Actinic keratosis: a clinical and epidemiological revision *

Queratoses actínicas: revisão clínica e epidemiológica

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Abstract: Actinic keratoses are benign intraepithelial skin neoplasms constituted by atypical proliferation of keratinocytes that may evolve to squamous cell carcinoma. They develop in photoexposed skin areas; they are induced mainly by ultraviolet radiation and are considered cutaneous markers of chronic exposure to sunlight. They develop mainly in adults and older, fair skinned individuals, and are the fourth most common cause of dermatologic consultation in Brazil. Damage to the apoptosis pathway in photoexposed epithelium favors cellular proliferation and the permanence of the lesions. In this revision, the authors assemble the main epidemiological data regarding this disease and suggest that strategies to identify risky phenotypes, early diagnosis, adequate treatment, clinical follow-up, stimulus to skin self examination, photoeducation and photoprotection should be promoted with the aim of avoiding the progression to malignancy and also the prevention and the diagnose of concomitant neoplasms also induced by ultraviolet radiation.
Keywords: Apoptosis; Carcinoma, squamous cell; Epidemiology; Keratosis, actinic; Ultraviolet rays

Resumo: Queratoses actínicas são neoplasias benignas intraepiteliais formadas por proliferações atípicas de queratinócitos com potencial de transformação em carcinoma espinocelular. Desenvolvem-se em áreas fotoexpostas da pele, são induzidas principalmente pela radiação ultravioleta e constituem marcadores de exposição solar crônica. Acometem indivíduos adultos e idosos, de fototipos claros, representando o quarto diagnóstico dermatológico mais comum no Brasil. Danos nas vias de apoptose do epitélio fotoexposto favorecem a proliferação celular e manutenção das lesões. Nesta revisão os autores reúnem os principais dados epidemiológicos sobre a doença e defendem que estratégias de identificação de fenótipos de risco, diagnóstico precoce, tratamento adequado, seguimento clínico, incentivo ao autoexame da pele, fotoeducação e fotoproteção devem ser promovidas, a fim de evitar a evolução das lesões, e também prevenir e diagnosticar neoplasias concomitantes também induzidas pela radiação solar.
Palavras-chave: Apoptose; Carcinoma de células escamosas; Ceratose actínica; Epidemiologia; Raios ultravioleta

INTRODUCTION

Actinic keratoses (AK), solar keratoses or senile keratoses are benign intraepithelial neoplasms formed by atypical keratinocyte proliferations, common in photoexposed areas of adult, elderly people with fair skin. They are mostly induced by ultraviolet radiation (UVR) and can develop into squamous cell carcinoma (SCC), and they constitute the most common pre-malignant lesions in humans. [1,2]

They were described by Dubreuilh in 1826, and their SCC precursor nature has been recognized for over a century. [3-5]

AKs are phenotypic expressions of cutaneous photo-ageing, together with deep, rest wrinkles, loss of skin elasticity, atrophy, telangectasias and pigmentation changes; they can also reflect individuals´ chronic photoexposure. [6,7]

FREQUENCY

AKs constitute a significant portion of dermatological practice, and they are considered the second cause for medical consultation with dermatologists in the United States of America. [8] According to an obser-

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vational study in that country, from 1990 to 1999, they were diagnosed in 47 million of consultations, corresponding to 14% of the visits to dermatologists. [9]

In a Brazilian case series from 2006, AK was the fourth most frequent diagnosis amongst 57.343 consultations, taking place in 5,1% of the visits, varying from 7,4% in the southern region to 2,9% on the north region. [10] Another cross-sectional study conducted in France in 2008 also had 4,7% of the lesions diagnosed as AK, from 78.300 dermatological visits. [11]

AK is a common condition in the adult population, mainly after 50 years of age. In Australia, it is estimated that 40-50% of the population aged 40 years or over present with at least one lesion. [12] Furthermore, an Italian study showed that patients presented with an average of six to eight AKs on the first dermatological consultation. [13]

Patients with AK typically have multiple lesions, which reflect the actinic damage to the "cancerization field". This concept suggests that the apparently normal skin surrounding the AK area would already have genetic changes associated with carcinogenesis. [14,15]

In a populational investigation conducted with 567 adults (>30 years of age) from a community of Japanese origin within the state of São Paulo, the prevalence of AK found was 13,4%, and the average age of onset of the lesions was 69 years. [16] On the other hand, an Italian study with more than12 thousand participants over 45 years showed a prevalence of only 1,4%, which evidences that multiple genetic and environmental factors may interfere with the risk of developing AKs. [13]

There are some indications that the incidence of AKs has increased over the last decades, despite the fact that studies with adequate methodology have not yet been conducted to identify this tendency or, yet, to exclude the role of longevity in this scenario. A recent South Korean research which checked the dermatology outpatients´ visits for the previous 16 years pointed to a 2,14 fold increase in the incidence of AKs in relation to the last decade of the last century.[17]

PATHOPHYSIOLOGY

AKs mostly develop as a consequence of long term UVR exposure in susceptible individuals.

A Dutch study with 966 patients observed an increased risk with both chronic exposure and sunburns experienced before the age of 20 years. [18]

The following are also considered secondary risk factors for the development of AKs: old age, male gender, place of birth with higher ultraviolet index, Caucasian ethnic group, history of previous cutaneous neoplasia, outdoor occupation, lower socio-economic status and light phototypes.[19]

The higher incidence of AKs and SCC in transplanted and other immune suppressed patients strengthens the importance of the apoptosis pathways efficiency and control of cell proliferation in the prevention of cutaneous carcinogenesis. [20-24]

UVR is considered a complete carcinogen, as it acts in the initiation and promotion of epithelial neoplasms, as it happens with the AKs.[3,25] Spectral evaluation indicates that UVB (290-320 nm) is the most damaging wavelength to the keratinocyte DNA however, it is believed that UVA (320-400 nm) could increase the damage caused by the UVB by stimulating the production of reactive oxygen species, immunesuppression and paracrine proliferative stimulus from fibroblasts.[26]

Occasionally, AKs can be caused by X rays and radiotherapy; furthermore, the occurrence of very similar lesions to AK, histologically, have been observed in areas chronically exposed to thermal radiation (erythema *ab igne*).[27]

Exposure to artificial UVR by phototherapy is also associated with a higher risk of AK and SCC (46% and 19%), mainly in treatments with cumulative high doses of psoralens and UVA (PUVA).[28]

UVB radiation specifically promotes the formation of thymidine dimers on the DNA and RNA which could mainly lead to mutations of the telomerase and p53 tumor suppressor genes.[15,25,29,30]

Changes to the p53 protein pathways promote angiogenesis and suppress apoptosis, which allow the growing and proliferation of mutated keratinocytes, with malignant potential. It has been observed that mutations in the p53 protein genes are more frequent in initial lesions, which creates a permissive environment for cell proliferation and mutations in other proteins of this pathway (p16 and Ha-ras) in more mature lesions. [15,22,31]

