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Systematic Review of the Natural Course of Actinic Keratosis
and their Relation to Squamous Cell Carcinoma

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Abbreviations

AK, AKs – actinic keratosis, actinic keratoses

ALA-PDT – aminolaevulinic acid-photodynamic therapy

NMSC – non-melanoma skin cancer

OTR – organ transplant recipients

Pts. – participants, patients

SCC – squamous cell carcinoma

UV radiation – ultraviolet radiation

1. Abstract / Abstrakt

1.1. Abstract

Background: For decisions about the treatment necessity, knowledge about the course of untreated actinic keratosis (AK) is essential, particularly with respect to spontaneous regression rates and the risk of progression to squamous cell carcinoma (SCC). The goal of the present study is to systematically assess the primary data on the natural history of AK and its relation to SCC.

METHODS: A systematic literature search was conducted. Cohort studies and control groups from clinical trials were included if they reported data on progression or regression rates, correlational data on the subsequent risk of SCC development, data on histologically contiguous AK in SCC specimens, changes in total AK counts over time and/or complete field regression and recurrence rates. High risk populations (history of non-melanocytic skin cancer (NMSC), concomitant immunosuppression) were reported separately. An extrapolation of the risk of development of an SCC for the 'standard patient', based on mean data from the source studies, was performed.

RESULTS: 33 studies reporting on at least one of the outcomes were eligible. A progression risk for single AK lesions of up to 0.075% per lesion-year was reported. With a progression rate of 0.53%, the risk was higher in patients with a history of NMSC. Extrapolating these data for the 'standard patient's' ten year-risk to develop SCC results in a disproportionately higher risk. Correlational data show a strong relation of AK and consecutive SCC, and indicate a higher risk for organ transplant recipients. Contiguous AK lesions were regularly found in SCC specimens. Regression rates of AK lesions varied from 15 to 63% after 12 months, with studies showing a subsequent recurrence of 15% to 53% of regressed lesions. Rates of complete field regression varied from 0 to 21%, with subsequent recurrences in 57% of the patients. Data on changes of total AK lesion counts were heterogeneous, ranging from -53% to +99.1%.

DISCUSSION: The close relation between AK and SCC is seen in correlational data and confirmed in observational studies following AK lesions. Several methodological limitations apply to the data and at the current time, any estimate on progression rates remains highly uncertain. This particularly applies to extrapolations based on

the respective data. Other results described below illustrate a dynamic interplay of progression and regression. Despite the relatively high regression rates, spontaneous complete field regressions rarely occur. Due to the low probability of spontaneous complete regressions and the inherent risk of progression, AK requires an appropriate treatment.

1.2. Abstrakt (German)

Hintergrund: Um klinisch relevante Entscheidungen über die Behandlung zu treffen, sind Kenntnisse über den unbehandelten Verlauf aktinischer Keratosen (AK) unumgänglich, insbesondere hinsichtlich spontaner Regression und Progression in spinözelluläre Karzinome (SCC). Ziel der vorliegenden Studie ist die systematische Erfassung der Primärdaten zum natürlichen Verlauf von AK und ihrer Beziehung zum SCC.

Methoden: Es wurde eine systematische Literaturrecherche durchgeführt. Kohortenstudien und Kontrollgruppen randomisierter Studien wurden eingeschlossen, wenn mindestens eines der folgenden Outcomes berichtet wurde: Progressions- und Regressionsraten einzelner AK, korrelationale Daten zum Risiko der Entwicklung eines SCC, Daten zu histologischen AK Korrelaten in SCC-Proben, Veränderung der Anzahl an AKs über den zeitlichen Verlauf und Raten vollständiger spontaner Regression und nachfolgendem Wiederauftreten. Hoch-Risiko-Populationen (Zustand nach nicht-melanozytärem Hautkrebs (NMSC), immunsupprimierte Patienten) wurden separat berichtet. Das theoretische individuelle 10-Jahres-Risiko eines 'Standardpatienten' wurde, basierend auf den Daten aus den entsprechenden Quellstudien, berechnet.

Ergebnisse: 33 den Einschlusskriterien entsprechende Studien wurden identifiziert. Es zeigte sich eine Progressionswahrscheinlichkeit einzelner AK-Läsionen von 0,075%/Jahr. Mit 0,53% pro Läsion und Jahr war die Progressionswahrscheinlichkeit für Patienten mit Zustand nach multiplen NMSC deutlich höher. Die theoretische Berechnung des 10-Jahres-Risikos eines 'Standardpatienten' für die Entwicklung eines SCC ergab ein unverhältnismäßig höheres Risiko. Korrelationale Daten zeigen eine starke statistische Beziehung des Risikos der Entwicklung eines SCC zur Anzahl vorbestehender AKs und weisen auf eine höhere Progressionswahrscheinlichkeit für immunsupprimierte Patienten hin. In Biopsien aus SCC wurden regelmäßig angrenzende AK histologisch nachgewiesen. Regressionsraten

von AKs nach 12-monatiger Beobachtung bewegten sich zwischen 15 und 63%, mit einem erneuten Wiederauftreten von 15% bis 53% der regredierten Läsionen. Vollständige spontane Regressionen wurden in 0 bis 21% der Patienten beobachtet, ein nachfolgendes Wiederauftreten von AK in 57% der Patienten. Daten zur relativen Änderung der Gesamtanzahl von AK im zeitlichen Verlauf zeigten ein breites Spektrum der Ab- und Zunahme, mit relativen Veränderungen von –53% bis +99,1%.

Diskussion: Nicht nur korrelationale und histologische Daten spiegeln die enge Verknüpfung von AKs und SCC wider, sondern auch Beobachtungsstudien, die den Verlauf einzelner AKs nachverfolgen. Verschiedene methodologische Aspekte schränken die Interpretierbarkeit der Ergebnisse ein und zum jetzigen Zeitpunkt bleiben Schätzungen zur Progressionsrate von AK in hohem Maße unsicher. Dies gilt insbesondere für die theoretische Berechnung des individuellen Progressionsrisikos. Insgesamt zeigt sich ein dynamischer Wechsel von qualitativer und quantitativer Progression und Regression aktinischer Keratosen. Trotz der relativ hohen Regressionsraten einzelner AK-Läsionen sind vollständige spontane Remissionen seltene Ereignisse. Aufgrund der geringen Wahrscheinlichkeit kompletter spontaner Regressionen und des inhärenten Progressionsrisikos, erfordern AKs eine adäquate und konsequente Behandlung.

2. Background

2.1. Introduction

Actinic keratoses (AKs, also referred to as solar or senile keratoses) are lesions of the skin that develop on areas chronically exposed to ultraviolet (UV) radiation. AKs are the most common skin lesions that have a supposed potential of progression into invasive, malignant skin cancer. AK lesions present as scaly, rough papules that may feel like patches of dry skin. Usually AKs are not symptomatic, but pruritus, pain and bleeding may occur. Different treatment options have been described for the management of AKs, including interventions aimed at the elimination of manifest areas (lesion-directed interventions) and interventions intended to reduce both manifest and latent areas of dysplastic skin (field-directed interventions). The treatment necessity itself is assumed to be due to the risk of malignant progression of AK lesions into squamous cell carcinoma (SCC) of the skin. Yet, the natural history of AK remains a matter of debate and especially the risk of progression into malignant disease has not been assessed systematically.

2.2. Terminology and significance of AK

Several expressions have been in use synonymously for AK, including 'solar keratosis', 'senile keratosis', 'senile keratoma', 'keratinocytic intraepidermal neoplasia',¹ and 'in situ squamous cell carcinoma Type AK'.² AKs on the lips are termed as 'actinic cheilitis'.³

AK is a medical condition of the skin that already had been described by the end of the nineteenth century^{1,4} and the debate about their malignant character or potential almost reaches back to that time.^{1,5} AKs can be considered as keratinocytic dysplasia ('precancerous lesion') or as in situ SCC ('neoplasia', 'carcinoma'). The former view tends to describe AK lesions as a premalignancy that does not necessarily have to be treated unless a malignant 'transformation' occurs, whereas the latter view characterizes AKs themselves as malignancies with the risk of 'progression' into invasive stages, imposing an absolute treatment indication.⁵ On the level of cytology, AKs are hardly distinguishable from SCCs^{2,5,6} and thus, more recent characterizations of AKs tend to accentuate the view of AK as 'superficial SCC'.^{1,2,7} This perspective characterizes AKs analogously to other epithelial in situ lesions that may progress into invasive disease, such as the cervical intraepithelial neoplasia

(CIN).⁸ Suggested clinical and histological classifications of AK attempt to adapt the nomenclature, so that the role of AK not as a 'dysplastic', 'precancerous' lesion but as an actual 'carcinoma' in situ is emphasized: suggestions include the classification of AK as "keratinocytic intraepidermal neoplasia (KIN) 1-3"⁹ and "in situ squamous cell carcinoma Type AK I-III".² However the debate on the terminology of AK is solved, studies evaluating molecular genetics and gene expression patterns clearly demonstrate the strong entanglement of AK and SCC. On this level, AK is characterized as a step on a continuous spectrum of accumulation of genetic alterations from (clinically) healthy skin to SCC.^{10,11}

2.3. Etiology of AK

Chronic and continuous unprotected exposure to sunlight has been found to be a major factor in the pathogenesis of AK,¹²⁻¹⁵ a fact that is also reflected by the term 'actinic' (referring to 'radiation') and the synonym 'solar' keratosis. UV radiation has three major effects promoting the development of AK and cancerogenesis in the affected keratinocytes: affection of the DNA, alteration of intracellular signaling cascades, and inflammatory effects.¹⁶

Direct DNA alterations in the keratinocytic cells of the epidermis are caused by the exposure to UVB radiation that leads to the development of UV photoproducts such as cyclobutane pyrimidine dimers.^{17,18} DNA mutations owing to UVB radiation result in characteristic C-T and CC-TT transitions and frequently cause a suppression of the function of tumor suppressor proteins such as p53, which plays a central role in the regulation of the physiologic cell cycle.¹⁶ The suppression of p53 leads to a clonal expansion of the affected keratinocytes and thus to the development of AK lesions.^{19,20} The dysregulation of the p53 pathway not only seems to play the most important role in the development of AK lesions, but also in the further possible development of SCC.^{6,11} Excessive exposure to sunlight radiation furthermore causes alterations of signaling pathways. Modifications of membrane tyrosine kinases, epidermal growth factor receptors, and activation of Ras, Raf and nuclear factor κB may occur. Inducing cytokine production (e. g. tumor necrosis factor, IL-6), the arachidonic acid cascade, and translocation of transcription factors into the nucleus, these events change the cellular gene expression and cause inflammatory effects.¹⁶ In consequence of the generation of reactive oxygen species (ROS), UVA radiation may increase DNA alterations that were caused by UVB radiation, as

described in the pathophysiology of melanoma.^{21,22} ROS furthermore induce lipid peroxidation and enhance cellular destruction, both factors that have been associated with a neoplastic development of cells.¹⁶

Human papilloma viruses appear to play a role as cofactors in the development of AKs,²³ particularly in cooperation with DNA alterations related to UV radiation.^{24,25}

2.4. Risk factors for the development of AK

The major risk factors that have been described to contribute to the susceptibility to develop actinic keratoses are cumulative exposure to sun light, fair skin type, increasing age and male sex.^{13,26,27} The medical condition of immunosuppression increases the risk for the development of AK. Several studies on immunosuppressed organ transplant recipients demonstrated the participants' manifold increased risk for developing AK and/or NMSC as compared to populations of patients without history of immunosuppression.²⁸⁻³¹ Melanin deficiency syndromes and insufficient DNA repair mechanisms increase the vulnerability of the keratinocytes towards UV radiation and thus account for an increased risk for developing AK and NMSC. The underlying genetic syndromes primarily include Xeroderma pigmentosum³² and Albinism,³³ but further genetic defects have been described to increase the risk for developing AKs: Bloom's syndrome, Cockayne's syndrome, and Rothmund-Thomson syndrome.²⁶ Vitiligo, as a skin disease that goes along with melanin deficiency, has been described to be related to AK development in a case report,³⁴ but generally, patients with vitiligo seem to be at a decreased risk for NMSC.³⁵

In a randomized trial, a continued 'normal' diet has also been shown to play a role as a risk factor for the development of AK as compared to a group that started a low-fat diet.³⁶

2.5. Epidemiology of AK

The worldwide epidemiology of AK has a wide range from country to country due to the variability of the various risk factors, with exposition to UV radiation and the dominant skin type of the inhabitants playing a major role for country-specific prevalence and incidence rates. Within countries, variations of prevalence and incidence rates are mainly attributable to age and sex.

Owing to its close proximity to the equator and its large percentage of fair-skinned inhabitants, the highest prevalence of AK has been described for Australia: Up to

60% of Australians over the age of 40 were found to have at least one AK lesion.^{27,37,38} In a population from the UK, aged 60 years or more, a prevalence of 23% and an incidence rate of 149 AK lesions in 1000 person-years were seen.³⁹ Another study on the prevalence of AK in the UK reported 34% of the men and 18% of the women in the age of 70 years or more to have AK.⁴⁰ In the USA, an age-adjusted prevalence of AK of 6.5% was calculated. In a subpopulation of the same study restricted to men aged 65 to 74 years, the prevalence of AK for participants with high and low sunlight exposure was 55% and 19%, respectively.¹² In an Italian population, a point prevalence of 1.4% was reported, with a prevalence correlated to the age of the participants: in the subgroup of participants aged 75 years or older, a prevalence of 3.0% was seen.⁴¹ A study on a Japanese population reported prevalence rates for an urban area (Kasai City) and a rural area with a higher occupational exposure to UV radiation (Ie Island) of 203 and 756 per 100,000, respectively.⁴²

2.6. Diagnosis of AK

2.6.1. Clinical features

AK lesions typically manifest as keratotic or scaly papules with an erythematous base. AKs may be colored as the surrounding skin, or have a pigmented, red or pink surface. Thus, they may be visible or only palpable, presenting as sandpaper-like patches. Lesions usually do not present with a diameter of more than 1.0cm.^{2,6} Wrinkles, teleangiectasias and elastosis of the surrounding skin may display the chronic exposure to UV radiation.⁴³

Symptomatic lesions can present with symptoms such as pruritus, burning, and tenderness; however, AKs may also be subjectively symptom-free. The impact of the presence of AK lesions on the quality of life of affected patients has not been well studied. One study could reveal a negative correlation between the total AK lesions count and the quality of life as measured by the Skindex-29 and KC (keratinocyte cancer)-specific questionnaire.⁴⁴

Different types of AK have been described, referring to their clinical and histological patterns. These different types of AK include pigmented, atrophic, bowenoid, lichenoid, and hyperkeratotic lesions.^{2,26} This differentiation is not consistent with an important impact on the clinical management of AK: Recent guidelines on the

management of AK do not refer to these criteria as criteria that are necessary for a differential therapeutic strategy.^{45,46}

The importance of the exposure to UV radiation for the pathogenesis of AK serves as an explanation for the anatomic distribution of AK lesions: the majority of lesions is located on typically sun exposed areas, with over 80% of AKs occurring on the upper limbs, head and neck.²⁶ The bald scalp, ears and face, dorsal forearms and hands are areas that are often affected.

