

# Progression of Actinic Keratosis to Squamous Cell Carcinoma Revisited: Clinical and Treatment Implications

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*Changes in the appearance of actinic keratosis (AK) suggest progression to invasive squamous cell carcinoma (SCC), though some dermatologists and dermatopathologists consider AK to be SCC in situ. Actinic keratosis is an indicator of cumulative UV exposure and the initial lesion in the majority of invasive cutaneous SCCs. The development of SCC on sun-damaged skin is*

*a gradual process; however, most AK lesions do not progress to invasive SCC and it currently is not possible to clinically or histopathologically determine which AK lesions will progress to SCC. Presently there is insufficient evidence to support the concept that AK is frank SCC. Although the rate of progression over time remains to be determined by large prospective studies, AK is a marker for an increased rate of nonmelanoma skin cancer (NMSC), even in the absence of specific lesion progression. Nevertheless, the risk for progression of AK to invasive SCC with the potential for metastasis provides the rationale for treatment, and AK lesions should be treated with lesion- or field-directed therapy or with a combined approach when indicated. We discuss the implications for treatment and review a variety of treatment options.*

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Actinic keratoses (AKs) (also known as solar keratosis) are discrete, premalignant, intraepidermal lesions that appear on chronically sun-exposed areas—face, scalp, lips, forearms, and hands—of fair-skinned, middle-aged, and older individuals (Figure 1). Multiple, less well-defined lesions also may occur on relatively large areas of sun-exposed skin. Cumulative exposure to UV radiation from sunlight, but not acute or intermittent exposure, relates to histologic evidence of actinic damage<sup>1</sup> and is considered the leading cause of AK.<sup>2</sup> Thus the incidence of AK increases with age. Data from the first National Health and Nutrition Examination survey (N=20,637) from 1971-1974 demonstrated that AK is uncommon in the United States before the age of 30 years; the prevalence is 55% in

individuals aged 65 to 75 years with high sun exposure but only 12% to 19% in those with low sun exposure.<sup>3</sup> More recent data from the National Ambulatory Medical Care Survey from 1996-2005 showed that a majority of patients presenting with AK lesions were male (58.9%), almost all were white (98.8%), and approximately 30% were aged 70 to 79 years (unpublished data). These findings are important because retrospective analysis data from 1992-1998 by the Medicare Current Beneficiary Survey revealed that the risk for nonmelanoma skin cancer (NMSC) and melanoma was more than 6 times higher in patients with AK ( $P \leq .0001$ ) compared with those without AK, particularly among white males and elderly patients ( $P \leq .01$  for both).<sup>4</sup>

Increased erythema, thickening, ulceration, an irregular border, induration, inflammation of the base, or change in size suggests progression of AK to squamous cell carcinoma (SCC).<sup>5-8</sup> Some dermatologists and dermatopathologists, however, consider AK to be SCC that is confined to the epidermis (SCC in situ).<sup>6,9-12</sup> In this article we will discuss the clinical significance of AK, reviewing the histology and pathogenesis of AK. With that background, we will consider if AK lesions are precancerous or actually SCC in situ, the risk for progression to invasive SCC, if AK is a marker for risk for NMSC even without progression, and implications for treatment.

### Histopathologic Appearance

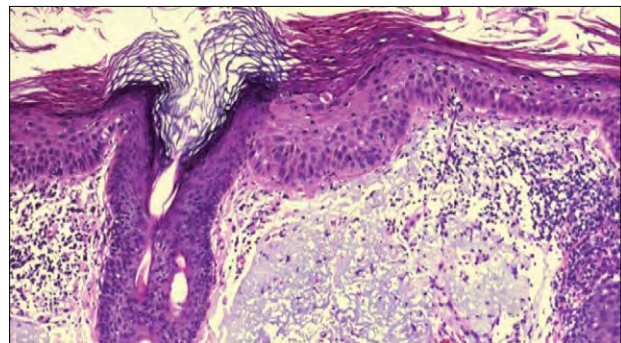
Actinic keratoses usually have extensive hyperkeratosis with sharply defined areas of parakeratosis sparing the hair follicles (Figure 2).<sup>9,11</sup> The granular layer is present in hyperkeratotic areas and absent in parakeratotic areas.<sup>13</sup> Underlying areas of parakeratosis, atypical (dyskeratotic) keratinocytes exhibit loss of polarity, variation in size, and eosinophilic-staining cytoplasm. Sharply defined budding proliferation can extend into the upper epidermis.<sup>8,11,12</sup> The nuclei of atypical keratinocytes are crowded, large, and pleomorphic.<sup>11</sup> The papillary dermis typically exhibits features of photoaging with elastosis and collagen fiber degeneration (actinic, or solar, elastosis), and there is almost always a perivascular lymphocytic infiltrate.<sup>8,12,13</sup>