While the type 1 cyclooxygenase enzyme has a constitutional expression in the skin, the type 2 cyclooxygenase (COX-2) has basically pro-inflammatory effects and it is expressed in pathological situations. However, inflammation is considered a critical component of tumorigenesis, and COX-2 is hyper-expressed in various neoplasias. [32] Furthermore, there is evidence that it has an important role in cutaneous carcinogenesis. [33]

Transgenic rats with high COX-2 production are more susceptible to UV induced cutaneous tumors, while rats deficient in COX-2 have a 75% lower rate of skin tumors than normal rats. [34,35] In humans, the presence of inflamed AKs is more associated with progression to carcinoma.[36]

Besides stimulating cell proliferation and angiogenesis, the increase in COX-2 is associated with resistance to apoptosis in various tumors, such as colonrectal, breast, lungs and prostate. It has been shown

that the activity of this enzyme is correlated with the expression of anti-apoptotic proteins from the Bcl2 family. [37,38]

Wu and Nijsten found significantly increased expression of COX-2 in SCC lesions (40%), Bowen´s disease (22%) and AKs (31%) when compared to normal skin. [39,40] Additionally, they noted that the tumor induction caused by arsenic uses COX-2 dependent pathways and KappaB nuclear factor.[41]

Survivine is an apoptosis inhibiting protein which participates in different pathways, especially the Wnt/βcatenine. Survivine is manifested especially in initial lesions of epithelial carcinogenesis, in the tumor stem-cells. Its expression was identified in the basal layer of AKs and diffusely in SCC´s epithelium, which reflects the anti-apoptotic activity necessary to the maintenance of the neoplasia.[42,43]

P63 protein is homologue to p53, and it is present in replicating keratinocytes. It has important positivity in all layers, which evidences its aberrant proliferation. Its functional and pathophysiological independence is suggested by the expression pattern independent of Ki-67 and p53. [43-46]

Some works have shown high sensitivity and specificity in the detection of p16 for the differentiation between Bowen´s disease and AK. [47] Numeric and structural changes in the chromosomes involving the chromosomal band 3p13, the centromeric region of the chromosome 3 and the loss of heterozygosity of 4 or more loci have been identified. [15] Likewise, numeric aberrations in the MYC proto-oncogene and in the epidermal growth factor receptor gene in AK and mostly in SCC have been identified, and there is a correlation between the level of genetic alteration and the cellular anaplasia of the lesion.[48,49]

The inflammatory process that surrounds AK lesions seems to be also involved in the development of these lesions into carcinomas and there is a change of the inflammatory infiltrate profile with the development of the disease. It has been observed that SCC lesions have more CD10+ cells (fibroblasts), more immature dendritic cells and lymphocytes with suppressor phenotype ($CD4^{*}CD25^{*}$ Tregs) and less Langerhans cells in the peritumoral infiltrate when compared to AK lesions. [50,51]

The role of virus in the development of AK is not clear. The association with infection by the papillomavirus (HPV) has been established for a few types of epithelial cancers, like cancer of the cervix, but there is no proven correlation with their presence in AKs since, usually, the viral DNA is identified in normal skin as well as in the lesions. A study conducted in Sweden evaluated the presence of HPV DNA in swabs and in biopsies of curetted lesions (without the stratum corneum) of AKs, and observed 83% positivity versus 11%, respectively, which suggests that the positivity is due to superficial contamination. [52]

However one retrospective study conducted for seven years in Australia observed a potentiating effect of betapapillomavirus in other risk factors like age, fair skin and solar exposure, and the persistence of the infection at the end of the study was associated with a higher number of AKs. [53,54] Moreover, a study which evaluated the HPV DNA load in AK lesions and invasive carcinomas showed higher detection in pre-malignant lesions than in advanced ones, which suggests that the persistence of the HPV is not necessary for the progression of the disease, but the viral infection could have a role in the initial stages of carcinogenesis induction. [55] Zaravinos also identified a higher detection of cytomegalovirus in BCC (40%) and in SCC (33%) in comparison with normal skin (0%) and AK (8%).[56]

The lack of cell control over oxidative stress seems to be also associated with an increased risk of carcinogenesis. Mutations that cause hypo-functioning of the glutathione S-transferase, which act on the intracellular oxidation control, are associated with higher risk of AK according to an Italian study. [57]

Xeroderma pigmentosum is an example of a genetic disease with increased risk of AK and SCC, as well as extreme photosensitivity, due to a defect in the repair of DNA damage caused by UV radiation. [58]

The accessibility of the skin to examination, the frequency of the disease, the morphological, molecular and evolutive changes of AK allow us to consider them as an interesting research model for the prevention of carcinogenesis in humans. [3,59]

RISK FACTORS

The natural history of AK depends on environmental factors like UVR exposure, carcinogens and ionizing radiation; as well as on factors related to the individual such as phototype, age, immune suppression and competence for DNA repair.

When considering only people with phototypes I to III, 80% have one or more AK after 60 years of age.[13] The relative risk to AK was 14,1 times higher in fair skinned patients when compared with the ones with dark skin. [9]

Despite being highly prevalent, some individuals are typically more affected by AK than others, as it is demonstrated by an Australian study which involved 96 people; 12% of the patients with AK had 65% of the lesions observed. This study also pointed out to the high evanescence of these lesions. During the 12 months of observation, 644 new lesions developed, while 526 pre-existent ones regressed spontaneously. [60] In another investigation, Criscione et. al verified, by photographic follow-up, that 55% of the

AK lesions registered were no longer present after 12 months of follow-up. [61]

Nowadays AKs are considered by many authors as keratinocyte intraepithelial neoplasias, with a cumulative chance of 5-20% of developing into invasive neoplasia, and the number of lesions maximizes this occurrence. On the other hand, it is estimated that up to 27-82% of the SCC evolve from AKs, and some 82-97% of the SCC have contiguous AKs. [3,62,63]

Due to the fact that AKs originate SCC with better histological differentiation, it is expected that such neoplasias have a lower risk of metastatization. On the other hand, this hypothesis has not yet been confirmed by studies with adequate methodology. [3]

Besides the fact that epidemiological data demonstrates the association between AK and SCC, it is worth noting that both diseases have very similar genetic expression profile, overlapping histological abnormalities and the presence of AKs contiguous to SCCs, which strengthens the hypothesis that one is another´s precursor. [2,64,65]

The length of time for the progression to invasive carcinoma from a prone lesion seems to be approximately two years, according to a study which assessed histologically confirmed lesions, and this progression would be quicker in immunesuppressed patients, the same way that these patients have more numerous AKs. [66]

A retrospective multivariate analysis reported that the elderly with AKs have a six times higher risk of developing malignant skin tumors in general, suggesting that AKs can also be markers for a neoplastic risk phenotype. [67]

Various environmental and individual risk factors for the development of AKs have been identified. A German study conducted in 2009 established an independent association between AKs and age over 66 years (OR=1,1), masculine gender (OR=3,9), fair skin (OR=2,2), personal history of skin cancer (OR=4,8), irregular use of sunscreen (OR=1,81) and occupational solar exposure (OR=1,7).[68]

