.0001	1.2 (0.8–1.6)	2.6 (1.9–3.2)
Controls	14,668	142 (1.0)	1.0 (ref)		0.3 (0.2–0.4)	0.9 (0.7–1.1)

[a]Squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and cutaneous malignant melanoma (CMM). *Multiple skin cancer types where present in 247 patients and 124 controls with the following distribution: BCC+SCC=200 (patients), 91 (controls), BCC+CMM=16 (patients), 21 (controls), SCC+CMM=12 (patients), 9 (controls), BCC+SCC+CMM=19 (patients), 3 (controls).
CI: confidence interval.

Table 3. Hazard ratio and 5- and 10-year cumulative incidence of skin cancer in 2,983 patients with actinic keratoses (AK) compared with 14,668 matched (age, sex and year of diagnosis) controls.

Table 4 shows the HRs for each of the different skin cancer types, as well as for all skin cancers. The HR of developing BCC was significantly lower for women than for men (p interaction< 0.001). The age group ≤ 59 years had the highest HR of developing SCC (p interaction< 0.01) and BCC (p interaction< 0.01) compared with the other age groups.

	Skin cancer[a]*		SCC		BCC		CMM	
	HR (95% CI)	$p_{interaction}$	HR (95% CI)	$p_{interaction}$	HR (95% CI)	$p_{interaction}$	HR (95% CI)	$p_{interaction}$
Overall	5.1 (4.7–5.6)		7.7 (6.7–8.8)		4.4 (4.1–5.0)		2.7 (2.1–3.6)	
Sex		<0.01		0.56		<0.001		55
Men	5.8 (5.1–6.6)		8.0 (6.6–9.7)		5.4 (4.7–6.4)		3.0 (2.0–4.3)	
Women	4.6 (4.1–5.2)		7.4 (6.1–8.9)		3.8 (3.3–4.4)		2.5 (1.7–3.7)	
Age		0.03		<0.01		0.01		0.78
≤59 years	6.9 (5.5–8.6)		16 (10–26)		6.9 (5.3–9.1)		2.3 (1.3–4.1)	
60–69 years	4.5 (3.8–5.4)		6.0 (4.6–8.0)		4.3 (3.5–5.4)		3.2 (2.0–5.2)	
70–79 years	4.9 (4.2–5.6)		7.3 (5.9–9.1)		4.1 (3.5–4.9)		2.5 (1.5–4.0)	
≥80 years	5.4 (4.5–6.5)		7.9 (6.1–10)		4.1 (3.2–5.2)		3.2 (1.6–6.3)	

[a]Squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and cutaneous malignant melanoma (CMM). *Multiple skin cancer types where present in 247 patients and 124 controls with the following distribution: BCC+SCC=200 (patients), 91 (controls), BCC+CMM=16 (patients), 21 (controls), SCC+CMM=12 (patients), 9 (controls), BCC+SCC+CMM=19 (patients), 3 (controls).
HR: hazard ratio; CI: confidence interval.

Table 4. Hazard ratios, stratified by sex and age, for the incidence of skin cancer in 2,983 patients with actinic keratoses (AK) compared with 14,668 matched (age, sex and year of diagnosis) controls.

Paper III

AK cohort:

The HRs for developing skin cancer, for the studied diagnoses in the AK cohort, are presented in **Figures 6 A-C**. Chronic lymphocytic leukaemia (CLL) was associated with an overall increased risk of all skin cancer, regardless of type (HR: 2.5; 95% CI: 1.33-4.69), (**see Figure 6A**). As shown in **Figure 6B**, an increased risk for KSC (HR: 2.64; 95% CI: 1.41-4.95) appears to be responsible for the overall risk increase for CLL. Other significant comorbidities found to be associated with an increased risk of KSC were Parkinson's disease (HR: 1.70; 95% CI: 1.02-2.84) and hypertension (HR: 1.16; 95% CI: 1.00-1.34), In contrast to the KSC group, hypertension in the MM group (**Figure 6C**) was found to have a reduced risk (HR: 0.54; 95% CI: 0.32-0.90). Among the MM patients, there were no recorded instances of Parkinson's disease, hyperthyroidism, or multiple sclerosis (MS) between the start date and the end of follow-up period.

