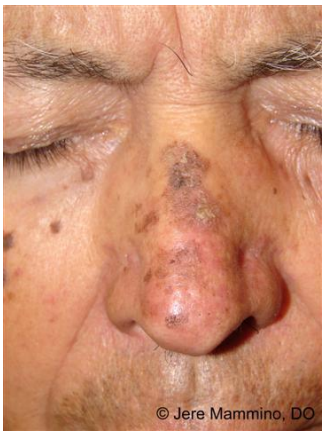
Cancer Association of South Africa (CANSA)

Fact Sheet
on
Actinic Keratosis

Introduction

Actinic keratosis (AK) forms on the face, lips, back of neck, hands, and bald scalp following sun exposure over a period of time. It appears as a rough, dry, scaly patch or growth on the exposed skin. The blemishes are often elevated, rough in texture and resemble warts. Individuals with Actinic Keratosis usually have more than one blemish.



[Picture Credit: Actinic Keratosis]

If it is left untreated, AKs may turn into squamous cell carcinoma. In some cases it may turn into basal cell carcinomas, the most common form of skin cancer, it is, therefore important that a dermatologist is consulted before any cancerous changes occur.

Marques, E. & Chen, T.M. 2020.
"Actinic keratoses (AKs), also referred to as senile keratoses or solar keratoses, are benign intra-epithelial neoplasms and represent one of the most common skin disorders evaluated by dermatologists. Often associated with chronic sun exposure, individuals with AKs may present with irregular, red, scaly papules or plaques on sun-exposed regions of the body. If left untreated, AKs have the potential to evolve into invasive squamous cell carcinoma, which underscores the importance of early detection and development of a treatment plan. There are a variety of management options that are available for AKs, which will be covered in this review."

Heppt, M.V., Ssteeb, T., Szeimies, R-M. & Berking, C. 2020. Actinic keratosis. *Hautarzt*. 2020 Aug;71(8):588-596.
"Actinic keratoses (AK) are common precancerous cutaneous lesions in fair-skinned individuals as a result of cumulative exposure to ultraviolet radiation. Due to their high prevalence, AK account for a large disease burden, in particular in older persons. As AK may potentially progress into invasive cutaneous squamous cell carcinoma, guidelines recommend early and consequent treatment. Numerous lesion- and field-directed interventions with different efficacy and safety profiles are currently licensed in Germany. The appropriate intervention should be chosen together with the patient based on his or her motivation and expectations towards the treatment."

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Incidence of Actinic Keratosis (AK) in South Africa.
The outdated National Cancer Registry (2016) does not provide any information regarding the incidence of Actinic Keratosis (AK) as it is a pre-cancerous condition.

Causes and Risk Factors of Actinic Keratosis (AK)
longterm sun exposure is the major cause of actinic keratosis. Sun damage to the skin is cumulative, so every period of sun exposure adds to the lifetime total.

Another important cause of actinic keratosis is exposure to the ultraviolet radiation given off by tanning beds.

[Picture Credit: Tanning Bed]

A further possible cause of actinic keratoses is extensive exposure to X-rays or certain industrial chemicals, like arsenic, coal tar, soot, pitch, creosote, shale oils, and petroleum products, such as mineral oil or motor oil.

[Picture Credit: Albinism]

The following individuals are also more vulnerable to actinic keratosis:

- Individuals whose immune defences are weakened by cancer chemotherapy, Aids, or organ transplantation
- People with fair skin, blonde or red hair, and blue, green, or grey eyes
- People with certain rare conditions that make the skin very sensitive to the sun's UV rays, such as albinism and xeroderma pigmentosum (XP), are also at higher risk.