An investigation including renal transplanted patients in Italy identified the presence of AK in this population as an independent risk factor for the development of cutaneous tumors, together with age at the time of the transplantation and time of immunesuppression. [69] Likewise, another European study performed in Germany identified a higher risk for the development of AK in this population and, as described in other works, the immunesuppressed ones had a much higher risk for the development of SCC when compared with BCC (SCC/BCC = 7/1), while in the general population the incidence rate between SCC and BCC is around 1/4.[24]

New drugs have shown contradictory adverse effects in AK lesions, like sorafenib and other tyrosine-kinase inhibitors biologic medications used in the treatment of advanced carcinomas. This medication seems to induce inflammation of pre-existent AKs, the development of SCC and keratoacanthoma-like lesions, which can regress with the suspension of the medication.[70,71]

AKs are more frequent in peoples who live in areas closer to the Equator line. [12] The influence of seasonality in the diagnosis of AK was also noted, and this characteristic was more prominent than in dermatoses like acne, dyschromia and psoriasis, which indicates that monthly changes in the temperature, the solar radiation or the level of exposure could affect the clinical presentation of these lesions. [72] The altitude affects the intensity of the UVB radiation, and there is an 8-10% increase in the incidence of AK every 300 meters of elevation.[73]

In addition to that, sunscreens significantly reduce the number of AKs in up to 40%,[59] and their protective effect (30%) has been verified even in post-transplantation immunesuppressed patients. [74]

As the lesions typically develop in the skin chronically exposed to solar radiation in people with low phototypes, they are more prevalent in men in the first decades of adult life, when the level of solar exposure varies significantly according to gender due to professional exposures, and there is a more uniform incidence between the sexes with ageing. [75]

The intensity of solar radiation to which individuals are exposed is directly related to the prevalence of AKs, as verified in the Japanese population, which observed three times more lesions in patients living in lower latitudes (25ºN versus 34ºN), who were exposed to double the incidence of ultraviolet radiation B (UVRB) in the reported comparison.[76]

Contact with environmental carcinogens is also related to a higher risk of non-melanoma skin cancer. The hydrocarbons are more related to contacting effect, whereas the arsenic would act mainly through contaminated water and alternative medication. It has been noted that arsenic ingestion is associated with a higher incidence of pre-malignant skin lesions and this effect is potentiated by other factors like solar exposure, smoking and pesticides. [77]

Vitiligo is associated with higher risk of developing AKs due the absence of UVR protection caused by the lack of melanin, as well as the prolonged therapy. [78]

A prospective nutritional study conducted for five years identified a preventive effect against AKs in people who ingested higher regular amounts of fish oil and wine, probably due to their anti-inflammatory and anti-oxidation effects. [79] Diets with low levels of fat have also been associated with resolution of pre-existent AKs and reduction in the incidence of new lesions

after 24 months of follow-up in 76 patients with skin cancer history. [80] Likewise, a cross-sectional study conducted in 93.676 Caucasian women showed a 30% reduction in the occurrence of non-melanoma skin cancer in regular users of more than six daily cups of coffee. [81]

Some epidemiological studies performed over the last decades have observed a protective effect of the regular use of oral and topical NSAIDs against SCC and AK, corroborating the anti-neoplastic effect of this class of drugs already observed in intestinal cancers, for example. [37,82-85]

Topical 3% diclofenac was shown to be efficient in the treatment and the prevention of the progress of AKs. [83-87] In an Australian study a reduction of up to 52% in the number of AKs and a lower incidence of SCCs were observed with regular use of systemic NSAIDs.[88]

In 2008, Tang et al. also demonstrated more than 50% reduction in the incidence of UV- induced skin tumors in nude rates which received nimesulide, a selective COX-2 inhibitor. [89] Bundscherer et al. observed that another selective inhibitor, celecoxib, inhibited the growth of melanoma cells, including in lineages that did not express COX-2. [90]

CLINICAL PRESENTATION

Because the genesis of the AKs relates to cumulative exposure to UVR, the most chronically exposed areas like the face, neck, chest, dorsum of the hands, shoulders and scalp (in men with androgenetic alopecia) are most commonly affected. [19]

Most AKs lesions are slow growing papules, less than 1 cm in diameter, dry, erythematous, pigmented with telangectasias, almost always covered by yellow or brown adherent scales with little or no infiltration. The level of infiltration, hyperkeratosis, pigmentation and secondary ulceration can be quite variable. The surrounding areas can show evidence of diffuse chronic solar damage with telangectasias, elastosis, wrinkles, pigmentation abnormalities, starry scars and yellow coloration (Figures 1 and 2).[13]

AKs on the dorsum of the hands and forearms are usually thicker and more hyperkeratotic, with some lesions occasionally having the aspect of cutaneous horn, and some of them (15,7%) are actually SCCs. [91,92]

Traditionally, the diagnosis of AK is based on the clinical presentation, but this issue has not yet been assessed in wide clinical essays. The positive predictive value of the clinical diagnosis varies from 74 to 94%.[93,94] It is worth noting that in a clinical research on the use of photodynamic therapy in the treatment of AKs assessing 271 lesions, one in every 25 lesions considered as AK, clinically, the histological diagnosis was

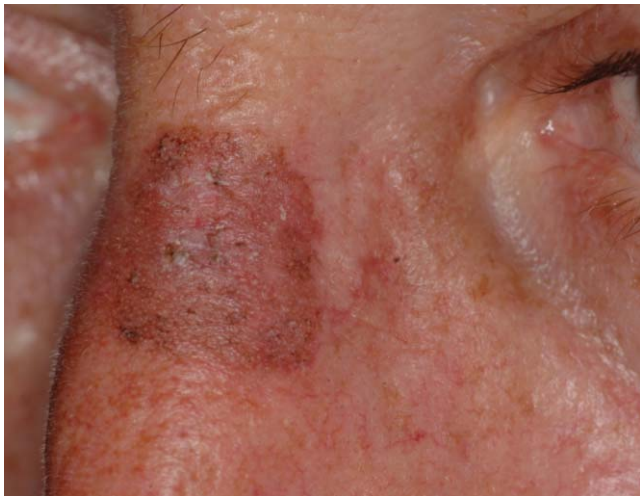

Figure 1: Actinic keratosis on the dorsum of the nose

invasive SCC. [95]

There are no pathognomonic clinical criteria for the diagnosis of AKs, however some works using *in vivo* confocal reflectance microscopy showed a high level of correlation with the histological diagnosis of these lesions. [96,97]

Some authors divide the clinical presentation of the lesions into three levels: level I, visible and slightly palpable; level II: visible and palpable; level III: frankly visible and hyperkeratotic. [98] Besides, other clinical variants can include lesions similar to lichen planus and actinic cheilitis.