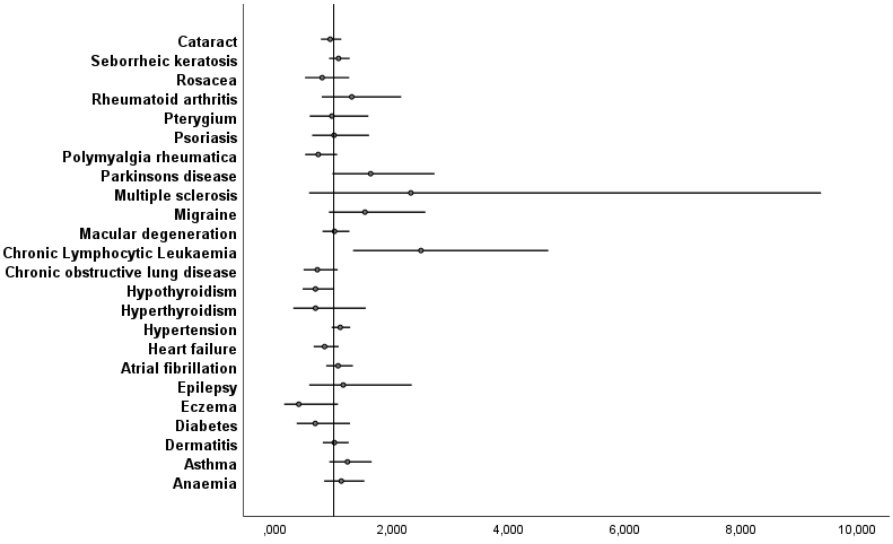

Figure 6A: Hazard ratios with 95% confidence intervals measuring 24 different comorbidities in the actinic keratosis (AK) cohort with keratinocytic skin cancer (KSC) + malignant melanoma (MM) as outcome.

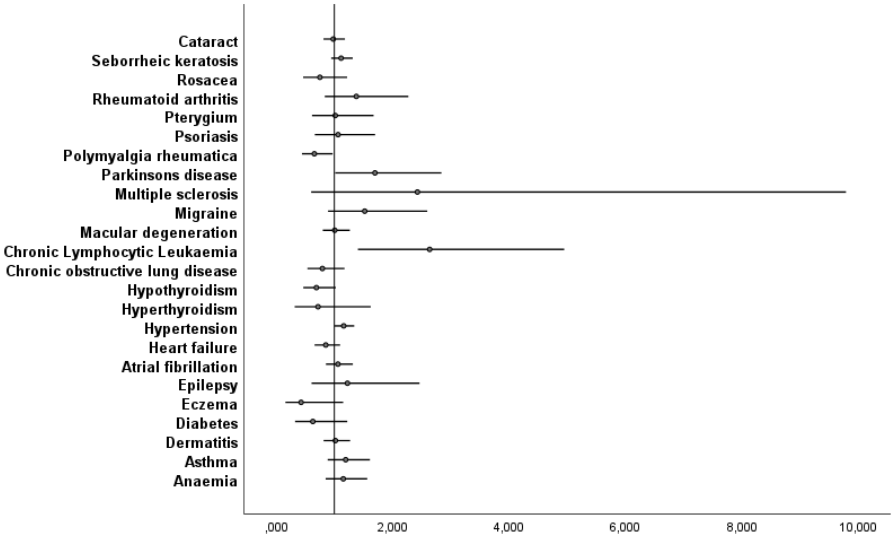

Figure 6B: Hazard ratios with 95% confidence intervals measuring 24 different comorbidities in the actinic keratosis (AK) cohort with keratinocytic skin cancer KSC as outcome.