AKs can present as singular, non-confluent lesions ('single lesions'), or as multiple, disseminated or confluent lesions ('multiple lesions'). When multiple AKs occur in a field of chronically sun-damaged skin, possibly contiguous to lesions that are suspected of being an SCC, the term of 'field cancerization' is applied. An adequate patient care requires differential therapeutic strategies for the treatment of these distinguishable subgroups of patients.⁴⁵⁻⁴⁸

2.6.2. Clinical diagnosis

In the clinical context, the diagnosis of AK is usually based on, and restricted to, the clinical examination of the skin. The clinical presentation mentioned above (see 2.6.1. 'Clinical features'), along with a history of the typical risk factors (see 2.4. 'Risk factors for the development of AK') serves as a sufficient condition for the diagnosis. The clinical diagnosis of AK was shown to reach a positive predictive value of between 74% and 94%.⁴⁹⁻⁵¹ Nevertheless, even among dermatologists, the interobserver reliability with respect to the diagnosis of single AK lesions was low, with a positive agreement in 23 to 26% of the cases. With respect to the identification of patients with multiple AK lesions, interobserver reliability was higher with a positive agreement in 53 to 63% of the cases. Positive agreement of the assessors with respect to the diagnosis of malignant skin lesions further rose to 65%, when the history of patients was included in the diagnostic considerations.⁵² The variability of total AK lesion counts among different assessors is high, corresponding to the poor interobserver reliability with respect to the detection of single AK lesions.⁵³ Comparison of primary care clinicians' clinical diagnoses to dermatologists' diagnoses of AK as reference, shows moderate diagnostic specifications for the primary care clinicians' diagnosis, with a sensitivity of 38 to 57% and a specificity of 88 to 95%.⁵⁴ Using dermoscopy for the clinical evaluation of lesions that are suspected for being an AK was shown to result in positive and negative likelihood

ratios of 19.74 and 0.01, respectively. The concordance between dermoscopy and histological diagnosis was 0.917.⁵⁵ Optical coherence tomography and reflectance confocal microscopy are non-invasive imaging techniques that are being evaluated and show promising preliminary results.⁵⁶ Reflectance confocal microscopy was shown to enable the assessor to identify subclinical AK lesions in fields of sun damaged skin, through the detection of pleomorphism and architectural disruption in the stratum spinosum of the affected skin.⁵⁷

For the clinical assessment of AK lesions, different clinical severity scales have been suggested: The grading system presented by Olsen et al. (1991) classifies AK lesions with respect to the degree of palpability and visibility of keratosis: grade 1, slightly palpable; grade 2, moderately thick and visible; and grade 3, very thick and hyperkeratotic.⁵⁸ Cockerell (2000) suggested a slightly modified scale.⁹

No guidelines on the clinical differentiation of AK and SCC have been established. Inflammation and increased tenderness or pain have been described as being possible clinical markers for AK lesions that should be suspected of progression to SCC.⁵⁹ Following analyses from a systematic review, six major clinical features were proposed as criteria to discriminate AK lesions suspected of progression to SCC: Induration or inflammation, diameter of more than 1 cm, rapid enlargement in diameter, bleeding, ulceration and erythema.⁶⁰ However, clinical criteria to securely differentiate AK from SCC lesions are not well established and remain a matter of an ongoing debate.

Differential diagnoses of AK lesions include (invasive) SCC, basal cell carcinoma, Bowens disease, porokeratosis, and seborrheic keratosis. If the respective lesion is pigmented, another possible differential diagnosis is lentigo maligna.^{61,62}

2.6.3. Histological features

Evaluation of the histological features of an AK lesion represents the gold standard and reference in the differentiation of AK, SCC and other differential diagnoses. However, performing a skin biopsy with histological assessment is only recommended for lesions that are clinically suspected of a progression to SCC. Further indications for performing a histological assessment are cases of clinical uncertainty of the diagnosis or an unresponsiveness of the respective lesion to therapy.

The presence of atypical keratinocytes is an indication of an architectural disorder of the epidermis, which is the main feature of the histopathology of AK lesions. This can be a focal aspect, affecting only the basal and / or suprabasal layers, or extend to the whole thickness of the epidermis.^{2,6} Typical characteristics of atypical keratinocytes are variability in size and shape, nuclear atypia and an alteration of the cellular polarity with respect to their orientation in the epidermis. Further histopathological characteristics as described by R wert-Huber et al.^{2,6} include the following:

- parakeratosis alternating with hyperkeratosis as a result of defective maturation of the keratinocytes within the epidermis
- facultative small round buds at the basal layer that protrude into the papillary dermis
- epidermal keratinocytes of the acrosyringia and acrotrichia are spared and thus the cornified layer is orthokeratotic and normal
- an acantholysis with suprabasal clefts may occur

Due to their pathogenesis, histological features of the epidermis typical for AK are usually accompanied with an elastosis of the dermis. A lymphocellular and plasma cellular dermal infiltrate may occur.^{2,6}

The degree of extension of atypical keratinocytes within the epidermis has been suggested as the most relevant histopathological feature for a histological classification of AK lesions with respect to severity. The following classification has been published by Cockerell (2000)⁹ and R wert-Huber et al. (2007)² (Table 1. Severity degrees of AK):

Table 1. Severity degrees of AK

Cockerell (2000) ⁹ : Keratinocytic intraepidermal neoplasia (KIN)	Röwert-Huber et al. (2007) ² : In situ SCC Type AK	Histological characterization	Clinical equivalent (Cockerell, 2000)⁹
KIN I	Early in situ SCC type AK I	Atypical keratinocytes in the basal and suprabasal layers (the lower third) of the epidermis	Flat macule on sun-damaged skin, background mottling, no roughness or hyperkeratosis
KIN II	Early in situ SCC Type AK II	Atypical keratinocytes extending to the lower two thirds of the epidermis (+ focal hyperkeratosis, alternating orthokeratosis and parakeratosis; prominent acanthosis and buds of keratinocytes in the upper papillary dermis)	Papule or plaque with rough hyperkeratotic surface, variable induration
KIN III	In situ SCC Type AK III	Atypical keratinocytes extending to more than two thirds of the full thickness of the epidermis (+ parakeratosis, acanthosis, papillomatosis, involvement of adnexal structures)	Red, scaly, indurated plaques on sun-damaged skin, occasionally pigmented

2.6.4. Other diagnostic means

There is no general diagnostic indication for performing laboratory studies including blood testing on patients that present with AK. Melanocytic markers may play a role for the differentiation of melanocytic proliferations and pigmented AK lesions, but the clinical significance of this remains unclear.⁶³⁻⁶⁵ Other immunohistochemical tests do not have a significant function in assessing AKs.

2.7. Treatment options and recommendations

This chapter is based on the descriptions and recommendations made in the European Dermatology Forum (EDF) “Guidelines for the management of Actinic Keratoses”⁴⁵ and in the guidelines on the treatment of AK by the German society for dermatology (Deutsche Dermatologische Gesellschaft, DDG).⁴⁶

2.7.1. Lesion-directed interventions

The aim of lesion-directed treatment options for AK is the physical destruction or removal of atypical keratinocytes that constitute a single, circumscribable AK lesion. Consequently, only clinically manifest, visible or palpable lesions can be directed. A

destruction or removal of a field of multiple, confluent AK lesions or field cancerization including areas of latent keratinocytic dysplasia, usually is not desirable due to the massive traumatization of huge areas of skin that this would involve. Lesion-directed interventions include all ablative treatments that attain a direct physical or chemical destruction of circumscribable areas of the skin: all types of surgical excision (curettage, dermabrasion), cryotherapy and laser therapy (carbon dioxide laser, Er:YAG laser).

2.7.2. Field-directed interventions

The physical or chemical destruction, removal or regression of atypical keratinocytes is also intended by field-directed interventions for AK. The difference between lesion-directed and field-directed treatment options is the additional treatment of latent, clinically not manifest areas of atypical keratinocytes that is only intended and achieved by field-directed interventions. A huge variety of field-directed interventions is available; this includes topical diclofenac in 2.5% hyaluronic acid, topical imiquimod and resiquimod, topical 5-fluorouracil, ingenol mebutate, and photodynamic therapy (PDT) using aminolevulinic acid (ALA) or methyl aminolevulinate (MAL).

The regular use of sunscreen can be considered as an indirect topical field-directed treatment that supports the innate capacity of the patients' immune system to clear areas of dysplastic keratinocytes.

2.7.3. Recommended treatment algorithms

The choice of treatment mainly depends on the localization and extent of the AK (single AK lesions, multiple lesions, or field cancerization), presence of specific risk factors (history of skin cancers, immunosuppression), age, comorbidities and compliance of the patients. The ablative, mainly lesion-directed treatment options (surgical excision, cryotherapy, laser therapy) are recommended for the use in patients presenting with single and clearly circumscribable AK lesions. In the case of doubtful malignant progression of single lesions, a surgical excision and histopathological assessment is recommended. Field-directed interventions can be used both for patients presenting with single AK lesions and for those presenting with multiple, confluent lesions or field-cancerization. For patients presenting with field cancerization and a history of special risk factors for the development of skin cancer

(e.g. immunosuppressed organ transplant recipients), field-directed treatment options such as photodynamic therapy or topical imiquimod are recommended.

As a preventive measure, all patients should be recommended to consistently avoid the exposure towards sunlight. This includes the regular use of sunscreen and of sun protective clothes as well as the avoidance of sun light during the hours of most intense radiation (noon, afternoon).

2.8. Rationale and objectives of the present study

As described above, there has been an ongoing debate about the terminology to be used when referring to AK lesions. This debate refers not only to theoretical approaches as the pathobiology, molecular genetics or terminology of AK lesions, but it directly affects recommendations regarding the general treatment necessity of patients presenting with AKs.

This systematic review critically appraises and discusses the available primary data on the clinical significance of AKs. Controversies regarding the natural course of AK are addressed, looking at the risk of progression into invasive SCC on the one hand and the potential of regression into healthy skin on the other. For this purpose, all available studies on the course of untreated AK matching the predefined inclusion criteria were assessed and analyzed systematically. Furthermore, correlational data on the prevalence/incidence of AK and SCC, and data on histologically contiguous AK in SCC specimens were systematically assessed. Clinically relevant subgroups of patients were defined and analyzed separately.

This is a preliminary study in preparation for an international evidence-based guideline on interventions for actinic keratoses. It aims to establish treatment implications for actinic keratosis: only well-founded knowledge on the course of untreated AK lesions empowers experts to take sensible decisions on recommendations for interventions.

Partial results of the present study were published by the British Journal of Dermatology, entitled 'The Natural History of Actinic Keratosis: A Systematic Review'.⁶⁶ Further partial results were submitted as an abstract and poster to the 47th conference of the German Dermatological Society (Deutsche Dermatologische Gesellschaft, DDG), entitled 'Progression und Regression aktinischer Keratosen: Ein systematischer Review'.

Texts on the clinical background of AK worked out for the present study will be used as drafts for the international evidence-based guideline on interventions for actinic keratosis. The fragments will be adapted by subgroups of the guidelines' expert committee.

A publication of further results of this study will be considered.

3. Methods

3.1. Introduction

A systematic search for studies reporting primary data on different outcomes with respect to the natural history of AK was conducted. The results of the search were systematically checked for predefined eligibility criteria and data were systematically extracted from included publications. All included studies were assessed for the methodological quality and sources of bias. The results are reported in overview tables with respect to each relevant outcome. For the risk of progression from AK to SCC, a theoretical extrapolation of the overall risk of the 'standard' patient affected by AK to develop an SCC is presented, based on the results of the systematic review.

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.⁶⁷

3.2. Search for literature

An electronic systematic literature search was performed using the databases Cochrane Library, Medline, Medline in Process and Embase. Medline, Medline in Process and Embase were searched using OvidSP. The search covered the time period from the beginning of the databases to end of July 2012. The detailed electronic search strategies used for the search in each database are presented as supplemental documents (see 7.2. 'Search strategies'). Further eligible trials were yielded through a systematic check of the reference lists of all included studies.

3.3. Outcomes of interest

To be included in this systematic review, studies had to explicitly report on at least one of the following predefined outcomes:

- Rate of progression of single AK lesions to SCC per time unit
- Relative risks or odds ratios for developing SCC relative to the baseline number of AK lesions
- Rate of contiguous AK lesions in SCC specimen
- Rate of regression of single AK lesions per time unit
- Rate of subsequent recurrence of AK lesions after spontaneous regression
- Rate of participants who experience a complete AK field regression over time ('complete clearance rate', 'total clearance rate')

- Rate of subsequent recurrence of AK lesions in participants after spontaneous complete field regression
- Changes in total counts of AK lesions over time

Data from studies reporting on more than one of the selected outcomes were reported in each category of evaluation.

3.4. Eligibility criteria

Uncontrolled cohort studies and data on control groups (placebo-treated, vehicle-treated or without intervention) from RCTs were included into this systematic review as available data sources if the studies reported on at least one of the selected outcomes (see 3.3. 'Outcomes of interest'). The studies had to report primary and original data in English or German languages to be eligible. The assessment of AK and/or SCC lesions in the studies could be based on clinical and/or histological diagnosis.

Data from studies reporting on populations with varying degrees of susceptibility to the development of AK and SCC were reported separately. Depending on the respective characteristics of the included population, studies reporting on a population of participants without a history of NMSC or immunosuppression, studies reporting on organ transplant recipients, and studies reporting on participants with pre-existing or preceding NMSC were differentiated.

Studies were excluded from the review if they reported on participants with a particular predisposition for the development of NMSC and melanoma (e. g. Xeroderma pigmentosum), if they had a follow-up interval of less than 6 months, or if the sample size was less than 10 participants. Studies that reported on subsequent recurrence rates in participants who received an explicit treatment at study entry (e. g. recurrence of AK in patients with field cancerization after photodynamic therapy) were also excluded.

An exception with respect to the exclusion criteria was only made for studies reporting on rates of contiguous AK lesions in SCC specimen: For these studies, a cross-sectional or retrospective study design was accepted and a 'follow-up of less than six months' was therefore no reason for exclusion. All other inclusion and exclusion criteria were applied to these studies as to the other identified publications.

3.5. Selection of eligible studies

All search results were individually and independently screened for eligibility by two assessors (Dr. med. Adel Sammain, Dr. med. Vanessa Hartmann / Ricardo Niklas Werner), checking titles and abstracts for the inclusion and exclusion criteria. Full texts of all publications that were considered as potentially relevant during the abstract screening were obtained. Eligibility of the full text studies was similarly checked by two independent assessors (Ricardo Niklas Werner, Dr. med. Adel Sammain). Cases of dissent during the independent abstract or full text screening were discussed, involving a third assessor (PD Dr. med. Alexander Nast).

3.6. Data extraction

Extraction of the data was done using a standardized data extraction form for all studies. Two assessors (Ricardo Niklas Werner, Dr. med. Adel Sammain) independently extracted the relevant data from the publications. The two data sheets were compared with each other and any mismatch was reviewed and discussed.

Collected data included author and year, study characteristics (study type, country of the study, number of the included participants, reported outcomes, period of inclusion of patients, length of follow-up), characteristics of the included population (age, sex, number of AK lesions at baseline, medical history of NMSC or immunosuppression), assessment of the methodological quality (see 3.7. 'Assessment of the methodological quality of included trials'), and results (with respect to the reported relevant outcomes).

3.7. Assessment of the methodological quality of included trials

3.7.1. Methodological quality of the included prospective longitudinal studies

To assess the methodological quality of the included studies, a modified version of the Newcastle-Ottawa-Scale⁶⁸ was used. The Newcastle-Ottawa-Scale is a tool suggested by the Cochrane Handbook for Systematic Reviews of Interventions⁶⁹ to assess the risk of bias in non-randomized studies. In this systematic review, 5 of the criteria suggested by the Newcastle-Ottawa-Scale were suitable for assessing the risk of bias in the included trials:

- Representativeness of the study population
- Ascertainment of the exposure (clinical diagnosis of AK at baseline)

- Assessment of the outcome (clinical or histological diagnosis with a real participant contact)
- Sufficiently long follow-up (at least 12 months)
- Adequacy of follow-up (less than 20% of participants lost)

In addition to these items suggested by the Newcastle-Ottawa-Scale, the included publications were checked for additional risks of confounding:

- Provision of data on sunscreen use and sun exposure (or alternatively provision of information on recommendations that were given to the participants at the beginning of the study)
- Provisions of data on therapies applied during the follow-up period

3.7.2. Methodological quality of the included cross-sectional/retrospective studies

For publications reporting data on contiguous AK lesions in SCC specimens, modified methodological quality characteristics had to be applied due to the different study design. Methodological quality assessment for these studies consisted of a check for the representativeness of the selection of SCC specimens, the mode of the ascertainment of contiguous AK in the specimens (high quality: histological (re)evaluation of the specimen, low quality: chart review), the provision of a definition of the meaning of 'contiguous', the provision of a definition of the histological differences between AK and SCC, and check for a blinding of the assessor to the original chart diagnosis. Studies were further evaluated for the provision of information on the rate of incomplete excisions of the analyzed specimens.