There is no definite way to distinguish between AK and microinvasive SCC, but by the histological examination. According to a wide bibliographic revision, the clinical parameters that indicate lesions with an

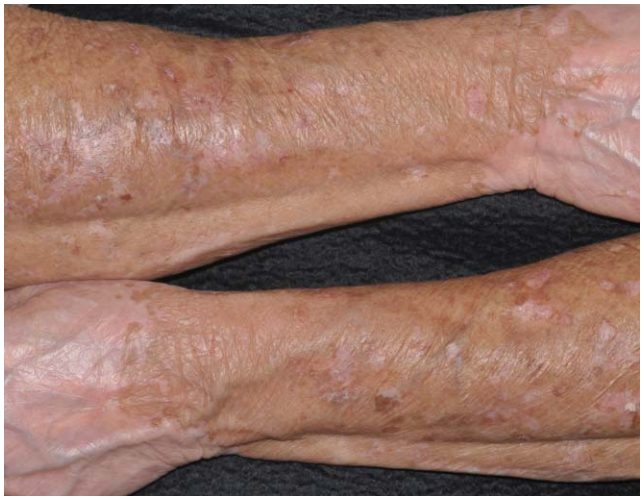

Figure 2: Multiple actinic keratoses on the forearms in a patient with vitiligo under phototherapy. Note hyperkeratotic lesions and signs of photoageing on the adjacent skin

increased risk of malignancy would be induration, inflammation, more than 1cm in diameter, rapid growth, bleeding, erythema and ulceration. [99]

AKs which develop in mucosa, especially the actinic cheilitis, develop into SCCs with a higher metastatic potential, however this is beyond the scope of the text.[100,101]

Despite being considered a low morbidity dermatosis, a significant compromise of the quality of life (Skindex-29) in those affected was observed, which seems to be proportional to the quantity of lesions the patient has. [102]

Despite being highly characteristic, AK lesions can be clinically mistaken for seborrheic keratosis, Bowen´s disease, SCC, basal cell carcinoma, discoid lupus erythematosus, stucco keratosis, solar lentigo, porokeratosis and viral warts.

HISTOPATHOLOGY

The diagnosis of AK is defined by the histopathological examination of the lesion. Histologically, AK is characterized by the loss of organized maturation with atypical keratinocytes in the epidermis and increased number of mitosis. The keratinocytes reveal loss of polarization and atypical cells have pleomorphic nuclei, increased in size and hyperchromatic, with pale or vacuolized eosinophilic cytoplasm. [15,103] This nuclear alteration seems to follow a continuous progression related to the level of solar damage sustained. [104]

Typically, the inter-adnexial epidermis is compromised and the epidermis around the hair follicles and eccrine ducts is spared. This gives an aspect of consecutive vertical stripes of hyperkeratosis and parakeratosis, corresponding to the healthy epidermis and the ill inter-adnexial epidermis, respectively. The protection from epidermal damage conferred by the hair follicle is called by some pathologists the "umbrella phenomenon". [103,105]

There is usually solar elastosis and lymphocytic infiltrate, perivascular or lichenoid of variable intensity, on the dermis. [15]

Bartels observed that the cariometry of the keratinocytes coming from the skin considered normal was altered in proportion to the level of photo exposure at histology, indicating a possible pre-clinical progression of AKs developing more extensively over the affected areas. [106]

Cytologically, the findings from AKs are indistinguishable from SCCs. [103]

At histopathological examination the AKs can be divided into six types: hypertrophic, atrophic, bowenoid, acantholytic, lichenoid and pigmented. [107]

The hypertrophic type shows pronounced hyperkeratosis, thickened epidermis in some areas, with irregular growth of proliferative projections limited to the upper dermis, with no evident invasion. In the atrophic type there is mild hyperkeratosis and diffuse epidermal atrophy with atypical cells on the basal layer. The bowenoid type presents with atypia all over the extension of the epidermis, similar to Bowen´s disease, differing from the latter because it does not affect the follicular sheath epithelium. The acantholytic type presents with gaps and intercellular lacunae derived from anaplasic alterations of the keratinocytes. In the lichenoid type there is a band-like infiltrate on the basal membrane zone and in the pigmented type there is an excess of melanin especially in the basal cells and a higher concentration of melanophages in the dermis. Lastly, it must be highlighted that these characteristics can be overlapping and the histological type is defined by the most prominent characteristic. [13,15]

A different classification scheme for AKs was developed, taking into consideration the level of atypia on the epidermis. Similarly to the pattern used in assessing pre-malignant lesions of the cervix, the lesions are divided into three levels of keratinocyte intraepithelial neoplasia (KIN): level I, with atypia restricted to the basal and suprabasal layers; level II, with atypia extending to the lower two thirds of the epidermis; level III, with atypia all over the epidermal thickness. [108]

Some authors believe that this approach to histological description would promote therapeutic measures according to the risk of malignant progression of each lesion of the patient. [15]

Finally, some authors defend that AK is considered a *in situ* SCC, due to the possible progression to invasive neoplasia and the similar microscopic alterations and genetic markers between both diseases, however there are sufficient clinical, epidemiological, molecular and natural history differences which warrant the individuality of the diagnoses. [103,109-114]

FINAL CONSIDERATIONS

Fair skinned individuals, submitted to chronic solar exposure are a significant proportion of the Brazilian population and must be identified as under risk to AKs and cutaneous neoplasias.

Policies of photoprotection, photoeducation and early diagnosis in professionals exposed to solar radiation must be promoted by medical societies and trade unions as preventive strategies of occupational damage.

As well as portraying the cumulative solar aggression, the evidence that AKs are SCC precursors and develop in areas accessible to clinical and laboratorial assessment make the amenable to the study of human carcinogenesis, as well as favor therapeutic and preventive clinical essays.

There are many effective therapeutic modalities for AKs, like direct destructive techniques such as cryotherapy, the use of trichloroacetic acid, lasertherapy, electrocoagulation, dermabrasion, shaving and excision with primary closing. Non-surgical strategies have the advantage of treating wider areas with the potential to act over the cancerization field. They are: photodynamic therapy, 3,75 to 5% imiquimod, 0,5 to 5% 5-fluorouracil, 3% diclofenac, 0,1% topical treinoin, 10% masoprocol and 0,5 to 1% colchicine. Medium peels, laser ressurfacing and epithelial dermabrasion are also described in the treatment of multiple lesions. Most approaches offer complete cure for over 30% of the patients at each session, and usually additional sessions are required for remaining lesions. Infiltrated or hyperkeratotic AKs are more resistant to therapy. Detailed analysis of the treatments is beyond the scope of this text. There is, however, significant discussion about the cost-benefit of the effectiveness of therapies which treat only the lesions but not all the cancerization field. [81,115-123]

The diagnosis of AK should involve not only the treatment, but also orientation in terms of occupational and recreational photo exposure to the patients, as well as clarification in terms of exposure time, clothing, use of sunscreen (FPS≥15) and periodic skin self-examination. [3,29,75]

As the perilesional epithelium also has abnormalities due to photo exposure, understanding the existence of a "cancerization field" should be explained to the patients, reinforcing the importance of preventive clinical follow-up.