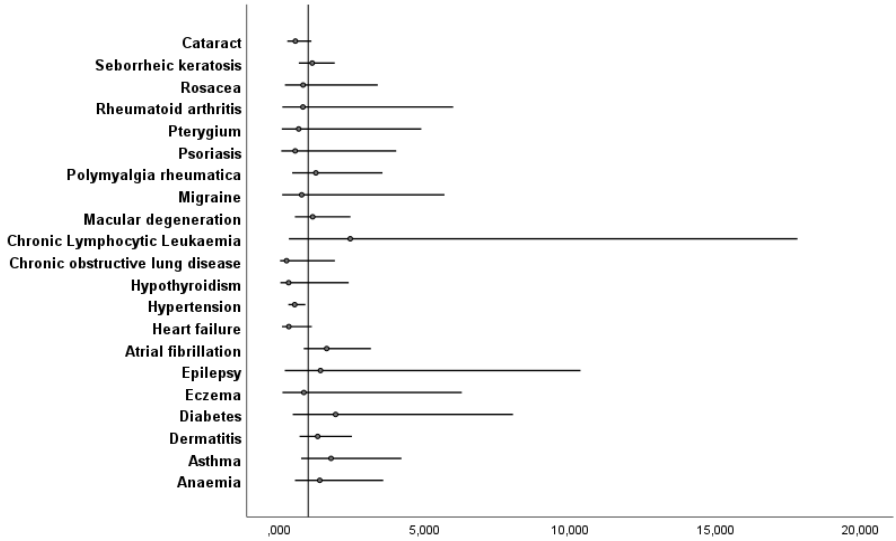

Figure 6C: Hazard ratios with 95% confidence intervals measuring 21 different comorbidities in the actinic keratosis (AK) cohort with malignant melanoma (MM) as outcome. There were no recorded instances of Parkinson's disease, hyperthyroidism, or multiple sclerosis between the start date and the end of the follow-up period (why these are not included in the figure).

Control cohort:

In the control cohort (**Figures 7A-C**), the following comorbidities were statistically associated with an overall increased risk of skin cancer, regardless of type: seborrheic keratosis (HR: 2.23; 95% CI: 1.85-2.70), rheumatoid arthritis (HR: 1.45; 95% CI: 1.02-2.06), hypertension (HR: 1.21; 95% CI: 1.08-1.37), and dermatitis (HR: 1.38; 95% CI: 1.14-1.67), see **Figure 7A**. Increased risk of KSC (**Figure 7B**) was observed for seborrhoeic keratosis (HR: 2.25 (95% CI 1.846-2.742), rheumatoid arthritis (HR: 1.45; 95% CI: 1.01-2.10), hypertension (HR: 1.19; 95% CI: 1.04-1.35) and dermatitis (HR: 1.36; 95% CI: 1.11-1.66). For MM (**Figure 7C**), increased risk was seen for seborrhoeic keratosis (HR 2.16; 5% CI: 1.33-3.49), CLL (HR: 5.10 (95% CI: 1.26-20.68), hypertension (HR: 1.456 (95% CI 1.040-2.039)), and atrial fibrillation (HR: 1.74; 95% CI: 1.11-2.73). Within the control cohort of MM patients, there were no instances of hyperthyroidism, multiple sclerosis (MS), or eczema.

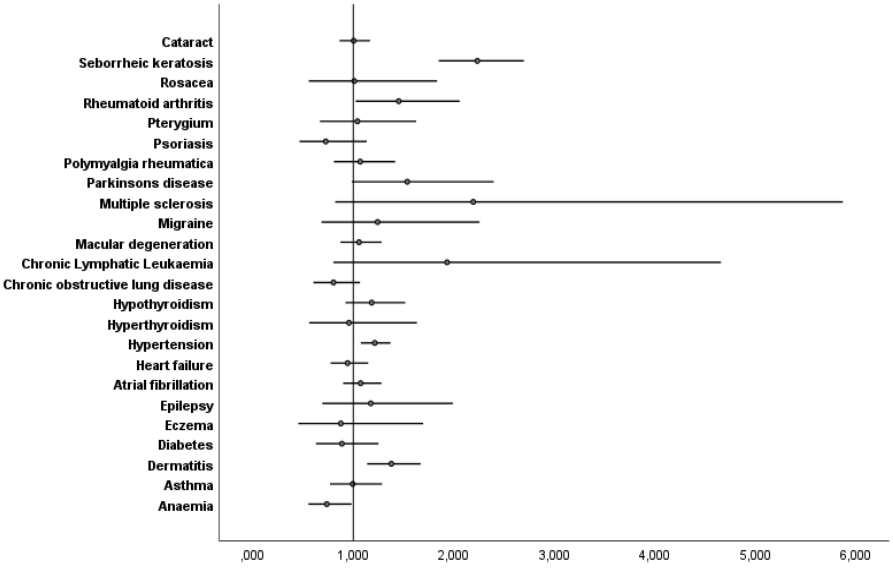

Figure 7A: Hazard ratios with 95% confidence intervals measuring 24 different comorbidities in the control cohort with keratinocytic skin cancer (KSC) + malignant melanoma (MM) as outcome.