3.8. Analysis and presentation of the results

3.8.1. Presentation of the results of the systematic review

Data on the study characteristics and the methodological quality of the prospective longitudinal studies included into the systematic review are presented in Table 8 (see 7.1.1. 'General characteristics of the included prospective longitudinal studies (Table 8)'). Data on study characteristics and the methodological quality of cross-sectional/retrospective studies reporting on rates of contiguous AK lesions in SCC specimens are presented in a separate table due to the different quality assessment for these studies (see 7.1.2. 'General characteristics of the included cross-sectional/retrospective studies (Table 9)').

The results of the systematic literature search and appraisal with respect to the defined relevant outcome data are presented using overview tables concerning each outcome:

- Data on the progression of AK to SCC or on the relation of AK to SCC
 - Rates of progression of single AK lesions to SCC per year (Table 2, see chapter 4.4.1.)
 - Risk or odds ratios for developing SCC relative to the number of preexisting AK (Table 3, see chapter 4.4.2.)
 - Rates of contiguous AK lesions in SCC specimens (Table 4, see chapter 4.4.3.)

- Data on the natural history of AK with respect to quantitative changes
 - Rates of regression of single AK lesions per time unit and rates of subsequent recurrence (Table 5, see chapter 4.5.1.)
 - Rates of complete field regression of AK lesions over time and rates of subsequent recurrence of AK lesions after spontaneous complete field regression (Table 6, see chapter 4.5.2.)
 - Changes in total counts of AK lesions over time (Table 7, see chapter 4.5.3.)

Due to the expectably low number of comparable high quality studies, a meta-analysis of the data was not carried out. The results obtained from the systematic assessment were analyzed descriptively, taking into account the risk of bias of the individual studies.

3.8.2. Extrapolation of the overall risk of the ‘standard AK patient’ to develop an SCC

Rates of a single AK lesion to progress to SCC are not the most interesting information for healthcare providers, physicians and patients. As most patients with AKs are affected by multiple AK lesions and have them over a time interval longer than 12 months, the risk of development of SCC in the individual patient is considerably higher.

A statistical method of extrapolating the risk of a patient with the condition of multiple AK to develop at least one SCC over a certain time period has been outlined by Dodson et al.⁷⁰:

$$\text{Risk_of_SCC} = 1 - [(1 - \text{ROP})^{nm}]$$

This calculation extrapolates the risk of a patient to develop at least one SCC (Risk_of_SCC) within a certain time period (m = number of years), based on a given risk of a single AK lesion to progress to SCC per year (ROP), and a given number of AK lesions per patient (n).

Dodson et al.⁷⁰ derived the equation as follows: If the risk of progression for one lesion in a year of follow-up is ROP, then the probability of no progression within that year is $1 - \text{ROP}$. The probability of no progression within one year for more than 1 AK lesion is $(1 - \text{ROP})^n$, where n is the number of lesions in a patient. Exponentiation of that probability with the number of years (m) yields the probability that none of the n AK lesions progresses to SCC over the time period of m years: $(1 - \text{ROP})^{nm}$. Finally, the probability that at least one of the n AK lesions progresses to SCC within the time period of m years (Risk_of_SCC) is calculated as the complementary probability: $1 - [(1 - \text{ROP})^{nm}]$.

In the present study, the equation was applied for the obtained data on the risk of progression of a single AK lesion to SCC (ROP) for the respective populations. As number of AK lesions (n) in the 'standard patient', the data on mean baseline AK counts from the studies were used. A time interval of 10 years ($m = 10$) was chosen for the calculation.

4.Results

4.1. Study selection

The systematic literature search generated 4741 hits (3090 after removal of duplicates). 2967 of these were excluded during the screening of the titles and abstracts. After assessment of the full texts of the remaining 123 publications, 31 were evaluated as eligible for inclusion into this systematic review. Three further studies were identified through reviews of the reference lists of the assessed full text articles. Two of these three additional studies were included into the analysis. Altogether, 33 publications were included into the evaluation. Figure 1 illustrates the process of study selection.

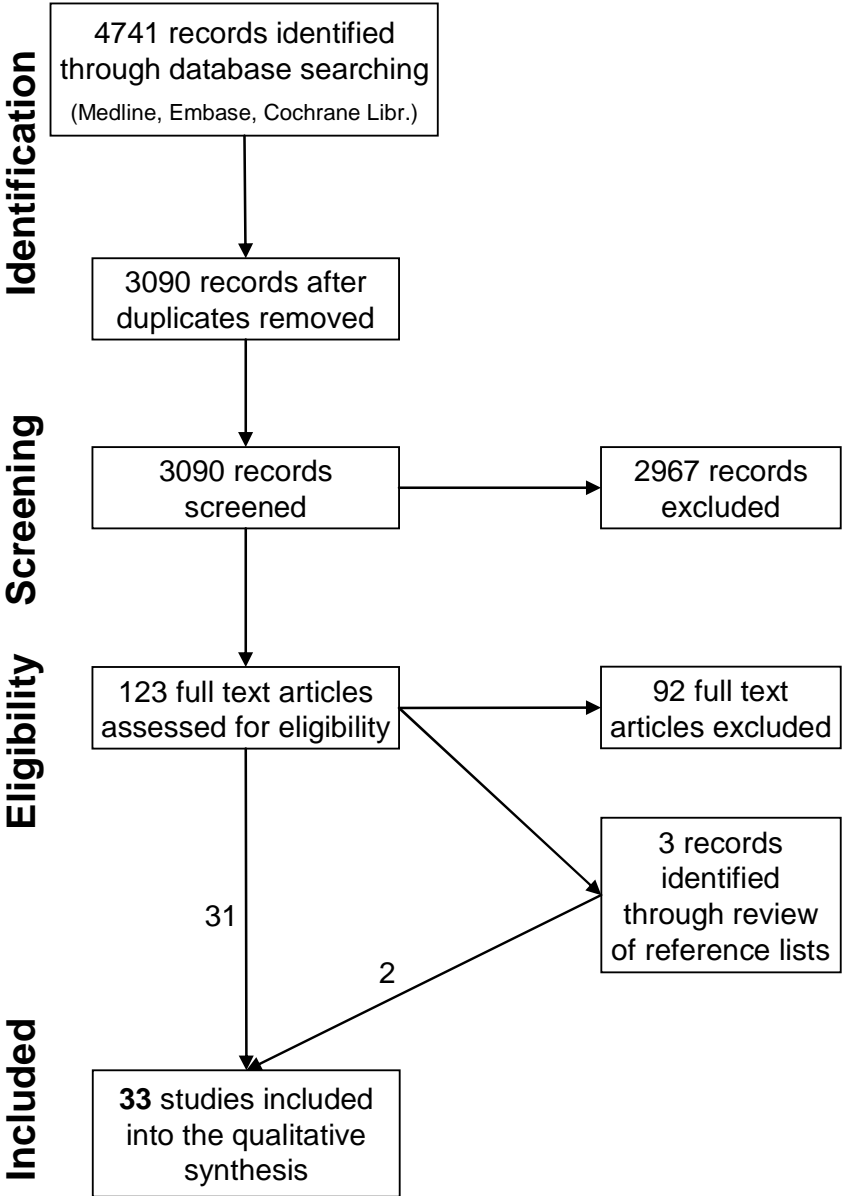


Figure 1. Process of study identification and selection

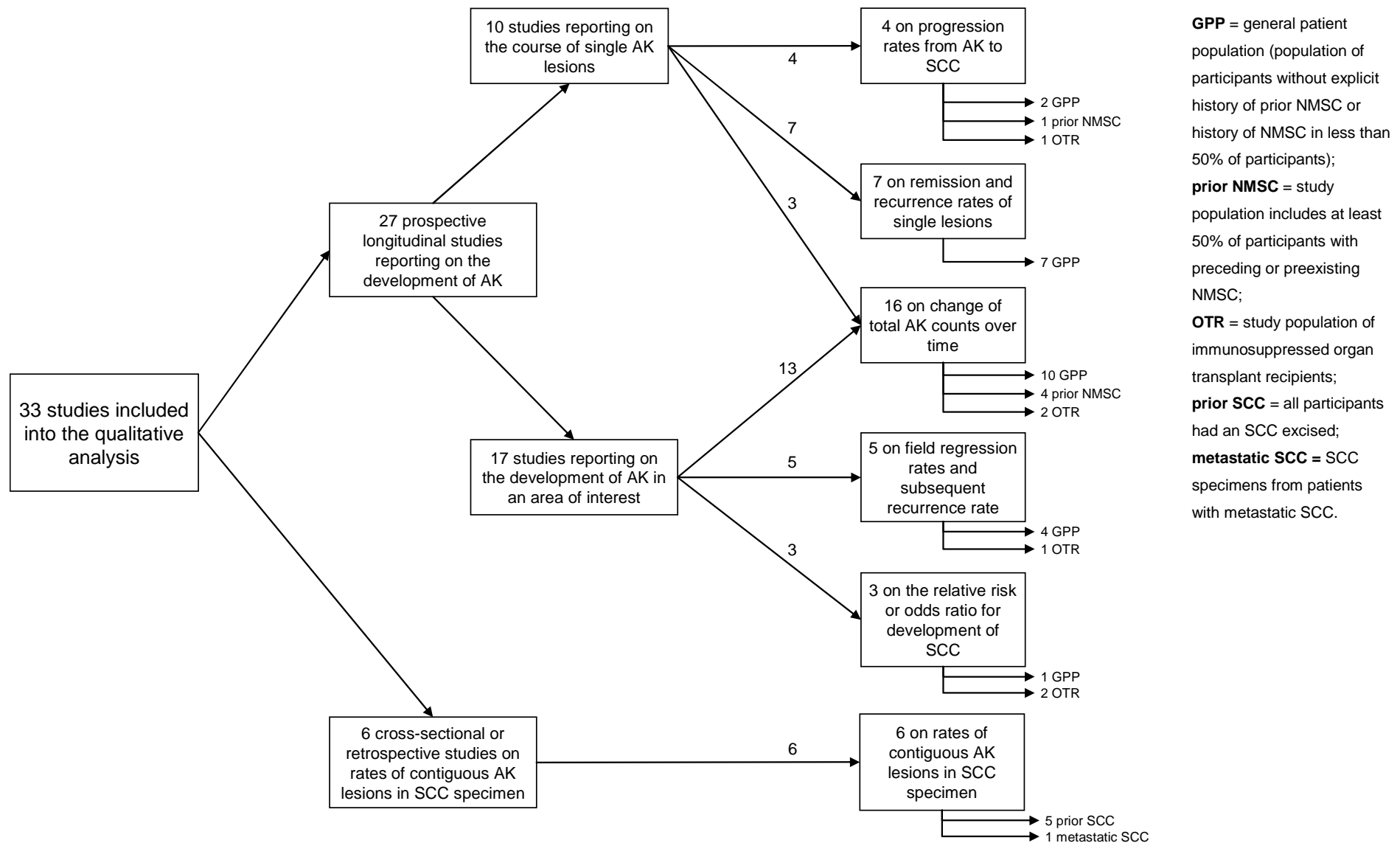
4.2. Characteristics of the included studies

The total of 33 included studies^{37-39,50,71-99} contained fifteen RCTs with data that were obtained from the non-interventional (or placebo/vehicle) group,^{71,72,75-79,81-84,86,88,89,99} two RCTs^{50,74} and one non-randomized controlled trial⁸⁵ comparing the effects of sunscreen versus no sunscreen use, nine prospective cohort studies^{37-39,73,80,87,91,94,97} and six cross-sectional/retrospective studies.^{90,92,93,95,96,98}

As several studies reported on more than one outcome, the total number of studies reporting on each of the relevant outcomes was higher than the number of included studies. The following list summarizes the number of publications identified for each outcome:

- 4 of the identified publications reported data on rates of progression of a single AK lesion to SCC^{39,73,80,86}
- 7 studies contained data on remission and recurrence rates of single AK lesions^{37-39,50,82,87,99}
- 16 studies reported on the change of total AK lesion counts^{38,50,71,72,74-77,79,81,83-85,87-89}
- 5 studies on complete field regression and/or subsequent recurrence rates^{72,78,79,83,84}
- 3 studies on relative risk / odd ratios for the development of SCC^{91,94,97}
- 6 studies on contiguous AK lesions in SCC specimen^{90,92,93,95,96,98}

Figure 2 further illustrates numbers of study types, reported outcomes and population characteristics.



GPP = general patient population (population of participants without explicit history of prior NMSC or history of NMSC in less than 50% of participants);

prior NMSC = study population includes at least 50% of participants with preceding or preexisting NMSC;

OTR = study population of immunosuppressed organ transplant recipients;

prior SCC = all participants had an SCC excised;

metastatic SCC = SCC specimens from patients with metastatic SCC.

Figure 2. Types of studies, numbers of studies reporting on each outcome, and specification of population

4.3. Quality and risk of bias assessment

4.3.1. Quality assessment and risks of bias within the prospective longitudinal studies

The methodological quality of the included prospective trials was generally low. The following list summarizes the most important methodological limitations:

- Study population with risk of selection bias and/or missing information on the selection/recruitment of participants^{71-73,75-79,81-84,86-89,91,97,99} (19/27)
- Missing information on intermittent treatment of lesions during the observation period of the study^{71,72,76,77,79,81-84,86-89,91,94,97} (16/27)
- Missing information on sunscreen use or sun avoidance recommendations given to the participants and/or on the participants' respective behavior^{38,39,71,78-80,82-84,86-89,91,94,99} (16/27)
- Follow-up period of less than twelve months^{50,56,71,75,76,79,81,83,87-89,91} (12/27)
- Dropout rate of more than 20% of the participants or not reported^{39,50,72,74,77,78,80,84,87,89} (10/27)
- The mode of the outcome assessment was not reported in one study⁸⁷ and outcome assessment was based on a questionnaire survey in one study⁹⁴ (2/27)
- The mode of the ascertainment of the baseline diagnosis was not reported in one study⁸⁷ (1/27)

Treatment of lesions became necessary during the observation period of some studies, because clinical assessment could not always clearly differentiate between AK and invasive SCC, and participants with treatment during the course of the study often were excluded from the analysis or participation.^{37-39,50,73,74,80,85} Excluding these potentially more severely affected participants from participation or evaluation introduces a risk of selection and/or reporting bias. The treatment itself may have an impact on the surrounding skin and therefore influence the development of other lesions in the area.

Sixteen of the 27 prospective studies did not report whether a recommendation with respect to sunscreen use or sun avoidance during the study period was given to the participants^{38,39,71,78-80,82-84,86-89,91,94,99} (thirteen of these reporting on a population of participants without history of prior NMSC or immunosuppression, three on organ transplant recipients). Eight studies explicitly reported to have encouraged the use of

sunscreen or the avoidance of sun exposure^{37,72,73,75-77,81,97} (three reporting on a population of participants without a history of prior NMSC or immunosuppression, four on participants with a history of NMSC and one on organ transplant recipients). Three trials compared the effects of regular use of sunscreen with no sunscreen use^{50,74,85} (one study reporting on a population of participants without history of prior NMSC or immunosuppression, one study on participants with a history of NMSC and one study on organ transplant recipients).

Prospective cohort studies following up specific patient populations (e.g. organ transplant recipients) were included into the review, and some of the cohorts included participants without AKs at baseline. When assessing the mean numbers of baseline AKs and the mean changes of total AK counts, the participants not affected by AK result in a reduction in the mean counts of AKs and in a lowering of the average change in total AK counts. This effect could have played a role in three studies.^{74,77,85}

Table 8 presents the study characteristics, quality rating and outcome categories of the included prospective studies (see 7.1.1. 'General characteristics of the included prospective longitudinal studies (Table 8)').