Patients with AKs must be taken as having a risk for other cutaneous neoplasias and must be followed clinically not only for the purpose of treating the AKs, but also for the early diagnosis of others dermatoses, amongst them carcinomas and melanoma. [124,125]

Skin cancer prevention campaigns must encourage medical and populational education to the diagnosis of AKs aiming at increasing the patients´ and doctors´ perception to significant skin changes, which, indirectly, would increase the number of dermatological diagnosis in the population, reducing the morbidity from diseases which occur due to delayed diagnosis. Secondarily, this would valorize the specialty before the society.[126,127]

Finally, the periodic follow-up of patients with AK should be taken as an opportunity to re-examine the patients, promote skin health and encourage photoprotective measures. ❑

REFERENCES

1. Goldberg LH, Mamelak AJ. Review ofactinic keratosis. Part I: etiology, epidemiology and clinical presentation. J Drugs Dermatol. 2010;9:1125-32.
2. Babilas P, Landthaler M, Szeimies RM. [Actinic keratoses]. Hautarzt. 2003;54:551-60.
3. Castro IA, Schütz LC, Capp E, Bakos L. Ceratoses actínicas. Rev HCPA. 2006;26:66-72.
4. Anwar J, Wrone DA, Kimyai-Asadi A, Alam M. The development of actinic keratosis into invasive squamous cell carcinoma: evidence and evolving classification schemes. Clin Dermatol. 2004;22:189-96.
5. Lanssens S, Ongenae K. Dermatologic lesions and risk for cancer. Acta Clin Belg. 2011;66:177-85.
6. Glogau RG. Aesthetic and anatomic analysis of the aging skin. Semin Cutan Med Surg. 1996;15:134-8.
7. Chia A, Moreno G, Lim A, Shumack S. Actinic keratoses. Aust Fam Physician. 2007;36:539-43.
8. Feldman SR, Fleischer AB Jr, McConnell RC. Most common dermatologic problems identified by internists, 1990-1994. Arch Intern Med. 1998;158:726-30.
9. Lebwohl M. Actinic keratosis: epidemiology and progression to squamous cell carcinoma. Br J Dermatol. 2003;149 Suppl 66:31-3.
10. Sociedade Brasileira de Dermatologia SBD. Perfil nosológico das consultas dermatológicas no Brasil. An Bras Dermatol. 2006;81:549-58.
11. Bernard P, Dupuy A, Sasco A, Brun P, Duru G, Nicoloyannis N, et al. Basal cell carcinomas and actinic keratoses seen in dermatological practice in France: a cross-sectional survey. Dermatology. 2008;216:194-9.
12. Frost CA, Green AC. Epidemiology of solar keratoses. Br J Dermatol. 1994;131:455-64.
13. Rossi R, Mori M, Lotti T. Actinic keratosis. Int J Dermatol. 2007;46:895-904.
14. Vatve M, Ortonne JP, Birch-Machin MA, Gupta G. Management of field change in actinic keratosis. Br J Dermatol. 2007;157 Suppl 2:21-4.
15. Roewert-Huber J, Stockfleth E, Kerl H. Pathology and pathobiology of actinic (solar) keratosis - an update. Br J Dermatol 2007;157 Suppl 2:18-20.
16. Ishioka P, Marques SA, Hirai AT, Marques ME, Hirata SH, Yamada S. Prevalence of precancerous skin lesions and non-melanoma skin cancer in Japanese-Brazilians in Bauru, São Paulo State, Brazil. Cad Saude Publica. 2009;25:965-71.
17. Kim HS, Cho EA, Bae JM, Yu DS, Oh ST, Kang H, et al. Recent trend in the incidence of premalignant and malignant skin lesions in Korea between 1991 and 2006. J Korean Med Sci. 2010;25:924-9.
18. Kennedy C, Bajdik CD, Willemze R, De Gruijl FR, Bouwes Bavinck JN; Leiden Skin Cancer Study. The influence of painful sunburns and lifetime sun exposure on the risk of actinic keratoses, seborrheic warts, melanocytic nevi, atypical nevi, and skin cancer. J Invest Dermatol. 2003;120:1087-93.
19. Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol. 2000;42:4-7.
20. Garg S, Carroll RP, Walker RG, Ramsay HM, Harden PN. Skin cancer surveillance in renal transplant recipients: re-evaluation of U.K. practice and comparison with Australian experience. Br J Dermatol. 2009;160:177-9.
21. Ulrich C, Kanitakis J, Stockfleth E, Euvrard S. Skin cancer in organ transplant recipients--where do we stand today? Am J Transplant. 2008;8:2192-8.
22. Dornelas MT, Rodrigues MF, Machado DC, Gollner A, Ferreira AP. Expressão de marcadores de proliferação celular e apoptose no carcinoma espinocelular de pele e ceratose actínica. An Bras Dermatol. 2009;84:469-75.
23. Chinem VP, Miot HA. Epidemiology of basal cell carcinoma. An Bras Dermatol. 2011;86:292-305.
24. Keller B, Braathen LR, Marti HP, Hunger RE. Skin cancers in renal transplant recipients: a description of the renal transplant cohort in Bern. Swiss Med Wkly. 2010;140:w13036.
25. Leffell DJ. The scientific basis of skin cancer. J Am Acad Dermatol 2000;42:18-22.
26. Berking C. [The role of ultraviolet irradiation in malignant melanoma]. Hautarzt. 2005;56:687-96.
27. Arrington JH 3rd, Lockman DS. Thermal keratoses and squamous cell carcinoma in situ associated with erythema ab igne. Arch Dermatol. 1979;115:1226-8.
28. Eskelinen A, Halme K, Lassus A, Idänpään-Heikkilä J. Risk of cutaneous carcinoma in psoriatic patients treated with PUVA. Photodermatol. 1985;2:10-4.
29. Balogh TS, Velasco MVR, Pedriali CA, Kaneko TM, Baby AR. Proteção à radiação ultravioleta: recursos disponíveis na atualidade em fotoproteção. An Bras Dermatol. 2011;86:732-42.
30. Lever LR, Farr PM. Skin cancers or premalignant lesions occur in half of high-dose PUVA patients. Br J Dermatol. 1994;131:215-9.