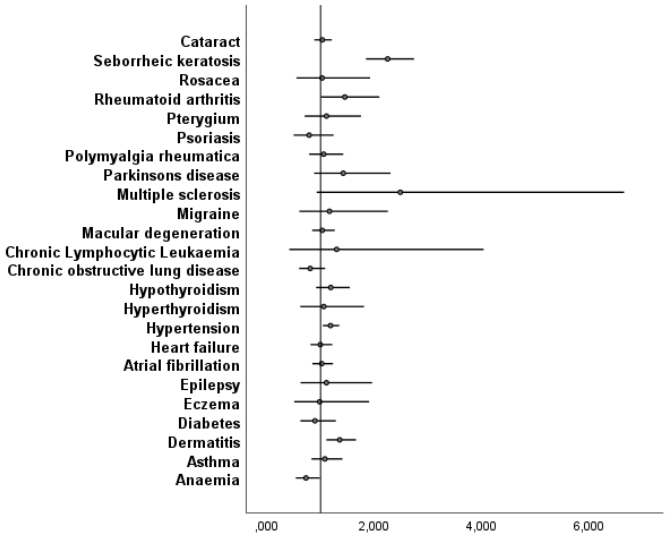

Figure 7B: Hazard ratios with 95% confidence intervals measuring 24 different comorbidities in the control cohort with keratinocytic skin cancer (KSC) as outcome.

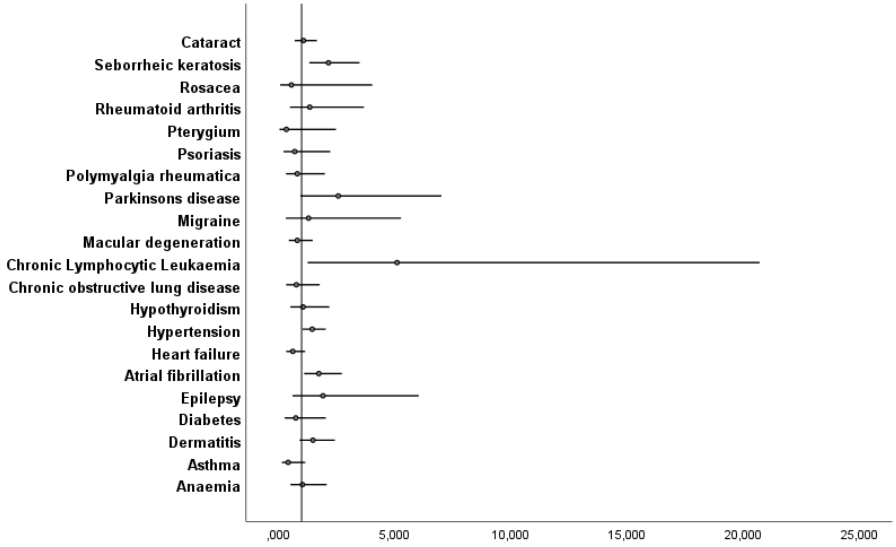

Figure 7C: Hazard ratios with 95% confidence intervals measuring 21 different comorbidities in the control cohort with MM as an outcome. There were no recorded instances of hyperthyroidism, multiple sclerosis, or eczema between the start date and the end of the follow-up period, why these are not included in the figure.

Paper IV

The case cohort comprised 195 patients (84 males, 111 females) with a mean age of 69 years, and the average follow-up period for this cohort was 8 years. The diagnosis of AK in the cancer cohort was made either at a primary healthcare clinic (50 patients) or a dermatology clinic (145 patients). The control cohort comprised 182 patients (59 males, 123 females) with a slightly lower mean age of 66 years. This cohort had a longer mean follow-up period of 11 years. As in the case cohort, the control cohort received the diagnosis of AK either at a primary healthcare clinic (51 patients), a dermatology clinic (128 patients), or other clinics (3 patients) (see ***Table 5)***.