4.3.2. Quality assessment and risk of bias within the cross-sectional / retrospective studies

The methodological quality of the included cross-sectional or retrospective studies reporting on rates of contiguous AK lesions in SCC specimens was low as well. The following list summarizes the most important methodological deficits:

- No information on rates of incomplete excisions in the evaluated specimens presented^{92,93,95,96,98} (5/6)
- No definition of the meaning of 'contiguous' provided^{90,92,93,95,98} (5/6)
- No information with respect to blinding of the assessor to the chart diagnosis^{90,93,95,96,98} (5/6)
- Selection bias or missing information on the mode of recruitment / selection of the analyzed specimens^{93,95,96,98} (4/6)
- No definition of the histological differences of AK and SCC provided^{90,92,93} (3/6)
- Assessment based on chart review and not on re-evaluation of SCC specimens^{90,98} (2/6)

None of the studies contained information on the medical history of the patients from whom the specimens were taken with respect to preceding NMSC, numbers of AK or immunosuppression. One study reported on the evaluation of specimens of SCC on sun-damaged skin⁹⁵ and one study reported on that of specimens of metastatic cutaneous SCC.⁹³ In the same study, 9 of 22 specimens were reported to be present as transections of the tumor, which implies that a determination of the level of invasion of the identified contiguous 'AK lesions' was not possible.⁹³

Table 9 presents the study characteristics, quality rating and outcome categories of the included cross-sectional and retrospective studies (see 7.1.2. 'General characteristics of the included cross-sectional/ retrospective studies (Table 9)').

4.4. Results of individual studies: Data on the relation of AK to SCC

4.4.1. Progression rates of single AK lesions to SCC

A rate of progression from a single AK lesion to SCC of 0.075% per year was reported by Marks et al.,⁸⁰ following up a cohort of participants with at least one AK at baseline. The risk of progression rose up to 0.096% per year, when SCCs for which the baseline diagnosis of AK in the corresponding localization was not clear were included into the analyses. The participants were recruited as a cohort of citizens from Maryborough (Australia), who were at least 40 years old and had at least one AK lesion at baseline. The mean age of the participants was 60.1 years. A study on a cohort of 560 participants of whom 23% had at least one AK at baseline³⁹ did not show any progression of the observed AK to SCC during the follow-up period (mean follow-up of 17.2 months). The cohort similarly was community-based, set up as a random sample of citizens from the county of South Glamorgan in the UK. Mean age of the participants in this cohort was 71.2 years.

A 0.53% risk of progression from a single AK lesion into invasive SCC per year was identified by Criscione et al.⁷³ in a population of patients with a history of at least 2 NMSC in the last 5 years. When the risk of progression from single AK lesions into 'in situ SCC' or invasive SCC was analyzed, the progression rate was reported to be 0.89% per AK lesion per year. A 5 year risk of progression of a single AK lesion into invasive SCC of 2.88% was reported for the same population. The participants of this study were recruited from a medical center and were part of a clinically controlled trial on the use of 0.1% topical tretinoin for the prevention of skin cancer. 81 of the 182

participants received the verum during the observational period. Mean age was 68 years.

No progression from AK to SCC was reported in a trial that included 28 immunosuppressed organ transplant recipients.⁸⁶ The study was a split-patient trial with a follow-up of 12 months, including participants with a mean age of 57 years.

The data are summarized in table 2.

Table 2. Risk of progression of single AK lesions to SCC

Publication	No. pts. / mean no. of lesions p.p. / absolute no. of lesions in study	Follow-up time (months)	Advice to use sun-screen	Risk of progression to SCC per AK lesion per year	Further results	Comments
Participants without history of prior NMSC or immunosuppression						
Harvey, 1996 ³⁹	560 / mean 1.9 AK per affected pt. / 239 lesions	12-24 (mean: 1.43 years)	-	0%	-	Prevalence of AK at baseline: 23%, unclear data on dropouts (>30%)
Marks, 1988 ⁸⁰	1689 / no data / no data	12	-	0.075% (including doubtful cases: 0.096%)	Percentage of SCC that developed at a site with preexistent AK (new SCC with knowledge about the previous skin condition): 58.8%	see comment in overview table 8
Participants with history of NMSC						
Criscione, 2009 ⁷³	182 / 12 lesions p.p. in affected pts. / 1960 lesion	4-71 (mean 42)	+	risk of progression of baseline AK to invasive SCC: 0.53%; risk of progression of BL-AK to 'in situ' and invasive SCC: 0.89%	Percentage of SCC that developed at a site with preexistent AK: 65%; 5-year risk of progression of BL-AK to invasive SCC: 2.88%	Pts. with history of NMSC; prevalence of AK at baseline: 95%; see comment in overview table 8
Participants with immunosuppression						
Wulf, 2006 ⁸⁶	28 / mean 2.9 lesions / 80 lesions	12	-	0%	-	OTR

Abbreviations: AK = actinic keratosis, BL = baseline, NMSC = non-melanoma skin cancer, no. = number, OTR = organ transplant recipients, p.p. = per person, pts. = participants, SCC = squamous cell carcinoma

4.4.2. Risk or odds ratios for developing SCC relative to the number of pre-existing AK

On a community-based cohort of participants of whom 40% had AK at the baseline, Green et al.⁹⁴ showed age- and sex-adjusted relative risks for the development of SCC of 1.7 for participants with 1-5 facial AK at baseline, of 4.2 for participants with 6-20 facial AK at baseline, and of 11.0 for participants with more than 20 facial AK at baseline (reference were participants without facial AKs at baseline). The age ranged from 20 to 69 years in the respective population, no mean age was specified.

For populations of organ transplant recipients, a relative risk of developing a subsequent SCC of 6.9⁹¹ and an odds ratio of 56.4⁹⁷ was reported for patients presenting with AK at baseline (reference were patients without AK at baseline). Ramsay et al.⁹⁷ further differentiate their results, reporting an odds ratio of 17.9 for patients presenting with 1-10 preexisting AK and of 89.4 for patients presenting with more than 10 preexisting AK (reference were patients without preexisting AK). The data from both studies were derived from hospital-based populations. Mean age in one study was 49 years,⁹¹ in the other study it was not specified.⁹⁷

No data were available for populations of participants with a history of NMSC.

Table 3 summarizes the data obtained on the risk or odds ratios for the development of SCC relative to the number of preexisting AK.

Table 3. Relative risks and odds ratios for developing SCC relative to the number of pre-existing AK

Publication	No of pts. / Prevalence of AK at baseline	Follow-up time (months)	Advice to use sun-screen / avoid sun exposure	Relative risk (RR) / odds ratio (OR) [Reference: no pre-existing AK]	Further results	Comments
Participants without history of NMSC or immunosuppression						
Green, 1990 ⁹⁴	2095 pts./ prevalence of AK at baseline: 40%	24	-	- 1-5 facial AK: RR = 1.7 - 6-20 facial AK: RR = 4.2 - >20 facial AK: RR = 11.0	-	Follow-up was based on a postal survey
Participants with immunosuppression						
Caforio, 2000 ⁹¹	300 pts./ prevalence of AK at baseline: 25.7%	Mean 55.2	-	preexisting AK: RR = 6.9 (p=.001)	Hazard ratio for developing SCC (Reference: no preexisting AK) with preexisting AK = 6.87 (p=.001)	OTR (heart transplant); RR only presented in the abstract; in the full text, the hazard ratio is referred to
Ramsay, 2000 ⁹⁷	182 pts./ prevalence of AK at baseline: 15.4%	Mean 15.36	+	- preexisting AK: OR = 56.4 (p<.001) - 1-10 preexisting AK: OR = 17.9 (p<.001) - > 10 preexisting AK: OR = 89.4 (p<.001)	Prevalence of AK was descriptively correlated to the time since transplantation: - < 5y: 4.9% - 5-10y: 12.7% - > 10y: 25.9%	OTR (renal transplant)

Abbreviations: AK = actinic keratosis, BL = baseline, no. = number, OR = odds ratio, OTR = organ transplant recipients, pts. = participants, RR = relative risk, SCC = squamous cell carcinoma

4.4.3. Rates of contiguous AK lesions in SCC specimens

Rates of SCC specimens with contiguous AK lesions ranged from 15.9% to 97.2%.^{90,92,93,95,96,98} In a study on metastatic cutaneous SCC, 44% of the specimens had contiguous AK lesions and further 17% of the analyzed specimens had overlying or adjacent AK lesions.⁹³ The mean age of the patients at the time of excision ranged from 75 years⁹⁵ to 83.3 years⁹⁰ in the included studies. No data on the mean age were available in two studies.^{93,96}

Table 4 summarizes the data obtained on the rates of SCC specimens with contiguous AK lesions.

Table 4. Rates of SCC specimens with contiguous AK lesions

Publication	No of pts. / no. of SCC specimens	Rate of SCC specimens with contiguous AK lesions	Comment
Ang, 2004 ⁹⁰	57pts. / 63 SCC specimens	15.9%	Evaluation of all excised SCC during 1991 to 1995, SCC treated with other modalities were excluded
Czarnecki, 2002 ⁹²	208 SCC specimens	72%	-
Dinehart, 1997 ⁹³	22 SCC specimens	44% contiguous; 17% overlying or adjacent, but not contiguous	Metastatic cutaneous SCC; SCC from the vermillion border of the lips were excluded
Guenther, 1999 ⁹⁵	859 pts. / 1011 SCC specimens	97.2%	Authors report contiguous “in situ SCC” in SCC specimens
Mittelbronn, 1998 ⁹⁶	145 pts. / 165 SCC specimens	82.4% of SCC with concomitant AK	-
Takemiya, 1990 ⁹⁸	53 SCC specimens	58.5%	-

Abbreviations: AK = actinic keratosis, no. = number, pts. = participants, SCC = squamous cell carcinoma

4.5. Results of individual studies: Data on the natural history of AK

4.5.1. Regression and recurrence rates of single AK lesions

In 5 studies on populations of participants without history of NMSC or conditions of immunosuppression, the reported regression rates of single AK lesions ranged from 18 to 62.9% after a follow-up of 7, 11, 12 or 17 months.^{37-39,50,87} Frost et al. (2000)³⁷ reported an at least transient regression of 74% of AK lesions present at baseline, but 15% of the regressed lesions subsequently recurred. A calculation showed that 62.9% of AK lesions regressed without subsequent recurrence during the 12 months follow-up. This study excluded participants with field cancerization and recommended the participants to continue their usual sunscreen use. The age of the included participants ranged from 30 to 69 years. Age ranges of the participants from the other studies reporting on this outcome were 39-79,⁸⁷ ≥60,³⁹ 40-99,³⁸ and 40-93⁵⁰ years. Harvey et al. (1996)³⁹ reported that 21% of the AK lesions present at baseline regressed during the follow-up period (mean follow-up of 1.4 years). The authors of the study extrapolate a lesion-year adjusted regression rate of 15% of AK lesions. In an RCT on the effects of sunscreen use, a statistically significant difference of the regression rates during 7 months of follow-up between the sunscreen group and the placebo group of 25% and 18%, respectively, was shown.⁵⁰ No data on regression

rates in populations of participants with a history of NMSC or of organ transplant recipients were found.

With respect to rates of subsequent recurrence of AK lesions after an initial regression, again only data on populations of participants without history of NMSC or immunosuppression were identified. As described above, a recurrence rate of 15% after an initial regression rate of 74% of the individual AK lesions present at baseline was reported in one trial³⁷ on a community-based population. In two publications reporting on three trials following up AK lesions for 12 months after their spontaneous regression, 15%, 53%,⁹⁹ and 20.2%⁸² of the lesion recurred. Data on recurrences from these trials were derived from hospital-based populations with sample sizes of 12, 22,⁹⁹ and 98⁸² participants, respectively. In a prospective cohort study with very limited information on methods and participants' characteristics, 32.6% regressed and recurred, and 10.6% of the lesions present at baseline regressed twice within a follow-up period of 11 months.⁸⁷

The available data on regression and subsequent recurrence rates of single AK lesions are summarized in Table 5.

Table 5. Regression and recurrence rates of single AK lesions

Publication	No of pts. / mean no. of lesions p.p. / total no. of lesions in study (BL)	Advice to use sun-screen	Regression of AK lesions present at BL after 12 months	Recurrences of single lesions	Comments
Participants without history of NMSC or immunosuppression					
Cantrell, 2009 ⁸⁷	27 pts. / mean 23.5 lesions / 635 lesions	-	29.7%*	Percentage of lesions present at baseline with regression and recurrence: 32.6%; Percentage of lesions present at BL that regressed twice: 10.6%	Pts. with extensive sundamage; n. i. on methods and confounders; only abstract available
Frost, 2000 ³⁷	96pts. / 11.49 lesions p.p. in affected pts. / 494 lesions	(-)	74.0% (percentage of lesions present at BL that regressed without recurrence: 62.9%)	Percentage of regressed AK that recurred during the study period: 15%	Prevalence of AK at BL: 46%; pts. with field cancerization or more than 50 AK at one site were excluded; see comment in table 8
Harvey, 1996 ³⁹	560 / mean 1.9 lesions in affected pts. / 239 lesions	-	21%***; calculated rate of regression: 15% of AK lesions / year	-	Prevalence of AK at BL: 23%, unclear data on dropouts (>30%)
Marks, 1986 ³⁸	618 pts. / mean 7.7 lesions / 4759 lesions	-	25.9%	-	Pts. with treatment were excluded
Stockfleth, 2012 ⁸²	98 pts. / no data / no data	-	-	Percentage of regressed lesions that recurred within 12 months after regression: 20.2%	-
Szeimies, 2010 ⁹⁹	34 pts (12 and 22) / 5.5 and 5.9 lesions / 476 lesions	-	-	Percentage of regressed lesions that recurred within 12 months after regression: 15% and 53%	Pts. with recurrence of all lesions were withdrawn, see comment in overview table 8
Thompson, 1993 ⁵⁰	588 pts. / mean 8.12 lesions / 3498 lesions	+/-	Sunscreen group: 25%**; Placebo group: 18%**	-	> 20% dropouts; any lesion treated during the course of the study was excluded from analysis

Follow-up periods: * = 11 months; ** = 7 months; *** = 12-24 months (mean = 1.43 years);

Abbreviations: AK = actinic keratosis, BL = baseline, n. i. = no information, NMSC = non-melanoma skin cancer, no. = number, p. p. = per person, pts. = participants

4.5.2. Rates of complete field regression und subsequent recurrences

Complete field regression rates from AK that were reported in the identified studies on populations of participants without history of NMSC or concomitant immunosuppression varied from 0% to 7.2% of the included participants for observed areas on the face or scalp.^{72,79,83} A complete field regression rate from AK for an observed area on the upper extremities of 21% was reported on a small study group of 14 participants.⁷² Partial field regressions (regression of at least 75% of the lesions present at baseline) were seen in 4.3 to 13.6% of the observed participants without history of prior NMSC during the 6 months of follow-up.^{79,83}

In a small population of organ transplant recipients (14 participants), a complete (100%) and partial (75%) field regression rate of 0% within a time period of 6 months was reported.⁸⁴ No data on field regression rates were available for participants with a history of NMSC.

Only one study reported data on the percentage of participants that had experienced a recurrence after a spontaneous complete field regression: 57% of participants from a population of 18 patients who had experienced a spontaneous complete regression of their observed field had a recurrence within a follow-up period of 12 to 14 months.⁷⁸

The mean age of the included participants was 61.6 years,⁸⁴ 65.9 years,⁷⁹ 70.9 years,⁸³ or not reported.^{72,78} All data on field regression and recurrence were derived from inpatient or outpatient populations.

The available data on rates of spontaneous complete field regression rates and rates of subsequent recurrence are shown in Table 6.