### Pathogenesis of AK

**Environmental Factors**—Actinic keratosis lesions are caused by cumulative exposure to UV radiation from sunlight.<sup>2,14,15</sup> The increasing emphasis on tanning, clothing styles that expose skin, and outdoor activities, as well as greater longevity, all contribute to increased cumulative UV exposure.<sup>16</sup> UVB radiation, predominantly through the formation of reactive oxygen species in the skin, catalyzes the formation



**Figure 1.** Single actinic keratosis lesion on the scalp.



**Figure 2.** In actinic keratoses, the stratum corneum usually shows extensive hyperkeratosis with sharply defined, alternating areas of parakeratosis, except above hair follicles where the keratin layer is nonnucleated orthokeratosis (H&E, original magnification  $\times 100$ ). Photograph courtesy of Timothy Berger, MD, University of California, San Francisco.

of thymidine dimers (covalent bonding of 2 adjacent thymine residues) within DNA and RNA molecules, resulting in genetic mutations in keratinocytes.

The key UV-related risk factors independently associated with AK include lifetime sun exposure ( $P < .0001$ )<sup>2</sup>; cumulative sun exposure (top quintile vs bottom quintile; odds ratio [OR], 3.3)<sup>14</sup>; high levels of occupational sunlight exposure during adult life (OR, 2.4 [for heavy/maximal adult exposure]) with an even stronger association in those with multiple AK lesions (OR, 4.3)<sup>15</sup>; a history of even 1 episode of sunburn in childhood (peak OR, 5.9 [for even 1 sunburn])<sup>15</sup>; painful sunburns before 20 years of age (OR, 1.9)<sup>2</sup>; fair skin (OR, 14) and to a lesser extent medium skin (OR, 6.5)<sup>15</sup>; and Fitzpatrick skin type I (skin type I vs skin type IV; OR, 12.4).<sup>14</sup> Accordingly, lifetime sun exposure and fair skin are the most important of these risk factors, with geographic factors such as latitude and altitude playing contributory

roles. Older patients and those spending more time in the sun during the preceding 2 years are most likely to develop new AK lesions.<sup>14</sup>

Other risk factors for AK include age ( $\geq 80$  years vs 60–64 years; OR, 3.7)<sup>14</sup>; gender (male vs female; OR, 2.2)<sup>14</sup>; the use of tanning beds, which increases the risk for AK on areas of skin that are ordinarily not exposed to sunlight<sup>17</sup>; clinical signs of sun damage such as solar lentigines, facial telangiectasia, and actinic elastosis of the neck<sup>18</sup>; and immunosuppression, particularly in organ transplant recipients.<sup>19</sup>

**Natural History**—Actinic keratosis is an indicator of cumulative UV exposure<sup>1</sup> and is the initial lesion in most cases of cutaneous SCC. Sixty percent to 80% of SCC cases begin as AK.<sup>20,21</sup> Invasive carcinoma often is found in deeper sections of lesions initially diagnosed as AK on biopsy.<sup>22</sup> However, the proportion of AK lesions that progress to invasive SCC varies from study to study and appears to be time dependent. In addition, the large majority of AK lesions remain stable and some even regress. It currently is not possible to clinically or histopathologically determine which AK lesions will progress to SCC, though new technologies may eventually allow this distinction.