	Case cohort (individuals developing skin cancer, *n* = 195)	Control cohort (individuals not developing skin cancer, *n* = 182)
Sex		
- Male, *n*	84 (43%)	59 (32,4%)
- Female, *n*	111 (57%)	123 (67,6%)
Mean age at diagnosis of AK, *(years)*	69	66
Localization (number of lesions):	206	190
- Head and neck	180 (87,3%)	166 (87,3%)
- Extremities	13 (6,3%)	15 (7,9%)
- Trunk	13 (6,3%)	9 (4,7%)
AK diagnosis received at (*n*):		
- Primary health care	50 (25,6%)	51 (28%)
- Dermatology Clinic	145 (74,4%)	128 (70%)
- Other clinic	0	3 (2%)

Table 5. Clinical characteristics of the individuals in the two study cohorts.

Table 6 shows the ORs for developing skin cancer with regard to the different clinical characteristics. We observed that both high age and male gender were factors associated with a minor but statistically significant increased risk of developing skin cancer, while no such risk increase was identified for any of the other clinical characteristics.

Similarly, in ***Table 7***, ORs for developing skin cancer depending on how the AK lesions were managed by the physician diagnosing the lesion, are shown, adjusted for age and gender. No statistically significant association with subsequent skin cancer development was observed for any of the different managements.

Covariables	***p*-value**	**Odds ratio (95% CI)**
Age	0.024	1.02 (1.00-1.04)
Gender	0.017	1.72 (1.10-2.66)
Head and neck	0.804	1.15 (0.39-3.41)
Extremities	0.829	0.90 (0.33-2.42)
Trunk	0.477	1.48 (0.50-4.34)
Total lesion number	0.304	1.06 (0.95-1.19)
Total lesions diameter *	0.381	1.01 (0.99-1.04)

Table 6. Odds ratios for developing skin cancer presented for different clinical characteristics, analysed with binary logistic regression. (* The sum of all AK lesion diameters in an individual).

Covariables	***p*-value**	**Odds ratio (95% CI)**
Clinical management:		
- No treatment	0.737	1.36 (0.22-8.36)
- Referral	0.314	0.52 (0.15-1.85)
- Biopsi	0.667	0.77 (.23-2.55)
- Curettage	0.998	1.00 (0.19-5.17)
- Excision	0.138	0.17 (0.02-1.76)
- Cryo therapy	0.449	0.63 (0.19-2.08)
- 5-Fluorouracil	0.616	0.60 (0.08-4.49)
- Diclofenac	0.452	0.41 (0.04-4.17)
- Photodynamic therapy	0.280	0.25 (0.02-3.11)
- Tretinoin	0.745	0.61 (0.03-12.17)
Age	0.004	1.03 (1.01-1.05)
Gender	0.008	1.81 (1.17-2.82)

Table 7. Odds ratios for developing skin cancer presented for the different lesion management reported, analysed with binary logistic regression, and adjusted for age and gender as covariables.

DISCUSSION

Main discussion

Time plays a critical role in preventing diseases associated with long-term exposures, such as chronic or repeated UV exposure. In **paper I** we investigated the sustainability of individually tailored sun protection advice delivered by the GP, we observed a gradual but discernible improvement in sun protection behaviour over an extended period. Ageing appears to be the predominant factor influencing this trend, but notably, individuals who received personalized advice directly from their doctor showed significantly lower Sun Exposure and Protection Index (SEPI) scores at the 10-year mark compared to those who received only written advice. This suggests that personal communication of sun protection advice by healthcare providers may be more effective and enduring. This finding aligns with previous research on addressing other health-risk behaviours, such as smoking cessation. The observed diminishing effect over time underscores the potential benefit of repeating the advice, thereby reinforcing its effectiveness.

The modest effect of personalized sun protection advice seen in our study may well be enhanced by repeating the advice at appropriate intervals such as during skin lesion checks or opportunistically during other medical consultations. With the global increase in skin cancer incidence, these findings highlight the importance of integrating sun protection advice into primary healthcare consultations, alongside other lifestyle guidance typically provided e.g. smoking, weight and alcohol.