Table 6. Rates of complete field regression and subsequent recurrence

Publication	No of pts. / mean no. of lesions p.p. / total no. of lesions in study (BL)	Follow-up time (months)	Advice to use sunscreen / avoid sun exposure	Rate of pts. with a complete field regression (100% of AK lesions in a defined field)	Rate of pts. with subsequent recurrence(s) after spontaneous complete field regression	Comment
Participants without history of prior NMSC or immunosuppression						
Alirezai, 1994 ⁷²	49 pts. / mean 7.8 (face); 9.7 (scalp); 8.4 (upper extr.) lesions / no data	12	+	Face: 2%; Scalp: 0%; Upper extr.: 21%	-	> 20% dropouts; pts. who had skin cancer or suspect lesions at baseline were not included; see comment in table 8
Jorizzo, 2007 ⁷⁸	18 pts. / median 6 lesions / no data	12-14	-	-	57%	> 20% dropouts; see comment in table 8
Korman, 2005 ⁷⁹	250 pts. / no data / no data	6	-	7.2%; 75%-regression: 13.6%	-	see comment in table 8
Szeimies, 2004 ⁸³	139 pts. / mean 5.5 lesions / 766 total lesions	6	-	2.2%; 75%-regression: 4.3%	-	see comment in table 8
Participants with immunosuppression						
Ulrich, 2007 ⁸⁴	14 pts. / no data / no data	6	-	0%; 75%-regression: 0%	-	OTR (kidney-, liver- or heart-Tx more than 3y prior to entering the study); > 20% dropouts; see comment in table 8

Abbreviations: AK = actinic keratosis, BL = baseline, NMSC = non-melanoma skin cancer, no. = number, OTR = organ transplant recipients, p. p. = per person, pts. = participants, Tx = transplant, y = years

4.5.3. Change in total AK counts over time

Numerous publications reported data on the relative changes of the mean AK counts in the participants over time, showing a broad range from -53% to +99.1%.^{38,50,71,72,74-77,79,81,83-85,87-89}

The range was narrower for studies on participants without history of NMSC or immunosuppression, from -37 to +57%.^{38,50,71,72,77,79,83,87-89} For populations including participants with history of NMSC, relative changes of total AK counts over time from -23% to +57% were observed.^{74-76,81} The broadest range was found in studies on populations of organ transplant recipients, with relative changes of total AK counts over time ranging from -53% to +99.1%.^{84,85}

The 'sunscreen use and/or sun avoidance recommendations' may serve as an explanation for the broad ranges of reported changes: In studies that explicitly reported having recommended participants to protect themselves from sun radiation, relative changes of AK counts with a trend towards a reduction in the numbers of AK lesions (range: -53% to +20%) were seen, with 7 of 8 studies reporting decreases in the total AK counts.^{50,72,75-77,81,85} In studies without information on sun protection recommendations given to the participants or in control groups of sunscreen trials, a trend towards increasing AK counts (range: -14.3% to 99.1%) can be seen, with 8 of 11 studies showing increasing AK numbers.^{38,50,74,84,85,87-89} These trends hold true for studies on populations of participants without history of prior NMSC or immunosuppression as well as for studies on populations of participants with history of prior NMSC and populations of organ transplant recipients.

The mean age of the participants who were included into the studies was 48 years⁷⁴ to 75 years.⁸⁹ Data on the mean age were not reported in three studies.^{71,72,87} Age was not a consistent modifier of the relative changes of AK counts: On participants with a mean age of 48 years and 50 years, one study reports an increase of 57%⁷⁴ and another study a decrease of 33% of the mean AK lesion counts per participant.⁷⁷ In studies on older populations, reported changes also include a broad range without any obvious correlation to the age of the participants.

The available data on relative changes of total AK counts over time are summarized in Table 7.

Table 7. Changes in the total AK lesion count over time

Publication	No of pts. / mean no. of lesions p.p. / total no. of lesions in study (BL)	Follow-up time (months)	Advice to use sun-screen / avoid sun exposure	relative Difference in total AK lesion counts from baseline to the end of study	Further results	Comment
Participants without history of prior NMSC or immunosuppression						
Alberts, 2000 ⁷¹	48 pts. / mean 29.2 lesions / 1402	6	-	- 2.4%	-	-
Alirezai, 1994 ⁷²	49 pts. / mean 7.8 (face); 9.7 (scalp); 8.4 (upper extr.) lesions / no data	12	+	Face: - 21.8% Scalp: - 37.1% Upper Extr.: - 11.9%	-	> 20% dropouts; pts. who had skin cancer or suspect lesions at BL were not included
Cantrell, 2009 ⁸⁷	27 pts. / mean 23.5 lesions / 635 lesions	11	-	+ 57%	-	Pts. with extensive sundamage; n. i. on methods and confounders; only abstract available
Green, 1998 ⁷⁷	35 pts. / mean 3.6 lesions / 126 lesions	12	+	- 33.3%	-	> 20% dropouts; all pts. with 'photoaging'
Kang, 2003 ⁸⁸	30 pts. / no data / no data	9	-	Mean increase in total no. of AK: + 1.5	-	No data for calculation of the relative difference of AK lesion counts from baseline to end of study presented
Korman, 2005 ⁷⁹	250 pts. / no data / no data	6	-	Median count reduction: -14.3%	Rate of pts. with increase in AK count at any point in the treatment period: 22.0%	see comment in table 8
Marks, 1986 ³⁸	618 pts. / mean 7.7 lesions / 4759 lesions	12	-	+ 21.8%	36.4% of pts. had a remission of at least 1 AK	Pts. with treatment were excluded
Szeimies, 2004 ⁸³	139 pts. / mean 5.5 lesions / 766 total lesions	6	-	- 8.7%	-	-
Thompson, 1993 ⁵⁰	588 pts. / mean 8.12 lesions /	7	+/-	Sunscreen group: - 6.7%;	-	> 20% dropouts; any lesion treated during the

	3498 lesions			Placebo group: +12.5%		course of the study was excluded from analysis
Zeichner, 2009 ⁸⁹	20 pts. / median 9.5 lesions / no data	7	-	Average change in total lesions number score*: +0.07	-	> 20% dropouts; *Total lesions number score: score 0 for 0 AKs; score 1 for 1-3 AKs; score 2 for 4-6 AKs; score 3 for > 6 AKs
Participants with history of NMSC						
Darlington, 2003 ⁷⁴	1621 pts. / mean 3.7 lesions / 4129 lesions	30	-/+	Sunscreen group: + 20%*; Control group: + 57%*	Prevalence of AK in the study population: 1992: 46%; 1994: 50%; 1996: 53%	Prevalence of AK at baseline: 46%; prevalence of a history of skin cancer: 27% (436 pts.); > 20% dropouts; *adjusted rates
Elmets, 2010 ⁷⁵	118 pts. / mean 24 lesions / 2832	9	+	-18.5%	-	Prevalence of a history of skin cancer at baseline: 59.3%
Foote, 2009 ⁷⁶	50 pts. / mean 34.3 lesions / 1715	6	+	- 23.3%	-	Prevalence of a history of skin cancer: 40.5% (17 pts.)
Moloney, 2010 ⁸¹	17 pts. / mean 23.5 lesions / 400 lesions	6	+	- 22.4%	-	'sundamaged' pts. with multiple prior skin cancers
Participants with immunosuppression						
Ulrich, 2007 ⁸⁴	14 pts. / no data / no data	6	-	+ 99.1%	-	OTR (kidney-, liver- or heart-Tx more than 3y prior to entering the study); > 20% dropouts
Ulrich, 2009 ⁸⁵	120 pts. / mean 3.18 lesions / 382 total lesions	24	-/+	Sunscreen group: - 53%; Control group: + 43 %	Incidence of SCC in sunscreen group vs. controls during study: 0 vs. 8 (p<.01)	OTR (heart-, liver-, and kidney-Tx, each 40 pts.)

Abbreviations: AK = actinic keratosis, BL = baseline, Extr. = extremities, NMSC = non-melanoma skin cancer, no. = number, OTR = organ transplant recipient, p. p. = per person, pts. = participants, SCC = squamous cell carcinoma, Tx = transplant

4.6. Extrapolation of the risk of development of an SCC for the 'standard' patient

Based on the calculation presented by Dodson et al.⁷⁰ and on the results of the systematic review, the risk of a hypothetical patient to develop at least one SCC over the time of 10 years ($m = 10$) can be extrapolated.

4.6.1. Patients presenting with AK without history of NMSC or immunosuppression

One study presented data on the risk of progression of single AK lesions to SCC in participants without a history of NMSC or immunosuppression.⁸⁰ The risk of progression was reported to be 0.075% per year ($ROP = 0.00075$). As data on the mean number of AK lesions per participant were not presented, the respective number from an earlier publication of the authors on an overlapping population,³⁸ with a mean of 7.7 AK lesions per participant was used ($n = 8$).

$$Risk_of_SCC = 1 - \left[(1 - ROP)^m \right] \Rightarrow Risk_of_SCC = 1 - \left[(1 - 0.00075)^{8 \times 10} \right] = 0.0583$$

For a patient without immunosuppression and without a history of NMSC who presents with 8 AK lesions, the equation extrapolates a 10 year risk of development of SCC of 5.8%.

4.6.2. Patients presenting with AK with a history of NMSC

One study presented data on the risk of progression of a single AK lesion to SCC in patients with a history of multiple NMSC.⁷³ For patients with at least 2 NMSC in the past 5 years, the risk of progression of a single AK lesion into invasive SCC was demonstrated to be 0.53% in one year ($ROP = 0.0053$). The mean number of AK lesions in the participants of the study was 12 AK lesions ($n = 12$).

$$Risk_of_SCC = 1 - \left[(1 - ROP)^m \right] \Rightarrow Risk_of_SCC = 1 - \left[(1 - 0.0053)^{12 \times 10} \right] = 0.4715$$

For a patient presenting with 12 AK lesions who had a history of at least two NMSC in the last 5 years, a 10 year risk for the development of at least one invasive SCC of 47.2% was extrapolated.

4.6.3. Organ transplant recipients presenting with AK

For the risk of progression of single AK lesions to SCC in organ transplant recipients, no applicable data were identified in the available literature. There was only one study on 28 organ transplant recipients that showed no progression within one year.⁸⁶ Therefore it is not possible to extrapolate the overall patient risk for patients with the condition of immunosuppression.

5. Discussion

5.1. *Brief summary of the main findings*

Methodological limitations of the studies identified through the systematic search for primary data on the natural history of actinic keratoses strongly restrict the interpretability, comparability and applicability of the results. Data on progression of single AKs indicate a risk of progression to SCC of up to 0.075% per lesion per year, when looking at participants without a history of NMSC or immunosuppression. The risk was seen to be higher in participants with a history of multiple NMSC, with a progression rate into invasive SCC of 0.53% per AK lesion and year. Because of the methodological limitations, the data obtained on progression rates are not suitable for a reliable estimate of the actual risk of progression. When extrapolating the data for the individual risk of a 'standard patient' with multiple AKs to develop at least one SCC within ten years, the reported lesion-based risks rise dramatically. Data on the relative risks indicate a higher risk of SCC development for organ transplant recipients as compared to participants without history of immunosuppression. In SCC specimens, histological correlates of AK are regularly found to be contiguous to the SCC lesion. Regression of AK occurs in around 20-30% of AK lesions and recurrences in 15-20% of the regressed lesions. Despite of these relatively high regression rates, a complete field regression is unlikely to happen.

5.2. *Overall limitations of the systematic review*

AK is discussed as being a premalignant or malignant in situ lesion of the skin. However this debate is resolved, performing trials on potentially malignant lesions or in situ carcinoma raises difficult questions with respect to methodology and ethics.

5.2.1. *Inclusion of control arms from clinical trials*

Following up cohorts of participants with skin lesions that potentially progress into invasive skin cancer raises severe ethical questions. A small number of observational studies on participants with AK lesions has been performed, probably for this reason. Therefore, control arms from clinical trials were included into this systematic review and considered as observational cohorts. The placebo effect or the possible effects of the vehicles used or placebo interventions has to be taken into account when interpreting the results on the natural history of AK. Especially the use of vehicle creams or gels

might have had an impact on the development of AK lesions, due to emollient or moisturizing effects, especially on hyperkeratotic AK lesions.

5.2.2. Definition of patient subgroups

Populations of the included studies were differentiated, due to the different risks for the development of further AK lesions and the progression to SCC, taking clinically relevant situations into account: Populations of participants without history of NMSC or immunosuppression were reported separately from populations of participants with a history of NMSC and populations of participants with concomitant immunosuppression due to their status as organ transplant recipients. The group of the 'organ transplant recipients' was well-defined, and studies reporting on this population had clear and explicitly reported inclusion criteria. The differentiation between the group of the 'participants without history of prior NMSC or immunosuppression' and the 'participants with a history of NMSC' was more difficult, since population-based cohort studies were included. Studies including a 'population of participants without history of NMSC or immunosuppression' usually did not report whether or how they assured that all included participants were free of preceding or preexisting NMSC. Studies categorized as reporting on a population of 'participants with a history of NMSC' included studies with a history of multiple NMSC as an inclusion criterion for participation as well as studies on mixed populations.⁷⁴⁻⁷⁶ Therefore, the differentiation between the 'population of participants without history of prior NMSC or immunosuppression' and the 'population of participants with a history of NMSC' is not very selective and missing information could have led to an over- or underestimation of the reported outcomes.

The age is another important variable that has to be taken into account when reporting on the natural history of AK. Unfortunately, the age specifications for the different study populations were very overlapping and most of the studies did not provide age-stratified data with respect to the reported endpoints. Partly, exact data on the mean age and range of the study populations were missing. In this review, age as a main influential factor is only discussed for outcomes where this was possible.

Since studies on 'community-based' populations were considered in this review,^{37-39,50,74,80} the terminology of 'patients' does not necessarily reflect the actual situation of some of the included individuals. Individuals presenting with the medical condition of AKs were termed as 'patients' when the population was derived from an inpatient- or

outpatient-based collective and as 'participants' when studies reported on 'community-based' populations. As the respective studies were included into this review with reference to the reported outcomes in participants with prevalent AKs, 'community-based' studies were not separately reported from 'inpatient-based' studies. Nevertheless, the source of participants may have an effect on the reported results.

5.2.3. Assessment and differentiation of AK and SCC

The diagnosis of AK lesions in the clinical trials is based on the clinical examination of the participants in most of the included trials. The validity of this assessment was shown in some studies,⁴⁹⁻⁵¹ but only the histological assessment of AK lesions offers a secure differentiation of AK and SCC. At the same time, a histological assessment would require a removal of the lesion and impede the follow-up. A description of the natural course of AK lesions would then be impossible.

Due to the ongoing discussions on the dignity of AK and the variety of clinical and histological definitions, the differentiation of AK and SCC is not standardized. Since the authors of the studies often fail to provide definitions of the terms they use with respect to 'AK', 'in situ SCC' and 'SCC', some results of the single studies are not comparable to each other, in particular concerning results on the rates of malignant progression of AK lesions and the rate of contiguous AK in SCC specimens.

5.2.4. Validity of AK lesion counts

For a substantial part of individuals affected by AK, a field cancerization with contiguous areas of chronic actinic skin damage, latent and manifest AKs and potentially evolving or manifest SCC can be expected. The validity of the clinical endpoint of total AK lesion counts as used in most research on the development of AK lesions is questionable. As described above (see 2.6.2. 'Clinical diagnosis'), positive predictive values of clinical diagnosis of AK were shown to be sufficient,⁴⁹⁻⁵¹ but the interobserver reliability of the identification of single AK lesions in patients was low, even among dermatologists.^{52,54} Inter-rater variability with respect to total AK lesion counts in patients is correspondingly high, especially in the case of untrained assessors,⁵³ and therefore the use of total AK lesion counts as a clinical endpoint in the evaluation of AK was recommended no longer to be used.¹⁰⁰ Nonetheless, the total AK lesions count remains the most frequently used clinical endpoint in research for assessing AK. Some means of assessment has to be applied, and for this systematic review, the available data reported in the literature were

assessed. The development of a valid alternative to AK lesion counts for use in further research is desirable.

5.2.5. Treatment of lesions during studies

As the assessment of AK usually was based on clinical diagnosis, treatment of suspect lesions during the observational period could become necessary in some studies. Lacking information on the amount of treatment, details of the treatment modality, statistical handling of treated lesions or influence of the treatment on the results introduced a risk of bias to the majority of the included studies. This imposes a major limitation when it comes to interpreting the results of this systematic review. The significance of this limitation is discussed in detail with respect to the reported outcomes in section 5.3. 'Discussion of the results on a study level'.

5.2.6. Measures to avoid unprotected exposure to sun radiation

As the continued exposition to sunlight is a major influential factor for the further development of AK lesions, the recommendations made to the participants at the beginning of the studies were assessed. Some authors reported that they had recommended all participants to avoid unprotected exposure to sun radiation (e.g. recommendation to avoid sun exposure in the afternoon or to use sunscreen on a daily basis). However, the majority of studies neither reported whether they recommended any behavioral aspects concerning exposure to sun radiation to their participants nor did they provide any data on the actual sun exposure of the participants. The knowledge on the role of sunlight as a risk factor for the development of AK and NMSC can be assumed to be general, and therefore, the actual behavior of participants cannot be predicted, unless the behavior is reported in the studies. The differentiation of 'studies with information on sunscreen use recommendations' and those 'without information on sunscreen use recommendations' is very basal, but it accounts for the low quality of the vast majority of the included trials in this respect.