Risk Factors Include individuals:

- Usually of the male gender
- A fair skin
- Light eye colour
- Who spend lots of time outdoors in the sun
- Who are organ transplant recipients
- High alcohol consumption
- β human papillomaviruses (HPVs)

Donà, M.G., Chiantore, M.V., Gheit, T., Fiorucci, G., Vescio, M.F., La Rosa, G., Accardi, L., Costanzo, G., Giuliani, M., Romeo, G., Rezza, G., Tommasino, M., Luzi, F. & Di Bonito, P. 2019.
"Many findings support the role of β human papillomaviruses (HPVs) in cutaneous squamous cell carcinoma (cSCC) and its precursor Actinic Keratosis (AK), in cooperation with UV radiation [1]. Differently from the mucosal high-risk types, which are required throughout the entire carcinogenic process, β-HPVs appear to play a role only at an early stage of skin carcinogenesis. Indeed, β-HPV

DNA is not present in all cancer cells and cutaneous HPV prevalence and/or viral load is higher in AK than in cSCC [2, 3, 4]."

Signs and Symptoms of Actinic Keratosis (AK)
The signs and symptoms of an actinic keratosis include:

- Rough, dry or scaly patch of skin
- Blemishes may range in size from a tiny spot to as much as an 2,5cm
- Flat to slightly raised patch or bump on the top layer of skin
- In some cases it may have a hard, wart-like surface
- Colour varies between pink, red or brown, or flesh-coloured patches
- There may also be itching or burning of the affected areas

Diagnosis of Actinic Keratosis (AK)
A medical practitioner (preferably a dermatologist) should be consulted when blemishes on the skin are noticed. He/she will:

- Conduct a full physical examination
- Obtain a biopsy to confirm the diagnosis

Valdés-Morales, K.L., Peralta-Pedrero, M.L., Cruz, F.J. & Morales-Sánchez, M.A. 2020.
Introduction: Dermoscopy is a tool that aids clinicians in the diagnosis of actinic keratosis; however, few diagnostic accuracy studies have determined its sensitivity and specificity for this diagnosis.
Objective: Determine the diagnostic accuracy of dermoscopy on actinic keratosis.
Methods: A systematic review was conducted on EMBASE, PubMed, Scopus and the Cochrane Central Registry of Controlled Trials from inception to August 2019.
Results: We screened 485 titles and abstracts. Two studies comprising 219 actinic keratoses were eligible for qualitative analysis. The number and heterogeneity of included studies limited a quantitative analysis.
Conclusions: Studies that focus specifically on the diagnostic accuracy of dermoscopy for actinic keratosis are lacking.

Reducing the Risk of Actinic Keratosis (AK)
The following will assist in reducing the risk for actinic keratosis:

- Avoiding the midday sun.
- Apply an effective sunscreen (SPF30 or higher) regularly at least 20 minutes before going out into the sun
- Pay special attention to the lips. Apply a lip balm that contains sunscreen (if available)
- Protect the skin with clothing, preferably with a good UPF value. Whenever possible wear:
    - A wide-brimmed hat
    - Long sleeves
    - Long pants
- Avoid tanning beds or other indoor tanning devices
- Check the skin as often as recommended by a dermatologist

- One should contact a dermatologist right away if patches:
    - Starts to itch or bleed
    - Become noticeably thicker
    - Remain after treatment
    - Change in size, shape, or colour.
- Avoid alcohol or, at least, reduce alcohol consumption

Guorgis, G., Anderson, C.D., Lyth, J. & Falk, M. 2020.
"Actinic keratosis is the most common actinic lesion in fair-skinned populations. It is accepted as an indicator of actinic skin damage and as an occasional precursor of squamous cell carcinoma. The aim of this study was to investigate, in a cohort of patients with a diagnosis of actinic keratosis, the relative risk of developing skin cancer during a follow-up period of 10 years. This registry-based cohort study compared a cohort of 2,893 individuals in south-eastern Sweden, who were diagnosed with actinic keratosis during the period 2000 to 2004, with a matched-control cohort of 14,668 individuals without actinic keratosis during the same inclusion period. The subjects were followed for 10 years to identify skin cancer development in both cohorts. Hazard ratios with 95% confidence intervals (95% CI) were used as risk measures. Individuals in the actinic keratosis cohort had a markedly higher risk for all skin cancer forms compared with the control cohort (hazard ratio (HR) 5.1, 95% CI 4.7-5.6). The relative risk was highest for developing squamous cell carcinoma (SCC) (HR 7.7, 95% CI 6.7-8.8) and somewhat lower for basal cell carcinoma (BCC) (HR 4.4, 95% CI 4.1-5.0) and malignant melanoma (MM) (HR 2.7 (2.1-3.6). Patients with a diagnosis of actinic keratosis were found to be at increased risk of developing SCC, BCC and MM in the 10 years following diagnosis of actinic keratosis. In conclusion, a diagnosis of actinic keratosis, even in the absence of documentation of other features of chronic sun exposure, is a marker of increased risk of skin cancer, which should be addressed with individually directed preventive advice."