Paper II of this thesis highlights a significant association between AK and the development of skin cancer. Patients with AK exhibited a fivefold higher risk of developing skin cancer over a 10-year follow-up period compared to the control group, with particularly high risks observed for those aged ≤ 59 years. A recently published study showed similar results (76). Notably, the AK group had a higher prevalence of excluding criteria related to previous skin cancer, indicating a general association of AK with both keratinocyte and melanocyte malignancies. The results point toward a consideration of AKs being a marker of chronic UV exposure, rather than an individual precursor of SCC, and that it is this concurrent UV exposure that lies behind the increased skin cancer risk in AK patients. This raises the question on the actual necessity of treating individual AK lesions, or

whether it would be more appropriate to for example use resources to enhance or promote regular skin examinations in individuals presenting with multiple or recurrent AKs. We reiterate the point that reinforcement of preventive messaging at these "skin check" occasions can be expected to increase long term efficacy.

Paper III focused on individuals with AK to explore a spectre of common and less common comorbidities potentially influencing skin cancer risk. In concordance with previous studies (77,78), we found associations with CLL, and increased skin cancer risk, which was somewhat more pronounced and comprising both melanoma and KSC in the AK cohort, compared to the control cohort. This might illustrate a combined risk increase due to having both CLL and being exposed to excessive chronic UV radiation during life, if regarding AK as an indicator of the latter. In the control cohort, associations with increased skin cancer risk were found between various conditions, such as seborrhoeic keratosis, rheumatoid arthritis, and hypertension. The reasons behind these associations remain speculative, but it seems likely that the association to seborrheic keratosis may be explained by the detection and documentation of incidental lesions which otherwise may not have led to a doctor's visit.

Paper IV aimed to identify predictive factors for skin cancer development in AK patients, considering factors such as lesion characteristics and management. The expected association to high age and male gender was confirmed, but otherwise the results did not reveal any other factors significantly contributing to increasing the risk for individuals with AK to develop skin cancer within 10 years following the diagnosis. It might have been expected that for example, AK occurrence on certain body locations would to some degree reflect differences in UV exposure habits, possibly also affecting future skin cancer risk. However, our results do not give any support to such a hypothesis. On an individual lesion level, ulceration in an AK has, for example, been found to be associated with an increased risk for the lesion to develop into skin cancer, and to more often arise on the head (24). In our material, data on lesion ulceration was not available, since this was seldom recorded by the examining physician. The lack of similar, more detailed information on lesion characteristics in our study is a methodological limitation related to the chosen study design and the information available in the charts reviewed. While most charts contained detailed AK lesion descriptions, some lacked clarity or completeness, posing challenges for comprehensive analysis.

Strengths, limitations, and methodological consideration

Paper I's main strengths lie in its prospective design, long-term follow-up, and high response rate, which offer valuable insights into the sustainability of short-term behavioural changes and their potential impact on skin cancer risk. These findings are instrumental in informing the development of effective, long-term interventions for skin cancer prevention while maximizing resource efficiency. It could even be useful for other diseases like diabetes and cardiovascular diseases, daily exercise and a healthy diet is crucial in reducing their health effects and complications.

However, the study is subject to limitations, including its single-centre design, potential selection bias, and the speculative clinical significance of observed behavioural changes. The absence of a true control group raises concerns, although the letter group serves as a minimal intervention control. The substantial increase in sun protection observed in the doctor's consultation groups suggests an intervention effect beyond the mere passage of time. Additionally, the relatively high age distribution of the study population may not align with the optimal target group for intervention but reflects the typical demographics seen in PHC settings.

We lack information regarding the health status of the individuals in the study both before and after the intervention. It is essential to assess the effects of the intervention on these individuals and determine if we genuinely prevented skin cancer. Moreover, we should consider if these individuals developed other diseases related to poor sun exposure, such as vitamin D deficiency. These aspects warrant further consideration and investigation.

A multicentre prospective with a control cohort who do not receive any intervention could be an idea for a future study.

Paper II and III: The selection of the study population from the registry has limitations that should be considered. Firstly, the reliance on registration in the local registry for diagnoses may result in under-reporting of AK, possibly because some patients do not seek medical assistance or due to inaccuracies in clinical diagnoses. Additionally, diagnoses were primarily clinical, lacking histopathological confirmation. Moreover, the study lacks specific data on AK characteristics, treatment methods, and lesion localization.