5.3. Discussion of the results on a study level

5.3.1. Risk of progression of AK lesions to SCC

All of the identified studies reporting on progression rates have severe methodological limitations.

Following the data presented by Marks et al. (1988),⁸⁰ a risk of progression from AK to SCC of 0.075% per AK lesion per year can be assumed for a (community-based) population of participants without history of NMSC or immunosuppression. Due to the design of this cohort study, no data on the number of dropouts are provided, which introduces a strong reporting bias (on the outcome level). An important reason for dropping out can be surgical intervention for an invasive SCC, and thus the risk of progression of an AK lesion may have been underestimated. Furthermore, an unknown number of participants was repeatedly reported: the authors counted each two contacts in consecutive years as one 'participant contact' if the participant had at least one AK lesion during the first presentation. When the same participant was seen on three different occasions in two consecutive years, the respective participant was reported as 'two occasions'. The multiple reporting of participants aggravates the possible bias towards underreporting progression rates. On the other hand, the invitation of all citizens from a community to participate in a skin cancer screening may have introduced a bias towards the participation of more severely affected citizens.

Criscione et al. (2009)⁷³ reported a progression rate of 0.53% per AK lesion per year in a hospital-based population of patients with a history of multiple prior NMSC and a mean age of 68 years. No histological or clinical definition of what was termed as 'AK', 'in situ SCC' and 'invasive SCC' is provided, which makes a comparison of the results to other studies difficult. The rate of 0.53% per AK lesion per year refers to the progression from an AK lesion present at baseline into invasive SCC at the 12 months follow-up visit. 81 of the 160 reported participants received tretinoin within the framework of the Veteran Affairs Topical Tretinoin Chemoprevention (VATTC) trial. The authors confirm that the progression rates did not differ between the interventional and the control groups, but do not provide subgroup analyses on that issue.

Two studies did not find a progression of the followed AK lesions at all. The number of included participants was probably too small for the detection of this rare event in the study by Wulf et al. (2006).⁸⁶ In the other study that reported no progression, conducted by Harvey et al. (1996),³⁹ more than 30% of the participants dropped out. As participants more severely affected by AK are more likely to search for surgical treatment outside the framework of the study, this introduces a risk of bias towards an underreporting of progression. Generally, from a methodological perspective, it is not

recommended to consider studies with 'no events' for the determination of event rates for rare events: e. g., if the expected event rate is lower than 1%, it is recommendable to exclude studies showing no events from metaanalyses.¹⁰¹

In summary, data on progression rates of single AK lesions remain highly uncertain due to various methodological limitations of the studies reporting on this outcome. Studies following the course of single AK lesions demonstrate the inherent potential of AK lesions to progress to SCC, but at the current time, no reliable estimates concerning the actual progression rates of untreated AK lesions can be given. The data obtained indicate that the risk of malignant progression may be higher in patients with a history of previous NMSC.

5.3.2. Risk or odds ratios for developing SCC relative to the number of pre-existing AK

Studies on different populations showed a strong correlation between the number of baseline AK lesions and the risk of developing a subsequent SCC during the observational period. As the individual studies refer to different locations of AK (e. g. only facial AK), different effect measures (risk ratio or odds ratio), or different independent variables (AK in general or certain number of AK compared to no AK), the data obtained are not directly comparable. Generally, increasing numbers of baseline AKs in the studies reviewed were consistent with increasing subsequent risks for the development of an SCC. Relative risks in participants without history of NMSC or immunosuppression were lower than relative risks for the development of SCC in organ transplant recipients with AK.^{91,94,97} This finding goes along with the results of other studies specifically reporting on this research question.²⁸⁻³¹

The data on the relative risk for a population of participants without history of NMSC or immunosuppression are based on follow-up data from a postal survey⁹⁴ and are therefore at a higher risk of recall bias.

Summarizing, the data on risk or odds ratios for developing SCC, relative to the number of AK lesions at baseline, show a strong interdependency between AKs and subsequent SCC development. The data are based on sample sizes of at least 180 participants. Although the risk or odds ratios obtained are not comparable, the risk seems to be higher in immunosuppressed patients than in a community-based sample from the general population.

5.3.3. Rates of contiguous AK lesions in SCC specimens

Rates of SCC specimens with contiguous AK lesions ranged from 15.9% to 97.2%.^{90,92,93,95,96,98} The main limitations to these data were missing data on the rates of incomplete excision and lacking definitions of the meaning of 'contiguous lesions' in most of the studies. The latter aspect impedes a meaningful comparison of the obtained data on rates of contiguous AK lesions. None of the studies contained information on the medical history of the patients; hence, a discrimination of studies on patients without history of NMSC or immunosuppression, on patients with history of NMSC, or on immunosuppressed patients was not possible.

Despite the low quality and comparability of the studies and their findings, histological changes that are attributable to AK lesions were frequently found to be present in SCC specimens. In studies including at least 150 analyzed specimens, rates of contiguous AK lesions in SCC specimens ranged from 72%⁹² to 97.2%.⁹⁵ This finding does not prove a causal relationship between these two 'entities'. Yet, it may provide support to the hypothesis of a stepwise development on a spectrum from healthy skin to AK and from AK to SCC.

5.3.4. Regression and recurrence rates of single AK lesions

The studies included reporting data on regression rates of single AK lesions showed a general rate of regression of 20 to 30% of the lesions from baseline until the end of the study. One study showed a regression of 63% of AK lesions that were present at baseline³⁷. The latter study included the youngest participants (range from 30 to 69 years) and excluded participants with a field cancerization, which might explain the outstanding rate of regressions in this study. No data on populations of participants with a history of NMSC or on organ transplant recipients were available. Recurrence rates after spontaneous regression of AK lesions of between 15% and 53% of the regressed lesions^{37,82,99} and 33% of the lesions present at baseline⁸⁷ were reported. Only the single lesion recurrence rate of 20.2% within 12 months of follow-up refers to data from more than 35 participants (the study in question⁸² included 98 participants).

Generally, the results of the studies concerning regression rates may have been biased towards overreporting remission rates due to AK lesions in which the development of invasive SCC was suspected and which therefore were excluded from analysis or treated. In the study with the high regression rate of 63% of AK lesions, 6% of the

lesions were treated by a dermatologist or a GP outside the framework of the study.³⁷ In some studies, the drop-out rates were high and the data provided on treatment during the course of the study insufficient.

Data on regressions of single AK lesions and consecutive recurrence of the respective lesions yield the most consistent results within this systematic review. Regressions may be expected in around 20-30% of AK lesions in immunocompetent patients without a history of NMSC. Recurrences occur in around 20% of the regressed lesions within 12 months. The data underline the assumption that AK is a dynamic disease of regressions and recurrences of lesions within a field of sun damage or field cancerization.

5.3.5. Rates of complete field regression and subsequent recurrence

Rates of spontaneous complete field regressions ranged from 0% to 7.2%. The rate of 21% of complete field regressions reported by Alirezai et al.⁷² refers to AK lesions on the upper extremity and is based on data from the observation of only 14 patients.

Data on spontaneous complete field regression rates are generally limited with respect to the number of studies and to the sample sizes in some of these studies. If only data from trials with more than 100 participants are considered, spontaneous regression of a defined field occurred in 2.2% to 7.2% of the participants included. It should be kept in mind that 'complete field regression' is an expression that was coined for the purpose of the present study, in analogy to the expression 'complete clearance' that is frequently used as an outcome in clinical trials. Clinical trials that assess 'complete clearance' refer to a well-defined treatment or control area and not to all AK on the whole body of a participant. The regression of all AK lesions on all body regions of affected individuals should consequently be assumed to be correspondingly lower. Moreover, the low rates of spontaneous complete field regression were counterbalanced by relatively high rates of recurrence: The authors of one study showed that 57% of the participants who experienced a spontaneous complete field regression developed at least one recurrence within 12 to 14 months of follow-up.⁷⁸ These data indicate that despite the relatively high single lesion regression rates, the probability of a complete regression of all AK lesions in a patient affected by multiple AK lesions is low and the presence of AK lesions is a chronic condition.

5.3.6. Change in total AK counts over time

The changes in the AK lesion counts were most frequently chosen as the primary outcome in the studies included in this review. Very heterogeneous results were obtained with respect to that outcome. The broad range from decreases to increases of the total AK counts is partly explained by the sunscreen use recommendations made to the participants of the studies. This finding is consistent with the results of various controlled trials that show a beneficial influence of the use of sunscreen on the course of AK lesions regardless of the population of study participants.^{50,74,85} For instance, one study showed a statistically significant difference in the relative ratio of increase of the total AK counts of 0.76 for the sunscreen group compared to sunscreen non-users.⁷⁴ Another study demonstrated an even more pronounced difference between the sunscreen group (mean decrease of 53% from baseline) and the control group (mean increase of 43% of the baseline AK lesion counts) in a population of organ transplant recipients.⁸⁵

An effect of the participants' age on the changes of the AK lesion counts was not seen throughout the included studies.

Similarly, data on the change in the AK counts from baseline until the end of the study show that AK is a dynamic condition with frequent (numeric) progressions and regressions. Continued unprotected exposure to UV radiation seems to be a major factor influencing the further development of AK lesions.

5.4. Discussion of the extrapolation results of the risk of development of an SCC for the 'standard' patient presenting with AK

The extrapolated risk of developing at least one SCC, based on the mean number of AK and the risk of progression of a single AK lesion to SCC per year in the given studies and on the set time of ten years, was 5.8% for a patient without immunosuppression and without a history of NMSC who presents with 8 AK lesions. For a patient who had a history of at least two NMSC in the last 5 years, presenting with 12 AK lesions, the corresponding risk was calculated to be 47.2%. No data for a risk extrapolation for organ transplant recipients were available. These data should not be used for estimating the actual risk of patients due to the severe limitations of the validity of the underlying data on the single AK lesions progression risk. Furthermore, the calculation itself introduces uncertainty:

As stated by Dodson et al.,⁷⁰ the extrapolation of risk is only valid under the hypotheses of independent development of each lesion and stability of each lesion over time. These are hypothetical presumptions that pose a major limitation to the interpretability of the extrapolated data. On the other hand, the risk of progression presented in the source studies is not differentiated over lesion age, lesion stability and interdependency of progression. The hypothetical premises may therefore be assumed to be valid for the specified risks of progression in the respective populations.

The calculated individual progression rate for immunocompetent patients without history of NMSC of 5.8% in ten years lies well within the range of previous estimations of the individual risk for the development of an SCC. Quaedvlieg et al.⁶⁰ reported estimations of rates of SCC development for patients affected by AK of between 1.6% and 14% in five years.

However, the extrapolated data on the individual risk of progression are not directly transferable to clinical situations. They are based on highly uncertain estimates of progression risks of single AK lesions. Applying a theoretical statistical method further decreases the validity of the results. The important and additional information that these calculations may provide is to demonstrate the disproportional increase in the risk for SCC development in an individual with several AK over a longer time period.

5.5. Conclusions

The findings of this systematic review reflect that AKs are not a static skin condition. If left untreated, AKs are a dynamic disease on the grounds of chronically sun damaged skin. The lesions have the potential of progression and regression, with respect to quantitative (e. g. changes in total AK lesion counts) as well as qualitative categories (e. g. progression of an AK lesion to SCC or regression into clinically healthy skin).

Correlational data suggest a strong relation between the number of AK and the risk of subsequent development of SCC. SCC specimens frequently contain contiguous AK lesions, a fact that equally underlines the strong entanglement of these two 'entities'. When single AK lesions are followed over time, a progression to SCC can be observed in a small number of cases. Extrapolations of the risk for an individual affected by AK demonstrate that the apparently low rates of progression of single AK lesions are only a fraction of the risk of development of SCC in a patient affected by several AK for several

years. At the current time any estimate about the risk of progression remains highly uncertain due to the limited number of trials and their severe methodological limitations.

The data on regression and recurrence rates of single AK lesions, on complete field regression and recurrence rates of observed areas and data on the relative changes of total AK lesion counts show that AK is a skin disease that has the potential to regress but only a small chance of a spontaneous complete regression. Whether AKs tend to regress or increase in total counts seems to depend on various factors. The function of the immune system is an influential factor, as well as the continued unprotected exposure to sun light. Therefore, the recommendation of consistent avoidance of unprotected sunlight exposure plays a central role in the care of patients presenting with AK.

The interpretation of the available data is very limited due to the manifold methodological limitations. To make reliable estimates about the natural course of AK, further well-designed studies are needed. An ideal setting would be a community-based prospective cohort study that includes sufficient participants to stratify the analysis with respect to the skin type, age, gender, severity of AK and history of prior NMSC. The exposure to important confounders, such as sun radiation, should be assessed and reported. The use of valid assessment tools is crucial and a reliable alternative to total AK lesion counts is strongly desirable. Confocal laser microscopy could be an option for following lesions with unclear status concerning their biologic behavior. Treatment of lesions should be limited to excision and histological evaluation whenever possible.

Summarizing the findings, AKs should be considered as lesions of the skin with the inherent potential of progression into malignant disease and a very low chance of spontaneous complete regression. Therefore a consistent and adequate treatment is necessary.

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7. Supplement

7.1. Tables of included studies

7.1.1. General characteristics of the included prospective longitudinal studies (Table 8)

Table 8. General characteristics and methodological quality rating of the included prospective longitudinal studies

Author, year, country	Participants						Study characteristics						Comments/ risks of bias	
	No. of pts. in study group, dropouts % (n)	Age (mean, \pm SD, range in years)	Sex (% male)	Pts. characteristics	Mean number of AK lesions at BL, \pm SD	Examined area	Study type and intervention(s)	L = lesions follow-up F = field observation	Sunscreen use recommendations	Recruitment period	Length of follow-up (months)	Provided outcome data		Methodological Quality Rating
Alberts, 2000 ⁷¹ USA	48, 12.5% (6 pts.)	n. i., inclusion criterion: age > 30y	76%	> 9 AK on each forearm --- General pt. population *	29.2 \pm 18.7	lateral forearms	placebo arm of intraindividual split-pt. RCT (DFMO BID vs. Placebo BID) included as prospective cohort study	F	0	n. i.	6	N	R-; AE+; AO+; F-; D*	n. i. on treatment during study; no detailed information on selection of pts.; n. i. on the source of participants
Alirezai, 1994 ⁷² FR	49, 20.4% (10 pts.)	n. i., inclusion criterion: age > 20y	n. i.	\geq 5 AK at BL; pts. who had skin cancer or suspect lesions at BL were excluded --- General pt. population *	7.8 (face); 9.7 (scalp); 8.4 (upper extr.)	face, scalp, and upper extremities	placebo group of RCT (isotretinoin vs. vehicle) included as prospective cohort study	F	1	n. i.	6 (24w)	N, C	R-; AE+; AO+; F-; D-	n. i. on treatment during study; no detailed information on selection of pts; outpatients recruited at 5 centers (hospital-based population)
Caforio, 2000 ⁹¹ IT	300, -	Mean 49; SD \pm 15	86%	25.7% of pts. with BL AK --- OTR (heart transplant)	n. i.	entire skin	Prospective cohort study, no intervention	F	0	n. i.	55.2	O	R-; AE+; AO+; F+; D*	n. i. on treatment during the study; no detailed information on selection/recruitment of pts.; hospital-based population
Cantrell, 2009 ⁸⁷ USA	27, n. i.	range 39-79	n. i.	pts. with 'extensive sun damage' --- General pt. population *	23.5 \pm 7.9	n. i.	prospective cohort study; no intervention	L	0	n. i.	11	R, N	R-; AE-; AO-; F-; D-	only abstract available; n. i. on methods and confounders; no detailed information on selection/recruitment of pts.; n. i. on the source of pts.; n. i. on treatment during the study