### Should AK Be Considered SCC?

**Pro**—Actinic keratosis traditionally has been considered a premalignant lesion representing the initial clinical manifestation of a continuum that eventually can progress to invasive SCC. With time, atypical keratinocytes comprising AK may become discontinuous with the epidermis as nests of tumor in the dermis.<sup>6</sup> There is a growing opinion among dermatopathologists that AK may already be the first stage of SCC (superficial SCC, SCC in situ).<sup>6,11</sup>

The following evidence supports the concept that AK is actually SCC: (1) the histopathologic findings in AK completely fulfill those of SCC<sup>11</sup>; (2) the morphologies of atypical cells in AK and SCC are identical<sup>6,20</sup>; (3) identical-appearing lesions are deemed AK when confined to the epidermis but are called SCC when they extend more deeply to involve the papillary and/or reticular dermis<sup>9</sup>; (4) there is no incontrovertible evidence for the assertion that AK commonly regresses<sup>11</sup>; (5) up to 80% of cutaneous SCC cases begin as AK<sup>21</sup>; and (6) untreated AK may eventually involve the dermis and potentially metastasize.<sup>6</sup>

**Con**—Actinic keratosis is in the middle of the spectrum between early sun damage and invasive SCC,<sup>23</sup> and up to 25% of lesions appear to spontaneously regress.<sup>24</sup> Although AK is clearly a premalignant lesion, it is benign by the definition that it has not breached any adjacent tissue borders.<sup>25</sup> Only when AK penetrates the basement membrane at the dermoepidermal junction and invades the dermis does

it become SCC. Analogous histopathologic situations include carcinoma in situ in colonic polyps and intraepithelial neoplasia in the cervix, breast, and prostate. Standardization of nomenclature has been recommended for squamous intraepithelial lesions, including epidermal lesions; suggested changes for AK include incipient intraepidermal SCC, keratinocytic intraepithelial neoplasia, solar keratotic intraepidermal SCC, proliferative AK, and inflamed AK. Grading systems similar to cervical intraepithelial neoplasia also have been proposed.<sup>11</sup>

**Conclusion**—The evidence reported to date is insufficiently persuasive to conclude that AK should be considered frank SCC. However, current evidence suggests that AK could be reclassified as cutaneous SCC in situ, similar to intraepithelial neoplasia in other organs. Although reclassification predominantly remains a subject of discussion among dermatopathologists, classification systems typically guide clinical practice and affect how dermatologists manage patients presenting with AK. Accordingly, the criteria for reclassification must be defined first, and then the classification that best meets these criteria can be identified and applied.

### Risk for Dermal Invasion

Only a few relatively short-term studies have been conducted to determine the risk for progression of AK to SCC (Table).<sup>24,26-30</sup> An estimated 0.075% to 0.24% of individual AK lesions progress to invasive SCC per year,<sup>24,26</sup> though 1 study showed no progression from AK to SCC over 1 year.<sup>28</sup> The 10-year risk for progression of at least 1 lesion has been estimated to range from 6.1% to 10.2% for an individual with an average of 7.7 lesions,<sup>27</sup> with an earlier report of up to 20% over 10 years.<sup>31</sup> A review of reports from 1988-1998 demonstrated an annual risk of 0.025% to 16% per year.<sup>32</sup> Averaging and extrapolating these results suggested a risk for progression of approximately 8%.

A retrospective study of 6691 patients with SCC found that 91 had a prior biopsy-confirmed AK at the same site.<sup>30</sup> Of these 91 patients, the mean time to progression was 24.6 months (range, 1.97–75.6 months), yielding a progression rate of 1.5% over 2 years. There was no significant relationship between time to progression and age, gender, or lesion location. Because of the relatively rapid rate of conversion of an AK to invasive SCC with no identifiable predictors for progression, the authors concluded that AK lesions should be treated soon after diagnosis because delay in treatment could result in progression.<sup>30</sup> Although it is important to treat AK in the large majority of patients, we disagree that all AK lesions must be treated. For example, we sometimes