31. Nindl I, Gottschling M, Krawtchenko N, Lehmann MD, Röwert-Huber J, Eberle J, et al. Low prevalence of p53, p16(INK4a) and Ha-ras tumour-specific mutations in low-graded actinic keratosis. Br J Dermatol. 2007;156 Suppl 3:34-9.
32. Wang HJ, Liu XJ, Yang KX, Luo FM, Lou JY, Peng ZL. [Effects of nonsteroidal anti-inflammatory drug celecoxib on expression of cyclooxygenase-2 (COX-2) in ovarian carcinoma cell]. Sichuan Da Xue Xue Bao Yi Xue Ban. 2006;37:757-60.
33. Muller-Decker K, Charyalertsak S, Albert C, Reinerth G, Marks F, Furstenberger G. Cyclooxygenase-2: a molecular target for chemoprevention of epithelial tumors of skin and colon. Adv Exp Med Biol. 2002;507:445-8.
34. Muller-Decker K, Neufang G, Berger I, Neumann M, Marks F, Furstenberger G. Transgenic cyclooxygenase-2 overexpression sensitizes mouse skin for carcinogenesis. Proc Natl Acad Sci U S A. 2002;99:12483-8.
35. Tiano HF, Loftin CD, Akunda J, Lee CA, Spalding J, Sessoms A, et al. Deficiency of either cyclooxygenase (COX)-1 or COX-2 alters epidermal differentiation and reduces mouse skin tumorigenesis. Cancer Res. 2002;62:3395-401.
36. Berhane T, Halliday GM, Cooke B, Barnetson RS. Inflammation is associated with progression of actinic keratoses to squamous cell carcinomas in humans. Br J Dermatol. 2002;146:810-5.
37. Fecker LF, Stockfleth E, Nindl I, Ulrich C, Forschner T, Eberle J. The role of apoptosis in therapy and prophylaxis of epithelial tumours by nonsteroidal anti-inflammatory drugs (NSAIDs). Br J Dermatol. 2007;156 Suppl 3:25-33.
38. Tjiu JW, Liao YH, Lin SJ, Huang YL, Tsai WL, Chu CY, et al. Cyclooxygenase-2 overexpression in human basal cell carcinoma cell line increases antiapoptosis, angiogenesis, and tumorigenesis. J Invest Dermatol. 2006;126:1143-51.
39. Nijsten T, Colpaert CG, Vermeulen PB, Harris AL, Van Marck E, Lambert J. Cyclooxygenase-2 expression and angiogenesis in squamous cell carcinoma of the skin and its precursors: a paired immunohistochemical study of 35 cases. Br J Dermatol. 2004;151:837-45.
40. Wu Y, Liu H, Li J. Expression of p63 and cyclooxygenase-2 and their correlation in skin tumors. J Huazhong Univ Sci Technolog Med Sci. 2007;27:206-8.
41. Ouyang W, Zhang D, Ma Q, Li J, Huang C. Cyclooxygenase-2 induction by arsenite through the IKKbeta/NFkappaB pathway exerts an antiapoptotic effect in mouse epidermal Cl41 cells. Environ Health Perspect. 2007;115:513-8.
42. Bowen AR, Hanks AN, Murphy KJ, Florell SR, Grossman D. Proliferation, apoptosis, and survivin expression in keratinocytic neoplasms and hyperplasias. Am J Dermatopathol. 2004;26:177-81.
43. Park HR, Min SK, Cho HD, Kim KH, Shin HS, Park YE. Expression profiles of p63, p53, survivin, and hTERT in skin tumors. J Cutan Pathol. 2004;31:544-9.
44. Bortoluzzi MC, Yurgel LS, Dekker NP, Jordan RC, Regezi JA. Assessment of p63 expression in oral squamous cell carcinomas and dysplasias. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;98:698-704.
45. Nylander K, Vojtesek B, Nenutil R, Lindgren B, Roos G, Zhanxiang W, et al. Differential expression of p63 isoforms in normal tissues and neoplastic cells. J Pathol. 2002;198:417-27.
46. Parsa R, Yang A, McKeon F, Green H. Association of p63 with proliferative potential in normal and neoplastic human keratinocytes. J Invest Dermatol. 1999;113:1099-105.
47. Salama ME, Mahmood MN, Qureshi HS, Ma C, Zarbo RJ, Ormsby AH. p16INK4a expression in actinic keratosis and Bowen's disease. Br J Dermatol. 2003;149:1006-12.
48. Toll A, Salgado R, Yébenes M, Martín-Ezquerra G, Gilaberte M, Baró T, et al. Epidermal growth factor receptor gene numerical aberrations are frequent events in actinic keratoses and invasive cutaneous squamous cell carcinomas. Exp Dermatol. 2010;19:151-3.
49. Toll A, Salgado R, Yébenes M, Martín-Ezquerra G, Gilaberte M, Baró T, et al. MYC gene numerical aberrations in actinic keratosis and cutaneous squamous cell carcinoma. Br J Dermatol. 2009;161:1112-8.
50. Takahara M, Chen S, Kido M, Takeuchi S, Uchi H, Tu Y, et al. Stromal CD10 expression, as well as increased dermal macrophages and decreased Langerhans cells, are associated with malignant transformation of keratinocytes. J Cutan Pathol. 2009;36:668-74.
51. Jang TJ. Prevalence of Foxp3 positive T regulatory cells is increased during progression of cutaneous squamous tumors. Yonsei Med J. 2008;49:942-8.
52. Forslund O, Lindelöf B, Hradil E, Nordin P, Stenquist B, Kirnbauer R, et al. High prevalence of cutaneous human papillomavirus DNA on the top of skin tumors but not in "Stripped" biopsies from the same tumors. J Invest Dermatol. 2004;123:388-94.
53. McBride P, Neale R, Pandeya N, Green A. Sun-related factors, betapapillomavirus, and actinic keratoses: a prospective study. Arch Dermatol. 2007;143:862-8.
54. Plasmeijer EI, Neale RE, de Koning MN, Quint WG, McBride P, Feltkamp MC, et al. Persistence of betapapillomavirus infections as a risk factor for actinic keratoses, precursor to cutaneous squamous cell carcinoma. Cancer Res. 2009;69:8926-31.
55. Weissenborn SJ, Nindl I, Purdie K, Harwood C, Proby C, Breuer J, et al. Human papillomavirus-DNA loads in actinic keratoses exceed those in non-melanoma skin cancers. J Invest Dermatol. 2005;125:93-7.
56. Zaravinos A, Kanellou P, Spandidos DA. Viral DNA detection and RAS mutations in actinic keratosis and nonmelanoma skin cancers. Br J Dermatol. 2010;162:325-31.