Author, year, country	Participants						Study characteristics						Comments/ risks of bias	
	No. of pts. in study group, dropouts % (n)	Age (mean, ±SD, range in years)	Sex (% male)	Pts. characteristics	Mean number of AK lesions at BL, ±SD	Examined area	Study type and intervention(s)	L = lesions follow-up F = field observation	Sunscreen use recommendations	Recruitment period	Length of follow-up (months)	Provided outcome data		Methodological Quality Rating
Criscione, 2009 ⁷³ USA	182, 7.1% (13 pts.)	mean 68; range 44-84	95%	95% of the pts. had at least 1 AK at BL; ≥ 2 NMSC during last 5y --- Prior NMSC	12	face and ears	prospective cohort study; no intervention	L	1	1998-2002	mean 42 (range 4-71)	M	R-; AE+; AO+; F+; D*	No diagnostic criteria or definitions of 'in situ SCC', and 'invasive SCC'; no detailed information on selection of pts.; pts. were recruited at a Veterans Affairs medical center (hospital-based population); 81 pts. received topical tretinoin 0.1% during the trial (authors state that groups did not differ in the rate of malignant transformation, no subgroup analyses); 38 treatments of AKs during study
Darlington, 2003 ⁷⁴ AU	1621, 31% (505 pts.)	Mean 48.8; range 25-74 **	43.7% **	46% of the pts. had at least 1 AK at BL; 436 (27%) had previous skin cancer ** --- Prior NMSC	3.7	complete skin examination	RCT (Daily sunscreen SPF 16 vs. sunscreen as usual and 30mg beta carotene/d vs. placebo)	F	2	1992-1996	54	N	R+; AE+; AO+; F+; D-	mean numbers of AK development probably refer to the whole population (prevalence of AK at baseline: 46%); no data on intermittent treatment; no blinding (no placebo control; control group is encouraged to continue the usual sunscreen use); community-based population
Elmets, 2010 ⁷⁵ USA	118, 18.6% (22 pts.)	mean 64.9 ± 10.4; range 37-88	81%	10-40 AK at BL; 70 pts. with history of skin cancer (average 2.4 previous skin cancers) --- Prior NMSC	23.5 ± 8.4; range 11-41	upper extremities, neck, face, and scalp	Placebo group of RCT (200mg celecoxib BID vs. placebo BID) included as prospective cohort study	L	1	2001-2006	11	N	R-; AE+; AO+; F-; D*	no detailed information on selection/recruitment of pts; n. i. on the source of pts.; no treatment of AK; FDA terminated study due to concerns about safety of celecoxib
Foote, 2009 ⁷⁶ USA	50, 16.0% (8 pts.)	mean 68.0., inclusion criterion: age > 30y	85.7%	>9 AK at BL, skin cancer history in 17 pts. (40.5%) --- Prior NMSC	34.3 ± 3.8	dorsal forearm	placebo arm of intraindividual split-pt. RCT (tocopherol 12.5g% vs. non-active cream base) included as prospective cohort study	F	1	n. i.	6	N	R-; AE+; AO+; F-; D*	n. i. on treatment during study; no detailed information on selection/recruitment of pts.; n. i. on the source of pts.

Author, year, country	Participants						Study characteristics						Comments/ risks of bias	
	No. of pts. in study group, dropouts % (n)	Age (mean, ±SD, range in years)	Sex (% male)	Pts. characteristics	Mean number of AK lesions at BL, ±SD	Examined area	Study type and intervention(s)	L = lesions follow-up F = field observation	Sunscreen use recommendations	Recruitment period	Length of follow-up (months)	Provided outcome data		Methodological Quality Rating
Frost, 2000 ³⁷ AU	96, 7.3% (7 pts.)	range 30-69	50%	46% of pts. had at least 1 AK at BL; pts. with field cancerization or more than 50 AK at 1 site were excluded --- General pt. population *	11.5	head, neck, hands, and forearms	prospective cohort study; no intervention	L	(1)	1992	12	R	R*; AE*; AO*; F*; D*	subsample analysis of another study population (data on changes in AK lesion counts reported by Darlington et al. (2003) are not further included in this review); 6% of the total AK numbers in the study were treated; 49% of pts. received β-carotene within another trial (Darlington et al., 2003); participants were recommended to continue their usual sunscreen use behaviors; community-based population
Green, 1998 ⁷⁷ UK	35, 37.1% (13 pts.)	mean 50; range 25-77	13.8%	n. i. on the prevalence of AK; all pts. with 'photoaging' --- General pt. population *	3.6	face, forearm, and hand	placebo group of RCT (retinyl propionate cream vs. vehicle) included as prospective cohort study	F	1	n. i.	12 (48w)	N	R-; AE*; AO*; F*; D-	means refer to the whole group of pts. (n. i. on the prevalence of AK); n. i. on treatment during study; no detailed information on selection of pts.; 'outpatients attending a dermatology center or other volunteers' (hospital-based population)
Green, 1990 ⁹⁴ AU	2095, 15.5% (325 pts.)	Not reported; inclusion criteria: 20-69	n. i.	40% of pts. had AK at BL --- General pt. population *	n. i.	Head, neck, back of hands, forearms	Prospective cohort study	F	0	1986	24	O	R*; AE*; AO-; F*; D*	Postal follow-up: pts. reported whether malignant skin lesions occurred, if so then the treating physician was contacted for confirmation; No detailed information on treatment of AK during study; community-based population
Harvey, 1996 ³⁹ UK	560, data on dropouts unclear; ~30.2% (169 pts.)	mean 71.2., inclusion criterion: age > 60y	42%	Prevalence of AK: 23% of pts. --- General pt. population *	Post hoc calc. of mean no. of AK in affected pts.: 1.9	head, neck, arms (from shoulder), legs (from knees), and feet	prospective cohort study; no intervention	L	0	n. i.	12-24 (mean 1.43y)	M, R	R*; AE*; AO*; F*; D-	community-based population

Author, year, country	Participants						Study characteristics						Comments/ risks of bias	
	No. of pts. in study group, dropouts % (n)	Age (mean, ±SD, range in years)	Sex (% male)	Pts. characteristics	Mean number of AK lesions at BL, ±SD	Examined area	Study type and intervention(s)	L = lesions follow-up F = field observation	Sunscreen use recommendations	Recruitment period	Length of follow-up (months)	Provided outcome data		Methodological Quality Rating
Jorizzo, 2007 ⁷⁸ USA	18, 22.2% (4 pts.)	n. i. ., inclusion criterion: age > 18y	n. i.	Prior 4-8 AK on scalp; but all pts. had a complete field regression at entrance to the follow-up --- General pt. population *	5.8	contiguous 25cm ² treatment area on face or balding scalp	follow-up of placebo group of RCT (imiquimod vs. vehicle) included as prospective cohort study	F	0	Aug 2001 and following 6m	12-14	C	R-; AE+; AO+; F-; D-	subsample of the population from Korman et al. (2005), data on follow-up: only pts. with a spontaneous complete field regression during the study by Korman et al. (2005) were eligible; pts. from 13 study centers were enrolled (hospital-based population)
Kang, 2003 ³⁸ USA	30, 6.7% (2 pts.)	mean 64.6; range 43-83	66.7%	5-25 AK at BL --- General pt. population *	n. i.	face, ear, and scalp	placebo group of RCT (adapalene 0.1% vs. adapalene 0.3% vs. vehicle for 4w, followed by application for up to 9 months) included as prospective cohort study	F	0	n. i.	9	N	R-; AE+; AO+; F-; D*	n. i. on treatment during study; n. i. on selection process; n. i. on the source of pts.
Korman, 2005 ⁷⁹ USA	250, 6.4% (16 pts.)	mean 65.9 ± 9.9; range 41-93	88.4%	4-8 AK at BL --- General pt. population *	n. i.	contiguous 25cm ² treatment area on face or balding scalp	placebo group of RCT (imiquimod 5% cream 3x/w vs. vehicle for up to 16w) included as prospective cohort study	F	0	Aug 2001 and following 6m	6 (24w)	N, C	R-; AE+; AO+; F-; D*	n. i. on treatment during the study; n. i. on recruitment/selection of pts.; patients from 26 study centers were enrolled (hospital-based population); data refer to a 25cm ² area on face or balding scalp
Marks, 1986 ³⁸ AU	1040, 0.3% (3 pts.)	mean 58.8; range 40-99	42.9%	59.2% of pts. had at least 1 AK --- General pt. population *	7.7	face, head, neck, hands, and forearms	prospective cohort study; no intervention	L	0	1983	12	R, N	R*; AE+; AO+; F*; D*	partly same population as in Marks et al. (1988), here: data on regressions (rate of malignant transformation not included into the review); pts. with treatment were excluded from the analysis; community-based population

Author, year, country	Participants						Study characteristics						Comments/ risks of bias	
	No. of pts. in study group, dropouts % (n)	Age (mean, ±SD, range in years)	Sex (% male)	Pts. characteristics	Mean number of AK lesions at BL, ±SD	Examined area	Study type and intervention(s)	L = lesions follow-up F = field observation	Sunscreen use recommendations	Recruitment period	Length of follow-up (months)	Provided outcome data		Methodological Quality Rating
Marks, 1988 ⁸⁰ AU	1689 , n. i. (see comment !)	mean 60.1 ±11.2., inclusion criterion: age > 40y	42%	only pts. with 2 visits in consecutive y and at least 1 AK at the 1st visit were included in analysis --- General pt. population *	n. i.	face, head, neck, hands, and forearms	prospective cohort study; no intervention	L	0	1982- 1986	12	M	R*; AE*; AO*; F*; D-	pt. contacts in consecutive years were reported as 1 'occasion' (e.g. pts. with 4 visits in 3 consecutive years were counted as 3 'occasions'); an unknown number of AK lesions and participants are multiply reported; data on dropouts are not reported; no treatment (in the reported participants); community-based population
Moloney, 2010 ⁸¹ AU	17, 11.8% (2 pts.)	mean 73; range 55-85	82.4%	≥ 4 non-hyperkeratotic AKs on face, scalp, upper limbs; pts. with sundamaged skin and multiple prior skin cancers --- Prior NMSC	23.5	face, scalp, and forearm	placebo group of RCT (nicotinamide 1% BID vs. vehicle BID) included as prospective cohort study	F	1	Mar 2008 - Jun 2008	6	N	R-; AE*; AO*; F-; D*	n. i. on treatment of lesions during study; n. i. on selection of pts.; pts. were recruited from a hospital (hospital-based population)
Ramsay, 2000 ⁹⁷ UK	182, 18.0% (33pts.)	n. i.	67%	OTR (renal transplant)	n. i.	Complete skin examination	Prospective cohort study	F	1	1997- 1999	15.4	O	R-; AE*; AO*; F*; D*	n. i. on treatment during study; no detailed information on selection/recruitment of pts.; recurrent lesion were excluded from analysis; hospital-based population
Stockfleth, 2012 ⁸² DE	98, 10.2% (10 pts.)	range 18-85	n. i.	4-10 AK grade I&II (Olsen) on face and scalp --- General pt. population *	n. i.	face, forehead, or bald scalp	placebo group of RCT (5-FU 0.5% + salicylic acid 10% QD vs. 3% diclofenac/hyaluronic acid BID vs. placebo BID) included as prospective cohort study	F	0	2008- 2009	12	R	R-; AE*; AO*; F*; D*	n. i. on selection of pts.; pts. were recruited from 38 study centers (hospital-based population)

Author, year, country	Participants						Study characteristics						Comments/ risks of bias	
	No. of pts. in study group, dropouts % (n)	Age (mean, ±SD, range in years)	Sex (% male)	Pts. characteristics	Mean number of AK lesions at BL, ±SD	Examined area	Study type and intervention(s)	L = lesions follow-up F = field observation	Sunscreen use recommendations	Recruitment period	Length of follow-up (months)	Provided outcome data		Methodological Quality Rating
Szeimies, 2004 ⁸³ UK, FR, ES, DE, NL	139, 14.4% (20 pts.)	mean 70.9; range 44-94	84.2%	5-9 histologically and clinically proven AK --- General pt. population *	5.51 (total: 766 AK)	contiguous 25cm ² treatment area on face or balding scalp	placebo group of RCT (imiquimod vs. vehicle) included as prospective cohort study	F	0	Jan 2002 - approx. Sep 2002	6 (24w)	N, C	R-; AE+; AO+; F-; D*	n. i. on treatment of lesions; n. i. on selection process; pts. were enrolled at 18 centers (hospital-based population); data refer to a 25cm ² area on face or balding scalp
Szeimies, 2010 ⁹⁹ DE	34, 14.7% (5 pts.)	mean 71.5; range 51-86 ***	79.5% ***	4-8 mild-to-moderate AK (Cockerell) --- General pt. population *	5.5 and 5.9 (range: 2-8 lesions, total: 476 lesions) ***	face and/or balding scalp	follow-up of placebo groups of 2 RCT (5-ALA-PDT vs. placebo-PDT, and 5-ALA-PDT vs. cryosurgery vs. placebo-PDT) included as prospective cohort study	F	0	n. i.	12	R	R-; AE+; AO+; F+; D*	n. i. on selection process; n. i. on the source of pts.; follow-up of regressed lesions after placebo intervention; pts. with recurrences of all lesions were withdrawn (possibly the case for 5/34 pts.)
Thompson, 1993 ⁵⁰ AU	588, 26.7% (157 pts.)	mean 63 ± 11; range 40-93	41.8%	1-30 AK at BL --- General pt. population *	8.1	head, neck, hands, and forearms	RCT (sunscreen SPF 17 vs. placebo)	L	2	Sep 1991	7	R, N	R+; AE+; AO+; F-; D-	Possibly subsample of populations from Marks et al. (1986/ 1988), but different setting and period of observation; lesions treated during the study were excluded from analysis; a randomized subsample of subjects was selected for biopsy of a lesion, if this lesion was not present at EOS, it was termed a remission; community-based population
Ulrich, 2007 ⁸⁴ DE, FR, UK, NL, IT, NO	14, 21.4% (3 pts.)	mean 61.64; range 37-76	92.9%	4-10 AK; kidney-, liver- or heart-Tx more than 3y prior to begin of study --- Organ transplant recipients	n. i.	100cm ² area on face, forehead or balding scalp	placebo group of RCT (imiquimod vs. vehicle 3x/week) included as prospective cohort study	F	0	n. i.	6 (24w)	N, C	R-; AE+; AO+; F-; D-	n. i. on treatment of lesions during study; n. i. on selection of pts.; pts. were recruited from 6 transplant centers (hospital-based population); data refer to a 100cm ² area on the face, forehead or balding scalp

Author, year, country	Participants						Study characteristics						Comments/ risks of bias	
	No. of pts. in study group, dropouts % (n)	Age (mean, ±SD, range in years)	Sex (% male)	Pts. characteristics	Mean number of AK lesions at BL, ±SD	Examined area	Study type and intervention(s)	L = lesions follow-up F = field observation	Sunscreen use recommendations	Recruitment period	Length of follow-up (months)	Provided outcome data		Methodological Quality Rating
Ulrich, 2009 ⁸⁵ DE	120, 0 dropouts	median 60.7; range 40-77	50%	prevalence of AK is not reported; 40 kidney-, 40 liver- and 40 heart-Tx --- Organ transplant recipients	3.2	head, neck, dorsum of hands and lower forearms	non-randomized controlled trial (sunscreen (SPF>50) vs. no sunscreen)	F	2	n. i.	24	N	R*; AE*; AO*; F*; D*	means and mean changes in total AK counts probably refer to the whole group of participants (prevalence of AK at BL is not reported and AK diagnosis is no inclusion criterion); grade III AKs were surgically removed; outpatients from a specialized OTR skin clinic (hospital-based population)
Wulf, 2006 ⁸⁶ NL, DK	28, 14.3% (4 pts.)	mean 57; range 32-75	63%	≥2 AK; ≤10 lesions (AK, NMSC, warts); renal OTR ≥ 3y prior to begin of study; pts. with prior SCC were excluded --- Organ transplant recipients	2.9	2 circular contralat. areas (5cm diameter), on the face or dorsal side of the hands	placebo group of intraindividual split-pt. RCT (ALA-PDT vs. no treatment) included as prospective cohort study	L	0	Jul 1999 - Mar 2000	12	M	R-; AE*; AO*; F*; D*	n. i. on treatment during the course of study; no detailed information on selection of pts.; outpatients from two hospital dermatology centers (hospital-based population); data refer to a circular area (5cm diameter) on the face or dorsal side of the hands
Zeichner, 2009 ⁸⁹ USA	20, 25.0% (5 pts.)	mean 75.4 ± 12.8, inclusion criterion: age > 18y	80%	> 5 AK (6 to >40) --- General pt. population *	median 9.5	20cm ² treatment area on the face, head or scalp	placebo group of intraindividual split-pt. RCT (imiquimod 5% 1/w vs. placebo) included as prospective cohort study	F	0	Apr 2005 and approx. following 5m	7 (28w)	N	R-; AE*; AO*; F-; D-	n. i. on treatment of lesions; n. i. on selection process; n. i. on the source of pts.; data refer to a 20cm ² area on the face, head or scalp

General abbreviations: - = no data, not applicable; AK = actinic keratosis; ALA = aminolaevulinic acid; approx. = approximately; Apr = april; Aug = august; BL = baseline; BID = bis in die (twice daily); d = day; DFMO = 2-(Difluoromethyl)-dl-ornithine; EOS = end of study; FDA = food and drug administration; FU = fluorouracil; GP = general practitioner; Jan = January; Jul = July; Jun = June; m = month/ months; Mar = march; n. i. = no information; NMSC = non melanocytic skin cancer; OTR = organ transplant recipients; PDT = photodynamic therapy; pt/pts. = participant/participants, RCT = randomized controlled trial; SCC = squamous cell carcinoma; Sep = September; SPF = sun protection factor; Tx = Transplantation; w = week / weeks; y = year / years.