### Summary of Studies: Progression of Individual AK Lesions to SCC

Reference (Year)	Type of Study	No. of Patients With AK	AK Progression to SCC
Marks et al <sup>24</sup> (1986)	Prospective, longitudinal	616	0.24% per year per lesion
Marks et al <sup>26</sup> (1988)	Prospective	1689	0.075%–0.096% per year per lesion
Dodson et al <sup>27</sup> (1991)	Retrospective	Unavailable	6.1%–10.2% over 10 years for at least 1 lesion for an individual with an average of 7.7 lesions
Harvey et al <sup>28</sup> (1996)	Cross-sectional	560	No progression over 1 year
Foote et al <sup>29</sup> (2001)	Randomized, controlled	918	14% over 5 years
Fuchs et al <sup>30</sup> (2007)	Retrospective	6691	1.5% over 2 years

Abbreviations: AK, actinic keratosis; SCC, squamous cell carcinoma.

choose not to treat AK lesions in patients who are terminally ill or extremely old. It seems clear that the actual long-term risk for progression remains to be defined by large prospective studies.

**Marker for NMSC**—Actinic keratosis is a marker for an increased rate of NMSC, which is as important as the risk for progression to SCC. In a study of 918 patients (mean age, 61 years) with multiple AK lesions but no history of skin cancer, initial SCC was diagnosed in 129 patients.<sup>29</sup> Independent predictors of SCC included older age, male gender, natural red hair color, and adult residence in a very sunny geographic area. Individuals aged 65 years and older with AK are at high risk for developing NMSC.<sup>4</sup>

**Conclusion**—Actinic keratosis generally should be treated, primarily because it is not known which lesions will progress to SCC; however, not all patients presenting with AK are necessarily candidates for treatment. In addition, follow-up is important because AK is a marker for an increased rate of NMSC.

### Implications for Treatment

Actinic keratosis lesions can be cleared with topical lesion-directed therapy and/or field-directed therapy.

Lesion-directed therapy includes cryosurgery with liquid nitrogen, electrodesiccation, curettage, shave excision, photodynamic therapy with 5-aminolevulinic acid or methylaminolevulinic acid, or laser therapy applied to individual lesions. Field-directed therapy includes patient-administered topical agents (ie, 5-fluorouracil [5-FU], imiquimod, diclofenac sodium), ablative laser resurfacing, dermabrasion, photodynamic therapy, and deep or medium-depth chemical peels. Because some lesions recur<sup>33-38</sup> and AK is a marker for an increased rate of NMSC, patients should be periodically monitored. For example, recurrence rates 12 to 18 months after treatment with imiquimod cream 5% applied 2 or 3 times daily for 16 weeks were 42.6% with twice-daily treatment and 24% with thrice-daily treatment,<sup>38</sup> and recurrence rates of up to 55% have been observed after treatment with 5-FU.<sup>36,37</sup>

A number of issues to consider when AK lesions are treated with topical agents include duration of treatment, poor compliance, severe local skin responses, less than ideal patient satisfaction, and expense. Retrospective analysis of a national survey of dermatologists and primary care physicians found that

74% of patients treated for AK (N=1743) received cryosurgery only and approximately 26% received field-directed therapy (16% treated with field-directed therapy only and 10% treated with both cryosurgery and field-directed therapy).<sup>39</sup> Nearly two-thirds of the patients indicated a preference for field-directed therapy. Patients treated by a dermatologist were 64% less likely to receive field-directed therapy compared to those treated by a primary care physician.<sup>39</sup>

Shorter dosing regimens to improve compliance with topical therapies are being evaluated. For example, 4 weeks of imiquimod treatment, with an optional second 4-week course for patients with residual lesions, may be as effective as 16 weeks of treatment.<sup>40</sup> In addition, pulse therapy 5-FU regimens may be effective but have not yet been fully evaluated.<sup>41</sup> Investigational agents such as resiquimod<sup>42</sup> and ingenol mebutate (PEP 005)<sup>43,44</sup> may address some of these unmet needs. For example, resiquimod has been studied in a once-daily, 3 times weekly dosage regimen for 4 weeks.<sup>42</sup> Ingenol mebutate gel currently is being evaluated for 2-day, field-directed treatment of AK.<sup>44</sup> It also has a shorter period of irritation, which is likely to have a substantial impact on patient compliance. Imiquimod cream 3.75% has been tested in daily use for two 2-week and 3-week cycles and can provide 40% to 50% of patients with complete clearance at 12 months.<sup>45,46</sup>