57. Guarneri F, Asmundo A, Sapienza D, Gazzola A, Cannavo SP. Polymorphism of glutathione S-transferases M1 and T1: susceptibility to solar keratoses in an Italian population. Clin Exp Dermatol. 2010;35:771-5.
58. Cleaver JE. Cancer in xeroderma pigmentosum and related disorders of DNA repair. Nat Rev Cancer. 2005;5:564-73.
59. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. N Engl J Med. 1993;329:1147-51.
60. Frost C, Williams G, Green A. High incidence and regression rates of solar keratoses in a queensland community. J Invest Dermatol. 2000;115:273-7.
61. Criscione VD, Weinstock MA, Naylor MF, Luque C, Eide MJ, Bingham SF, et al. Actinic keratoses: Natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. Cancer 2009;115:2523-30.
62. Mittelbronn MA, Mullins DL, Ramos-Caro FA, Flowers FP. Frequency of pre-existing actinic keratosis in cutaneous squamous cell carcinoma. Int J Dermatol. 1998;37:677-81.
63. Marks VJ. Actinic keratosis. A premalignant skin lesion. Otolaryngol Clin North Am. 1993;26:23-35.
64. Padilla RS, Sebastian S, Jiang Z, Nindl I, Larson R. Gene expression patterns of normal human skin, actinic keratosis, and squamous cell carcinoma: a spectrum of disease progression. Arch Dermatol. 2010;146:288-93.
65. Schwarze HP, Loche F, Gorguet MC, Kuchta J, Bazex J. Invasive cutaneous squamous cell carcinoma associated with actinic keratosis: a case with orbital invasion and meningeal infiltration. Dermatol Surg. 1999;25:587-9.
66. Fuchs A, Marmur E. The kinetics of skin cancer: progression of actinic keratosis to squamous cell carcinoma. Dermatol Surg. 2007;33:1099-101.
67. Chen GJ, Feldman SR, Williford PM, Hester EJ, Kiang SH, Gill I, et al. Clinical diagnosis of actinic keratosis identifies an elderly population at high risk of developing skin cancer. Dermatol Surg. 2005;31:43-7.
68. Hensen P, Müller ML, Haschemi R, Ständer H, Luger TA, Sunderkötter C, et al. Predisposing factors of actinic keratosis in a North-West German population. Eur J Dermatol. 2009;19:345-54.
69. Savoia P, Stroppiana E, Cavaliere G, Osella-Abate S, Mezza E, Segoloni GP, et al. Skin cancers and other cutaneous diseases in renal transplant recipients: a single Italian center observational study. Eur J Dermatol. 2011;21:242-7.
70. Dubauskas Z, Kunishige J, Prieto VG, Jonasch E, Hwu P, Tannir NM. Cutaneous squamous cell carcinoma and inflammation of actinic keratoses associated with sorafenib. Clin Genitourin Cancer. 2009;7:20-3.
71. Schmid-Wendtner MH, Wendtner CM. Intensified inflammatory reaction of actinic keratoses after single application of topical 5-fluorouracil in a patient treated with nilotinib for chronic myeloid leukemia. Dermatology. 2009;219:341-3.
72. Hancox JG, Sheridan SC, Feldman SR, Fleischer AB Jr. Seasonal variation of dermatologic disease in the USA: a study of office visits from 1990 to 1998. Int J Dermatol. 2004;43:6-11.
73. Rigel DS, Rigel EG, Rigel AC. Effects of altitude and latitude on ambient UVB radiation. J Am Acad Dermatol. 1999;40:114-6.
74. Ulrich C, Jürgensen JS, Degen A, Hackethal M, Ulrich M, Patel MJ, et al. Prevention of non-melanoma skin cancer in organ transplant patients by regular use of a sunscreen: a 24 months, prospective, case-control study. Br J Dermatol. 2009;161 Suppl 3:78-84.
75. Vitasa BC, Taylor HR, Strickland PT, Rosenthal FS, West S, Abbey H, et al. Association of nonmelanoma skin cancer and actinic keratosis with cumulative solar ultraviolet exposure in Maryland watermen. Cancer. 1990;65:2811-7.
76. Araki K, Nagano T, Ueda M, Washio F, Watanabe S, Yamaguchi N, et al. Incidence of skin cancers and precancerous lesions in Japanese--risk factors and prevention. J Epidemiol. 1999;9:S14-21.
77. Melkonian S, Argos M, Pierce BL, Chen Y, Islam T, Ahmed A, et al. A prospective study of the synergistic effects of arsenic exposure and smoking, sun exposure, fertilizer use, and pesticide use on risk of premalignant skin lesions in Bangladeshi men. Am J Epidemiol. 2011;173:183-91.
78. Akimoto S, Suzuki Y, Ishikawa O. Multiple actinic keratoses and squamous cell carcinomas on the sun-exposed areas of widespread vitiligo. Br J Dermatol. 2000;142:824-5.
79. Hughes MC, Williams GM, Fourtanier A, Green AC. Food intake, dietary patterns, and actinic keratoses of the skin: a longitudinal study. Am J Clin Nutr. 2009;89:1246-55.
80. Black HS, Herd JA, Goldberg LH, Wolf JE Jr, Thornby JI, Rosen T, et al. Effect of a low-fat diet on the incidence of actinic keratosis. N Engl J Med. 1994;330:1272-5.
81. Abel EL, Hendrix SO, McNeeley SG, Johnson KC, Rosenberg CA, Mossavar-Rahmani Y, et al. Daily coffee consumption and prevalence of nonmelanoma skin cancer in Caucasian women. Eur J Cancer Prev. 2007;16:446-52.
82. Grau de Castro JJ. [COX-2 inhibitors in cancer prevention]. Rev Clin Esp. 2005;205:446-56.
83. Ulrich C, Johannsen A, Rowert-Huber J, Ulrich M, Sterry W, Stockfleth E. Results of a randomized, placebo-controlled safety and efficacy study of topical diclofenac 3% gel in organ transplant patients with multiple actinic keratoses. Eur J Dermatol. 2010;20:482-8.
84. Dirschka T, Bierhoff E, Pflugfelder A, Garbe C. Topical 3.0% diclofenac in 2.5% hyaluronic acid gel induces regression of cancerous transformation in actinic keratoses. J Eur Acad Dermatol Venereol. 2010;24:258-63.
85. Kose O, Koc E, Erbil AH, Caliskan E, Kurumlu Z. Comparison of the efficacy and tolerability of 3% diclofenac sodium gel and 5% imiquimod cream in the treatment of actinic keratosis. J Dermatolog Treat. 2008;19:159-63.
86. Nelson C, Rigel D. Long-term Follow up of Diclofenac Sodium 3% in 2.5% Hyaluronic Acid Gel for Actinic Keratosis: One-year Evaluation. J Clin Aesthet Dermatol. 2009;2:20-5.
87. Fariba I, Ali A, Hossein SA, Atefeh S, Atarzadeh Behbahan SA. Efficacy of 3% diclofenac gel for the treatment of actinic keratoses: a randomized, double-blind, placebo controlled study. Indian J Dermatol Venereol Leprol. 2006;72:346-9.
88. Butler GJ, Neale R, Green AC, Pandeya N, Whiteman DC. Nonsteroidal anti-inflammatory drugs and the risk of actinic keratoses and squamous cell cancers of the skin. J Am Acad Dermatol. 2005;53:966-72.
89. Tang X, Kim AL, Kopelovich L, Bickers DR, Athar M. Cyclooxygenase-2 inhibitor nimesulide blocks ultraviolet B-induced photocarcinogenesis in SKH-1 hairless mice. Photochem Photobiol. 2008;84:522-7.
90. Bundscherer A, Hafner C, Maisch T, Becker B, Landthaler M, Vogt T. Antiproliferative and proapoptotic effects of rapamycin and celecoxib in malignant melanoma cell lines. Oncol Rep. 2008;19:547-53.
91. Yu RC, Pryce DW, Macfarlane AW, Stewart TW. A histopathological study of 643 cutaneous horns. Br J Dermatol. 1991;124:449-52.
92. Dergham AP, Muraro CC, Ramos EA, Mesquita LAF, Collaço LM. Distribuição dos diagnósticos de lesões pré-neoplásicas e neoplásicas de pele no Hospital Universitário Evangélico de Curitiba. An Bras Dermatol. 2004;79:555-9.
93. Venna SS, Lee D, Stadecker MJ, Rogers GS. Clinical recognition of actinic keratoses in a high-risk population: how good are we? Arch Dermatol. 2005;141:507-9.
94. Epstein E. Quantifying actinic keratosis: assessing the evidence. Am J Clin Dermatol. 2004;5:141-4.
95. Ehrig T, Cockerell C, Piacquadio D, Dromgoole S. Actinic keratoses and the incidence of occult squamous cell carcinoma: a clinical-histopathologic correlation. Dermatol Surg. 2006;32:1261-5.
96. Ulrich M, Forschner T, Röwert-Huber J, González S, Stockfleth E, Sterry W, et al. Differentiation between actinic keratoses and disseminated superficial actinic porokeratoses with reflectance confocal microscopy. Br J Dermatol. 2007;156 Suppl 3:47-52.
97. Mogensen M, Jemec GB. Diagnosis of nonmelanoma skin cancer/keratinocyte carcinoma: a review of diagnostic accuracy of nonmelanoma skin cancer diagnostic tests and technologies. Dermatol Surg. 2007;33:1158-74.
98. Butani AK, Arbesfeld DM, Schwartz RA. Premalignant and early squamous cell carcinoma. Clin Plast Surg. 2005;32:223-35.
99. Quaedvlieg PJ, Ostertag JU, Krekels GA, Neumann HA. Delayed wound healing after three different treatments for widespread actinic keratosis on the atrophic bald scalp. Dermatol Surg. 2003;29:1052-6.
100. Wood NH, Khammissa R, Meyerov R, Lemmer J, Feller L. Actinic cheilitis: a case report and a review of the literature. Eur J Dent. 2011;5:101-6.
101. Rossoe EWT, Tebcherani AJ, Sittart JA, Pires MC. Queilite actínica: avaliação comparativa estética e funcional entre as vermelhectomias clássica e em W-plastia. An Bras Dermatol. 2011;86:65-73.
102. Lee K, Weinstock M. Prospective quality of life impact of actinic keratoses: observations from the veterans affairs topical tretinoin chemoprevention trial. Acta Derm Venereol. 2011;91:101-2.
103. Cockerell CJ. Pathology and pathobiology of the actinic (solar) keratosis. Br J Dermatol. 2003;149 Suppl 66:34-6.
104. Krouse RS, Alberts DS, Prasad AR, Yozwiak M, Bartels HG, Liu Y, et al. Progression of skin lesions from normal skin to squamous cell carcinoma. Anal Quant Cytol Histol. 2009;31:17-25.
105. Roewert-Huber J, Lange-Asschenfeldt B, Stockfleth E, Kerl H. Epidemiology and aetiology of basal cell carcinoma. Br J Dermatol. 2007;157 Suppl 2:47-51.
106. Bartels PH, Krouse RS, Prasad AR, Yozwiak M, Liu Y, Bartels HG, et al. Actinic damage in histopathologically normal skin. Anal Quant Cytol Histol. 2008;30:316-22.
107. James C, Crawford RI, Martinka M, Marks R. Actinic keratosis. In: James C, Crawford RI, Martinka M, Marks R, editors. Pathology & Genetics, Skin tumors. Lyon: IARC Press; 2006. p.30-3.
108. Yantsos VA, Conrad N, Zabawski E, Cockerell CJ. Incipient intraepidermal cutaneous squamous cell carcinoma: a proposal for reclassifying and grading solar (actinic) keratoses. Semin Cutan Med Surg. 1999;18:3-14.
109. Röwert-Huber J, Patel MJ, Forschner T, Ulrich C, Eberle J, Kerl H, et al. Actinic