Countries: AU = Australia, DE = Germany, DK = Denmark, ES = Spain, FR = France, IT = Italy, NL = Netherlands, NO = Norway, UK = United Kingdom, USA = United States of America.

Methodological Quality Rating: R = Representativeness of the population; AE = ascertainment of exposure (initial clinical diagnosis of AK); AO = assessment of outcome (clinical or histological diagnosis with a real participant contact); F = follow-up long enough (≥ 12 months); D = adequacy of follow-up (dropout rate ≤ 20%); '-' = no information / not fulfilled; '*' = fulfilled criterion.

Provided outcome data: M = Risk of Progression from AK lesion to SCC; R = Regression/Recurrence rates; N = Change in total number of AK lesion counts; C = Complete field regression rate/recurrences; O = odds ratio or relative risk for the development of SCC with respect to numbers of preexisting AK.

Sunscreen use recommendations: 0 = no information; 1 = all pts. were recommended to use sunscreen/avoid sun exposure; 2 = sunscreen trial with placebo group.

* The term "General pt. population" refers to studies that included a population of participants that were randomly selected from a general population or had a history of prior NMSC as exclusion criterion.

** Data for Darlington et al. (2003) were partly extracted from Green et al., Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet*, 1999 354(9180):723-9.

*** Data on participant characteristics from Szeimies et al. (2010) were extracted from Hauschild A, Stockfleth E, Popp G et al. Optimization of photodynamic therapy with a novel self-adhesive 5-aminolaevulinic acid patch: results of two randomized controlled phase III studies. *Br J Dermatol*. 2009 May;160(5):1066-74.

7.1.2. General characteristics of the included cross-sectional / retrospective studies (Table 9)

Table 9. General characteristics and methodology rating of the included studies on contiguous AK lesions in SCC specimens

Author, year	Patients							Study characteristics				Comments/ risks of bias
	No. of pts. (No. of analyzed SCC specimen), dropouts	Age (mean, \pm SD, range in years)	Sex (% male)	Country	Pts. characteristics	Mean number of AK lesions at BL, \pm SD	Localizations of the SCC specimen	Study type	Information on sun exposure (0, n. i.; 1, information on sunscreen use or sun exposure of the patients)	Recruitment period	Methodological Quality Rating (modified Newcastle-Ottawa-Scale)	
Ang, 2004 ⁹⁰	57 (63), -	mean 83.3 (range 52-104)	52.6%	CN	n. i.	n. i.	Face, scalp, upper/lower limbs, genitals and trunk	Retrospective cohort study	0	1991-1995	R*; AE-; DC-; DO-; AO-	Chart revue; No data on outcome assessor; 15.9% incomplete excisions
Czarnecki, 2002 ⁹²	208, -	males: median 76 (range 31-94); females: median 78 (range 55-95)	71.2%	AU	n. i.	n. i.	Head, neck, extremities	Cross-sectional study	0	1999	R*; AE*; DC-; DO-; AO*	No data on the number of outcome assessors; No data on incomplete excisions
Dinehart, 1997 ⁹³	22, 18.2%	n. i.	n. i.	USA	Metastatic cutaneous SCC	n. i.	Specimens from SCC of the vermillion border of the lip were excluded	Retrospective cohort study	0	n. i.	R-; AE*; DC-; DO-; AO-	No information on incomplete excisions; no information on the selection of specimen; 9 of the specimens were reported to be present as transected, which means that the dignity of the lesion was not reportable
Guenthner, 1999 ⁹⁵	859 (1011), -	mean 75 (range 34-99)	66.6%	USA	n. i.	n. i.	Sun damaged skin	Cross-sectional study	0	1996-1998	R-; AE*; DC-; DO*; AO-	No data on incomplete excisions; No information on the selection of specimen; Authors refer to 'in situ SCC'

Author, year	Patients							Study characteristics				Comments/ risks of bias
	No. of pts. (No. of analyzed SCC specimen), dropouts	Age (mean, ±SD, range in years)	Sex (% male)	Country	Pts. characteristics	Mean number of AK lesions at BL, ±SD	Localizations of the SCC specimen	Study type	Information on sun exposure (0, n. i.; 1, information on sunscreen use or sun exposure of the patients)	Recruitment period	Methodological Quality Rating (modified Newcastle-Ottawa-Scale)	
Mittelbronn, 1998 ⁹⁶	145 (165), 5.7%	n. i.	n. i.	USA	n. i.	n. i.	Head, neck, extremities, trunk and unspecified	Cross-sectional study	0	1996	R-; AE+; DC* DO+; AO-	No data on incomplete excisions; No information on the selection of specimen
Takemiya, 1990 ⁹⁶	53, -	mean 77.7 (range 64-96)	69.7%	JP	n. i.	n. i.	Head, upper extremities	Cross-sectional study	0	1976-1988	R-; AE-; DC-; DO+; AO-	No data on incomplete excisions; specimens were sought among all histologic skin specimens in Ehime, Japan; no information if the selected specimens represent all cases of SCC specimen

General abbreviations: - = no data, not applicable, n. i. = no information available; no. = number; pts. = participants; SD = standard deviation; **Countries:** AU = Australia, CN = China, JP = Japan, USA = United states of America; **Methodological quality assessment:** R = representativeness of the population; AE = ascertainment of the diagnosis through (re)evaluation of specimen; DC = definition of the meaning of contiguous; DO = Definition of histological criteria to differentiate AK and SCC; AO = outcome assessment by an assessor blinded towards the original chart diagnosis; ‘-’ = no information / not fulfilled; ‘*’ = fulfilled criterion.

7.2. Search strategies

7.2.1. Search strategy used for the search in the Cochrane Library

2012-07-31 (155 Hits)

ID	Search	Hits
#1	MeSH descriptor Carcinoma, Squamous Cell explode all trees	1876
#2	(squamous cell carcino*):ti or (squamous cell carcino*):ab	1563
#3	MeSH descriptor Neoplasms, Squamous Cell explode all trees	2010
#4	(squamous cell neoplasm*):ti or (squamous cell neoplasm*):ab	10
#5	MeSH descriptor Carcinoma in Situ explode all trees	598
#6	MeSH descriptor Skin Neoplasms explode all trees	1029
#7	MeSH descriptor Neoplasm Regression, Spontaneous explode all trees	10
#8	MeSH descriptor Disease Progression explode all trees	4442
#9	(progress):ti or (progress):ab	4505
#10	(regression):ti or (regression):ab	15539
#11	(convers):ti or (convers):ab	0
#12	(decrease):ti or (decrease):ab	92333
#13	(reduc*):ti or (reduc*):ab	141000
#14	(clear*):ti or (clear*):ab	24120
#15	(natural course):ti or (natural course):ab	527
#16	(disease course):ti or (disease course):ab	4752
#17	(natural history):ti or (natural history):ab	979
#18	(transform):ti or (transform):ab	1447
#19	(evolution):ti or (evolution):ab	1693
#20	(involut*):ti or (involut*):ab	140
#21	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)	234758
#22	MeSH descriptor Keratosis, Actinic explode all trees	54
#23	(solar* near/3 keratos?s):ti or (solar* near/3 keratos?s):ab	21
#24	(a?tinic* near/3 keratos?s):ti or (a?tinic* near/3 keratos?s):ab	221
#25	(senil* near/3 keratos?s):ti or (senil* near/3 keratos?s):ab	0
#26	(senil* near/3 keratoma*):ti or (senil* near/3 keratoma*):ab	0
#27	(solar* near/3 hyperkeratos?s):ti or (solar* near/3 hyperkeratos?s):ab	0
#28	(#22 OR #23 OR #24 OR #25 OR #26 OR #27)	237
#29	(#21 AND #28)	155

7.2.2. Search strategy used for the search in Medline

2012-07-31 (1557 Hits)

#	Searches	Results
1	exp Carcinoma, Squamous Cell/	95405
2	"squamous cell carcino*".ab,ti.	52089
3	exp Neoplasms, Squamous Cell/	117612
4	"squamous cell neoplasm*".ab,ti.	57
5	exp Carcinoma in Situ/	19999
6	exp Skin Neoplasms/	89332
7	exp Neoplasm Regression, Spontaneous/	2687
8	exp Disease Progression/	101665
9	progress.ab,ti.	129740
10	regression.ab,ti.	303830
11	convers.ab,ti.	5
12	decrease.ab,ti.	592572
13	reduc*.ab,ti.	1828187
14	clear*.ab,ti.	503942
15	natural course.ab,ti.	5092
16	disease course.ab,ti.	5998
17	natural history.ab,ti.	31184
18	transform.ab,ti.	33378
19	evolution.ab,ti.	165488
20	involut*.ab,ti.	8220
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	3443204
22	exp Keratosis, Actinic/	341
23	(solar* adj3 keratos#s).ab,ti.	385
24	(a#tinic* adj3 keratos#s).ab,ti.	1763
25	(senil* adj3 keratos#s).ab,ti.	74
26	(senil* adj3 keratoma*).ab,ti.	12
27	(solar* adj3 hyperkeratos#s).ab,ti.	2
28	22 or 23 or 24 or 25 or 26 or 27	2222
29	21 and 28	1686
30	limit 29 to (humans and (english or german))	1557

7.2.3. Search strategy used for the search in Medline in Process

31.07.2012 (57 Hits)

#	Searches	Results
1	"squamous cell carcino*".ab,ti.	2426
2	"squamous cell neoplasm*".ab,ti.	3
3	"carcinom* in situ".ab,ti.	387
4	"skin neoplasm*".ab,ti.	16
5	"skin cancer*".ab,ti.	529
6	progress.ab,ti.	11174
7	regression.ab,ti.	18220
8	convers.ab,ti.	0
9	decrease.ab,ti.	30002
10	reduc*.ab,ti.	117560
11	clear*.ab,ti.	29828
12	natural course.ab,ti.	227
13	disease course.ab,ti.	332
14	natural history.ab,ti.	1578
15	transform.ab,ti.	9381
16	evolution.ab,ti.	19566
17	involut*.ab,ti.	278
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	216151
19	(solar* adj3 keratos#s).ab,ti.	6
20	(a#tinic* adj3 keratos#s).ab,ti.	78
21	(senil* adj3 keratos#s).ab,ti.	2
22	(senil* adj3 keratoma*).ab,ti.	1
23	(solar* adj3 hyperkeratos#s).ab,ti.	0
24	19 or 20 or 21 or 22 or 23	85
25	18 and 24	57

7.2.4. Search strategy used for the search in Embase

31.07.2012 - 2972 Hits

#	Searches	Results
1	exp squamous cell carcinoma/	93346
2	"squamous cell carcino*".ti,ab.	66740
3	"squamous cell neoplasm*".ti,ab.	64
4	exp carcinoma in situ/	14904
5	exp skin tumor/	176511
6	exp disease course/	1722869
7	exp tumor regression/	9355
8	progress.ab,ti.	178416

9 regression.ab,ti.	407130
10 convers.ab,ti.	11
11 decrease.ab,ti.	763845
12 reduc*.ab,ti.	2366350
13 clear*.ab,ti.	659700
14 natural course.ab,ti.	6995
15 disease course.ab,ti.	8850
16 natural history.ab,ti.	40890
17 transform.ab,ti.	43805
18 evolution.ab,ti.	216322
19 involut*.ab,ti.	10144
20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	5643670
21 exp actinic keratosis/	3658
22 (solar* adj3 keratos#s).ti,ab.	487
23 (a#tinic* adj3 keratos#s).ti,ab.	2574
24 (senil* adj3 keratos#s).ti,ab.	102
25 (senil* adj3 keratoma*).ti,ab.	16
26 (solar* adj3 hyperkeratos#s).ti,ab.	2
27 21 or 22 or 23 or 24 or 25 or 26	4604
28 20 and 27	3722
29 limit 28 to (human and (english or german))	2972

8. Eidesstattliche Versicherung

„Ich, Ricardo Niklas Werner, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Systematic Review of the Natural Course of Actinic Keratosis and their Relation to Squamous Cell Carcinoma“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE -www.icmje.org) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o) und werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Betreuer, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.

Datum

Unterschrift

Anteilserklärung an Publikationen

Ricardo Niklas Werner hatte folgenden Anteil an den folgenden (geplanten) Publikationen:

Publikation 1:

Werner RN, Sammain A, Erdmann R, Hartmann V, Stockfleth E, Nast A. The Natural history of Actinic Keratosis: A Systematic Review. Br. J. Dermatology, 2013.

Ricardo Niklas Werner conducted the title/abstract-screening partially, and was one main assessor for the eligibility check of the full texts, data extraction and quality assessment. The collected data were assembled and analyzed by Ricardo Niklas Werner. Ricardo Niklas Werner was the main author of the publication text.

Publikation 2:

Werner RN, Sammain A, Erdmann R, Hartmann V, Stockfleth E, Nast A. Progression und Regression aktinischer Keratosen: Ein systematischer Review. Abstract / poster accepted for publication on the conference of the German dermatological society (Deutsche Dermatologische Gesellschaft, DDG) in May 2013.

Ricardo Niklas Werner conducted the title/abstract-screening partially, and was one main assessor for the eligibility check of the full texts, data extraction and quality assessment. The collected data were assembled and analyzed by Ricardo Niklas Werner. Ricardo Niklas Werner was the main author of the published text and the presented poster.

Publikation 3 (geplant):

International (ILDS) Evidence-based Guidelines on Interventions for Actinic Keratosis and
Methods report and results of the International (ILDS) Evidence-based Guidelines on Interventions for Actinic Keratosis (full version)

Texts on the clinical background of AK from the present study will be used as basis for the guidelines texts on the clinical background. They will be adapted by subgroups of the guidelines' expert panel.

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers

Unterschrift des Doktoranden/der Doktorandin

9. Curriculum vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

10. List of publications

Werner RN, Sammain A, Erdmann R, Hartmann V, Stockfleth E., Nast A. The Natural History of Actinic Keratosis: A Systematic Review. *Br J Dermatol.* 2013; 169(3): 502-18. DOI: 10.1111/bjd.12420.

Nast A, Sporbeck B, Rosumeck S, Pathirana D, Jacobs A, **Werner RN**, Schmitt J. Which Antipsoriatic Drug has the Fastest Onset of Action? Systematic Review on the Rapidity of the Onset of Action. *J Invest Dermatol.* 2013; 133(8):1963-70. DOI: 10.1038/jid.2013.78.

Nast A, Rosumeck S, Erdmann R, **Werner RN**. Can physician's self estimates be used as a valid instrument to determine prescription frequencies of anti-psoriatic drugs? Comparison of the results of a cross sectional study using self estimates with actual prescription behavior documented in a cohort study. *Pharmacoepidemiol Drug Saf.* 2013. DOI 10.1002/pds.3453. [Epub ahead of print]

Nast A, Mrowietz U, Kragballe K, de Jong EM, Puig L, Reich K, Warren RB, **Werner RN**, Kopkow C, Schmitt J. Barriers to the prescription of systemic therapies for moderate-to-severe psoriasis – a multinational cross-sectional study. *Arch Dermatol Res.* 2013. [Epub ahead of print]

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