Lesion-directed approaches remain the standard of care<sup>47</sup> and cryosurgery with liquid nitrogen is the most common treatment choice for AK lesions among surveyed dermatologists.<sup>48</sup> Cryosurgery, however, is not standardized for frequency, duration, intensity, or temperature of the application,<sup>49</sup> leading to results that differ. A complete clinical response rate of 83% was reported with freezing times longer than 20 seconds and only 39% with freezing times of less than 5 seconds.<sup>50</sup> In other trials, complete clinical response rates for cryosurgery were 68%<sup>51</sup> to 75%,<sup>52</sup> but histologic confirmation of lesion clearance has been included in only 1 study.<sup>49</sup> Krawtchenko et al<sup>49</sup> observed initial clinical clearance in 68% (17/25) of patients treated with cryosurgery (liquid nitrogen applied for 20–40 seconds per lesion followed by repeat application 2 weeks later if the treated lesion was insufficiently cleared), 96% (23/24) of patients treated with 5% 5-FU, and 85% (22/26) of patients treated with imiquimod cream 5%. Histologic clearance, however, was confirmed in only 32% (8/25) of patients following cryosurgery compared with 67% (16/24) for 5-FU and 73% (19/26) for imiquimod. After 1 year, sustained clinical clearance of the total treatment field was observed in only 4% (1/25) of patients treated with cryosurgery compared with 33% (8/24) for 5-FU and 73% (19/26) for imiquimod. Only 4% of patients

in the cryosurgery group had an excellent cosmetic outcome. The authors concluded that if multiple AK lesions need to be treated, cryosurgery should be considered secondarily.<sup>49</sup>

Combined lesion- and field-directed therapy may be used in patients with many lesions because field-directed therapy is capable of clearing multiple foci of subclinical lesions. In a randomized controlled trial of 144 patients with 5 or more facial AK lesions, field-directed therapy before cryosurgery was significantly more effective at 6 months than cryosurgery alone. At 6 months, the mean lesion count was reduced by 67.0% in the 0.5% fluorouracil plus cryosurgery group versus 45.6% in the vehicle plus cryosurgery group ( $P=.01$ ), and complete clearance was achieved by 30% and 7.7% of patients, respectively ( $P<.001$ ).<sup>53</sup> In a randomized trial of 63 participants with AK, field-directed therapy after cryosurgery increased the clearance of subclinical and total AK lesions at 3 months, though the difference was not statistically significant versus cryosurgery alone. More participants treated with imiquimod versus vehicle achieved clearance of subclinical (58% vs 34%;  $P=.06$ ) and total (23% vs 9%;  $P=.21$ ) AKs.<sup>54</sup> We recommend combination therapy with liquid nitrogen for visible lesions plus a topical agent for any subclinical lesions or for multiple lesions within a contiguous anatomic area.

## Conclusion

Actinic keratosis is a premalignant lesion with the potential to progress to invasive SCC that may potentially metastasize. It currently is not possible to clinically or histopathologically determine which AK lesions will progress to SCC; as a result, dermatologists should consider treating all lesions when indicated. Actinic keratosis lesions should be cleared with topical lesion- or field-directed therapy or with a combined approach. A high sustained clearance generally is not achieved with a lesion-directed approach such as cryosurgery, which targets only clinically visible AK. Current topical field-directed therapies have limitations, including severe local skin responses and prolonged treatment periods. Shorter treatment protocols for currently available topical agents and shorter dosing regimens for investigational drugs could improve compliance and thereby potentially improve efficacy. Careful follow-up is necessary, not only because of the potential for recurrence of AK lesions but also because AK is a marker for increased risk for NMSC, even in the absence of specific lesion progression.

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