The onset of BCC registration after the studies' inclusion period could have led to under-reporting of BCC cases. The mixing of all subtypes of SCC and MM in the coding system further introduces diagnostic uncertainty.

The duration of comorbidities in participants was also unknown, potentially impacting their association with skin cancer development over time. Furthermore, important confounding factors such as smoking, alcohol habits, socioeconomic status, occupation, and actual sun exposure were not accounted for in the studies.

Despite these limitations, the studies have significant strengths. These include the involvement of healthy individuals in the control group, enhancing generalizability of the results, and that it is based on a large-sized full population, reducing selection biases. Moreover, the 10-year follow-up period is a reasonable time interval for detecting differences in subsequent skin cancer incidence. Finally, paper III may be one of the first to examine comorbidities in a large cohort followed for 10 years, providing valuable insights. Increasing the sample size further could strengthen interpretations, particularly regarding the absence of certain comorbidities in MM cases.

Paper IV: One fundamental limitation of the study is that the diagnosis of AK was primarily clinical and not histopathologically confirmed, since this is the common practice. Additionally, the examination of charts was limited to the time point when the AK diagnosis was recorded, preventing access to information about the type or location of subsequent skin cancer, hindering the assessment of the risk of individual AK lesions progressing to cancer.

Another limitation is the lack of additional information about subjects, including comorbidities, medical treatments, sun habits, and sun protection behaviours, both before and after AK diagnosis.

In favour of the study is its randomly selected data sample, which is likely to be representative of the patient population in general, enabling long-term follow-up on subsequent skin cancer development, retrospectively not possible to access in so many other ways. A prospective study with photo documentation of AK lesions and following these patients over a period, of 5, 10 years could be an idea for future research.

Implications for primary care practice

The introduction of skin lesion clinics in PHC, where patients can book appointments to have their nevi checked, is a promising approach to early detection of skin cancer. The incorporation of dermatoscopy and teledermoscopy have further improved this process. However, there are still important considerations of this for PHC, as this may, in competition with all other commitments, be time consuming. Also, from the dermatologist's perspective, this may possibly increase referrals to dermatologists who are already overwhelmed with skin cancer-related referrals. However, this highlights the significance of efforts aiming to reduce the burden of skin cancer to increase the knowledge of skin cancer risks already at the primary care level.

PHC aims to promote optimal health and well-being for all individuals, prioritizing accessibility and equitable distribution of services to sustainably support a healthy life without imposing financial burdens on patients. In recent years, the costs of healthcare have been rising due to various factors such as an ageing population, and global conflicts. As a specialist in general practice, directly involved in patient care from infancy to the end of life, I strive to provide comprehensive support, acting as both a detective in diagnosing diseases and a guardian for my patients. However, with finite resources, it is essential to prioritize care for those most in need while also promoting preventive measures like vaccination and empowering patients to seek timely healthcare.

CONCLUSIONS

General conclusion

Highlighting the roles of essential parts of the health care process regarding skin cancer risk and prevention, involving the primary care physicians, is likely to improve the requirements for successful and appropriate preventive measure, such as individualised sun protection advice.

Specific conclusions

I. Individualized sun protection advice from the GP can sustainably improve sun protective behaviour.

II. A diagnosis of AK, even in the absence of documentation of other features of chronic sun exposure, is a marker of increased risk of skin cancer, which should be addressed with individually directed preventive advice.

III. The findings concerning UV-associated comorbidities may influence the targeting of preventive strategies towards future skin cancer in this respect. The coexistence of CLL, and to a lesser extent hypertension and Parkinson's disease, independently enhances the risk of skin cancer, emphasizing the importance of individualised preventive guidance.

IV. Age and male gender are factors associated with an increased risk for AK patients to subsequently develop skin cancer, a finding which is in concordance with other studies.

Future research should explore the potential interactions between sun protection advice and other behavioural counseling, particularly in cases of conflicting advice (e.g., sun avoidance vs. outdoor physical activity). Additionally, further research is needed to assess the actual impact and effectiveness of repeated sun protection advice. Moreover, additional research, preferably with a prospective study design, is warranted to gain more detailed information on lesion and patient characteristics as predictors and comorbidities influencing future skin cancer risk, and thus of significance for the management of AK patients.

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