keratosis is an early in situ squamous cell carcinoma: a proposal for reclassification. Br J Dermatol. 2007;156 Suppl 3:8-12.
110. Lober BA, Lober CW, Accola J. Actinic keratosis is squamous cell carcinoma. J Am Acad Dermatol. 2000;43:881-2.
111. Person JR. An actinic keratosis is neither malignant nor premalignant: it is an initiated tumor. J Am Acad Dermatol. 2003;48:637-8.
112. Ko CJ. Actinic keratosis: facts and controversies. Clin Dermatol. 2010;28:249-53.
113. Petit A. [Actinic keratoses are still actinic keratoses]. Ann Dermatol Venereol. 2008;135:93-6.
114. Deltondo JA, Helm KF. Actinic keratosis: precancer, squamous cell carcinoma, or marker of field cancerization? G Ital Dermatol Venereol. 2009;144:441-4.
115. de Berker D, McGregor JM, Hughes BR; British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for the management of actinic keratoses. Br J Dermatol. 2007;156:222-30.
116. Rossi R, Calzavara-Pinton PG, Giannetti A, Peserico A, Santucci M, Vena GA, et al. Italian guidelines and therapeutic algorithm for actinic keratoses. G Ital Dermatol Venereol. 2009;144:713-23.
117. Del Rosso JQ. Current regimens and guideline implications for the treatment of actinic keratosis: proceedings of a clinical roundtable at the 2011 Winter Clinical Dermatology Conference. Cutis. 2011;88:Suppl 1-8.
118. Borgonjen RJ, van Everdingen JJ, Bik CM, Tuut MK, Spuls PI, van de Kerkhof PC. Prospective comparison of three guideline development methods for treatment of actinic keratosis. BMJ Qual Saf. 2011;20:832-41.
119. Muston D, Downs A, Rives V. An economic evaluation of topical treatments for actinic keratosis. J Dermatolog Treat. 2009;20:266-75.
120. Gold MH. Pharmacoeconomic analysis of the treatment of multiple actinic keratoses. J Drugs Dermatol. 2008;7:23-5.
121. Deonizio JMD, Mulinari-Brenner FA. Cryopeeling for treatment of photodamage and actinic keratosis: liquid nitrogen versus portable system. An Bras Dermatol. 2011;86:440-4.
122. Ritter CG, Kuhl ICP, Lenhardt C, Weissbluth ML, Bakos RM. Terapêutica fotodinâmica com ácido delta-aminolevulínico e luz de diodos em ceratoses actínicas. An Bras Dermatol. 2010;85:639-45.
123. Poziomczyk CS, Köche B, Dornelles MA, Dornelles SIT. Avaliação da dor em criocirurgia de ceratoses actínicas. An Bras Dermatol. 2011;86:645-50.
124. Fenske NA, Spencer J, Adam F. Actinic keratoses: past, present and future. J Drugs Dermatol. 2010;9:(5 Suppl ODAC Conf Pt 1):s45-9.
125. Strickland PT, Vitasa BC, West SK, Rosenthal FS, Emmett EA, Taylor HR. Quantitative carcinogenesis in man: solar ultraviolet B dose dependence of skin cancer in Maryland watermen. J Natl Cancer Inst. 1989;81:1910-3.
126. Sociedade Brasileira de Dermatologia. Análise de dados das campanhas de prevenção ao câncer da pele promovidas pela Sociedade Brasileira de Dermatologia de 1999 a 2005. An Bras Dermatol. 2006;81:533-9.
127. Feldman SR, Fleischer AB, Jr. Skin examinations and skin cancer prevention counseling by US physicians: a long way to go. J Am Acad Dermatol. 2000;43:234-7.

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