Treatment of Actinic Keratosis (AK)
Treatment may include:

- Application of liquid nitrogen
- Regular use of prescribed topical creams, gels and solutions

Dianzani, C., Conforti, C., Giuffrida, R., Corneli, P., di Meo, N., Farinazzo, E., Moret, A., Magaton Rizzi, G. & Zalaudek, I. 2020.
"Actinic keratosis (AK) is a very common skin disease caused by chronic sun damage, which in 75% of cases arises on chronically sun-exposed areas, such as face, scalp, neck, hands, and forearms. AKs must be considered an early squamous cell carcinoma (SCC) for their probable progression into invasive SCC. For this reason, all AK should be treated, and clinical follow-up is recommended. The aims of treatment are: (i) to clinically eradicate evident and subclinical lesions, (ii) to prevent their evolution into SCC, and (iii) to reduce the number of relapses. Among available treatments, it is possible to distinguish lesion-directed therapies and field-directed therapies. Lesion-directed treatments include: (i) cryotherapy; (ii) laser therapy; (iii) surgery; and (iv) curettage. Whereas, field-directed treatments are: (i) 5-fluorouracil (5-FU); (ii) diclofenac 3% gel; (iii) chemical peeling; (iv) imiquimod; and (v) photodynamic therapy (PDT). Prevention plays an important role in the treatment of AKs, and it is based on the continuous use of sunscreen and protective clothing. This review shows different types of available treatments and describes the characteristics and benefits of each medication, underlining the best choice."

Steeb, T., Wessely, A., Leiter, U., French, L.E., BERking, C. & Heppt, M.V. 2020.
"Actinic keratoses (AK) are common precancerous lesions of the skin. Numerous interventions exist for the treatment of AK, including lesion- and field-directed approaches. In daily practice, different treatment modalities are often combined to maximize clearance rates. However, whether a combination therapy is preferable to monotherapy in terms of efficacy and safety has been subject of intense debate. In this review, we summarize the current knowledge on the efficacy and safety of local combination therapies for the treatment of patients with AK. Combination approaches of cryosurgery followed by photodynamic therapy (PDT), laser-assisted PDT, PDT in combination with topical interventions and microneedling-assisted PDT have shown slightly better efficacy results with similar tolerability compared to the respective monotherapy. However, the individual usage of combination therapies should be checked on a case-by-case basis and take into account individual patient- and lesion-specific aspects as more resources are needed and because the individual monotherapies are already highly effective."

Cramer, P. & Stockfleth, E. 2020.
Introduction: Actinic keratosis (AK) is a chronic disease which is mainly located across areas of sun-exposed skin. Clinical and subclinical lesions coexist across a large area resulting in a field cancerization. As these lesions have the potential to transform into invasive squamous cell carcinoma (iSCC), treatment is crucial. With global prevalence increasing, AK is expected to be the most common in situ carcinoma of the skin.
Areas covered: In this article, we cover the established algorithm of treating AK and give an insight into the drugs under development. There are six compounds under development covering different treatment angles, from Sinecatechin a Polyphenon E which targets the link between HPV infection and development of AK, over Tirbanibulin which targets the SRC proto-oncogene and fast proliferating cells, to Tuvatexib a small-molecule dual VDAC/HK2 modulator that has shown that it can compete with the established therapies.
Expert opinion: These new treatment options are moving us further toward a more individually tailored treatment for each patient considering his abilities, the size and location of his lesions but also the genetic bases as well as individual risk of transforming into a iSCC and possibly other factors contributing to each patients individual AK lesions.

Sinclair, R., Baker, C., Spelman, L., Supranowicz, M. & MacMahon, B. 2020.
"While a wide range of treatments exist for actinic keratosis and skin field cancerisation, the long-term benefits of the most common topical therapies are poorly defined. This report reviews the efficacy of the most commonly used topical therapies to treat regional or field lesions. Limited clinical and histopathological data are available on clearance rates at 12 months post-treatment for the most commonly used agents, with varied outcome measures making any comparison difficult. In general, total field clearance rates at 12 months are suboptimal for the most commonly employed agents. Given the increasing incidence of actinic keratosis and skin field cancerisation due to an ageing population, further research into the efficacy of therapies is critical to guide treatment choice."

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

Reynolds, K.A., Schlessinger, D.I., Vasic, J., Iyengar, S., Qaseem, Y., Behshad, R., DeHoratius, D.M., Denes, P., Drucker, A.M., Dzubow, L.M., Etzkorn, J.R., Harwood, C., Kim, J.Y.S., Lee, E.H., Lissner, G.S., Marghoob, A.A., Matin, R.N., Mattox, A., Mittal, B.B., Thomas, J.R., Zhou, X.A., Zloty, D., Schmitt, J., Kirkham, J., Poon, E., Sobanko, J.F., Cartee, T.V., Maher, I.A. & Alam, M. 2020.
Importance: Although various treatments have been found in clinical trials to be effective in treating actinic keratosis (AK), researchers often report different outcomes. Heterogeneous outcome reporting precludes the comparison of results across studies and impedes the synthesis of treatment effectiveness in systematic reviews.
Objective: To establish an international core outcome set for all clinical studies on AK treatment using systematic literature review and a Delphi consensus process.
Evidence review: Survey study with a formal consensus process. The keywords actinic keratosis and treatment were searched in PubMed, Embase, CINAHL, and the Cochrane Library to identify English-language studies investigating AK treatments published between January 1, 1980, and July 13, 2015. Physician and patient stakeholders were nominated to participate in Delphi surveys by the Measurement of Priority Outcome Variables in Dermatologic Surgery Steering Committee members. All participants from the first round were invited to participate in the second round. Outcomes reported in randomized controlled clinical trials on AK treatment were rated via web-based e-Delphi consensus surveys. Stakeholders were asked to assess the relative importance of each outcome in 2 Delphi survey rounds. Outcomes were provisionally included, pending the final consensus conference, if at least 70% of patient or physician stakeholders rated the outcome as critically important in 1 or both Delphi rounds and the outcome received a mean score of 7.5 from either stakeholder group. Data analysis was performed from November 5, 2018, to February 27, 2019.
Findings: A total of 516 outcomes were identified by reviewing the literature and surveying key stakeholder groups. After deduplication and combination of similar outcomes, 137 of the 516 outcomes were included in the Delphi surveys. Twenty-one physicians and 12 patients participated in round 1 of the eDelphi survey, with 17 physicians (81%) retained and 12 patients (100%) retained in round 2. Of the 137 candidate outcomes, 9 met a priori Delphi consensus criteria, and 6 were included in the final outcomes set after a consensus meeting: complete clearance of AKs, percentage of AKs cleared, severity of adverse events, patient perspective on effectiveness, patient-reported future treatment preference, and recurrence rate. It was recommended that treatment response be assessed at 2 to 4 months and recurrence at 6 to 12 months, with the AK rate of progression to cutaneous squamous cell carcinoma reported whenever long-term follow-up was possible.
Conclusions and relevance: Consensus was reached regarding a core outcome set for AK trials. Further research may help determine the specific outcome measures used to assess each of these outcomes.

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