Actinic Keratoses

Final Report

Mark Helfand, MD, MPH
Annalisa K. Gorman, MD
Susan Mahon, MPH
Benjamin K.S. Chan, MS
Neil Swanson, MD

Submitted to the Agency for Healthcare Research and Quality
under contract 290-97-0018, task order no. 6

Oregon Health & Science University
Evidence-based Practice Center
3181 SW Sam Jackson Park Road
Portland, Oregon 97201

May 19, 2001

Structured Abstract

Objective: To examine evidence about the natural history and management of actinic keratoses (AKs).

Search Strategy: We searched the MEDLINE database from January 1966 to January 2001, the Cochrane Controlled Trials Registry, and a bibliographic database of articles about skin cancer. We identified additional articles from reference lists and experts.

Selection Criteria: We selected 45 articles that contained original data relevant to treatment of actinic keratoses, progression of AKs to squamous cell cancer (SCC), means of identifying a high-risk group, or surveillance of patients with AKs to detect and treat SCCs early in their course.

Data Collection and Analysis: We abstracted information from these studies to construct evidence tables. We also developed a simple mathematical model to examine whether estimates of the rate of progression of AK to SCC were consistent among studies. Finally, we analyzed data from the Medicare Statistical System to estimate the frequency of procedures attributable to AK among elderly beneficiaries.

Main Results: The yearly rate of progression of an AK in an average-risk person in Australia is between 8 and 24 per 10,000. High-risk individuals with multiple AKs have progression rates as high as 12-30 percent over 3 years. Indirect evidence suggests that 2 percent of squamous cell cancers originating in AKs metastasize, and 7 percent recur locally. Over the course of a year, from 20-25 percent of AKs regress.

There are no studies comparing the long-term efficacy or morbidity of topical treatment versus surgical treatment for AKs.

Conclusions: Available data are insufficient to determine whether immediate treatment of all AKs, or a strategy of selective treatment for AKs that develop suspicious characteristics, result in different outcomes. An important information gap is how often squamous cell cancer

metastasizes early in its course. The highest priorities for future research are controlled trials of different strategies for the long-term management of patients who have actinic keratoses; particularly multiple lesions; registry studies to assess morbidity and mortality related to squamous cell cancer in the elderly; and patient-centered research on patients' preferences for, and quality of life related to, different treatments.

Table of Contents

Executive Summary

The lifetime risk of developing squamous cell cancer (SCC) of the skin has been estimated to be 9-14 percent in men and 4-9 percent in women in the US. Rates vary geographically, with the highest incidence in the South and Southwest. SCC accounts for fewer than 0.1 percent of all cancer deaths. However, SCC has the potential to metastasize and may account for up to 34 percent of deaths from skin cancer among persons 65 through 84 years of age, and 56 percent of deaths from skin cancer among persons 85 years and older.

Actinic keratoses (AKs) are precursors of squamous cell cancers. AKs occur most frequently in the elderly, especially elderly men, who are also at highest risk for death or disfigurement from squamous cell cancer. In the United States, destruction of AKs is the single most commonly performed dermatologic procedure in the outpatient setting.

Various modalities are used to treat actinic keratoses. The options include destruction, topical therapy, resurfacing, excision, or combinations. When choosing the most appropriate treatment for a patient, clinicians may consider numerous factors, including the anatomical location, size, and extent of the lesion(s), changes in lesion growth pattern, previous treatment, medical stability of the patient, and patient preference among therapeutic options. Although the incidence of actinic keratoses is related to proximity to the Equator, there is no scientific rationale for using different treatments in different regions.

In this paper, we examine evidence for the assumptions about the natural history and effectiveness of treatment that underlie different strategies for the management of AKs. Our assessment focuses on the choice of treatment for asymptomatic AKs except those on the lip, ear, or eyelid, in normal hosts. There is consensus that all AKs on the lip, ear, or eyelid, and those in immunocompromised patients should be removed. We specify "asymptomatic" patients because, in many cases, AKs are treated for reasons other than preventing progression to cancer. AKs may be painful or pruritic, or may have an adverse affect on appearance. As Marks, the most notable advocate of a conservative approach to managing AKs, wrote:

"…the question (is) whether or not treatment is justified in the prevention of morbidity and mortality due to squamous cell carcinoma. This discussion needs to be kept on that focus. It

is not about whether or not AKs should be treated on the basis of symptoms, cosmetic appearance, or recent change, or merely because the patient does not want to have an abnormality. The treatment of AKs under these circumstances is justified and is part of overall patient care, not for preventing problems due to SCC."

Key Questions

Key questions for this report were developed by the Agency for Healthcare Research and Quality (AHRQ) in consultation with the Health Care Finance Administration. After a draft of the questions was reviewed by representatives of dermatologic professional societies, AHRQ finalized the questions and assigned them to the Oregon Health Sciences University Evidence-based Practice Center. In consultation with AHRQ, OHSU refined the key questions, and used them to guide the literature search. The questions concern the logic underlying two strategies for management AKs: treatment of all AKs versus monitoring plus selective removal of some AKs. The logic underlying treatment of all AKs depends on a series of assumptions about the course and treatment of AKs. Specifically, this strategy assumes that periodic treatment will reduce the number and duration of AKs in the long run; as a result, fewer invasive squamous cell cancers will develop; and reducing the incidence of SCC will prevent the longer-term consequences of deeply invasive or metastatic cancer. The alternative approach—monitoring patients with AK and selectively removing lesions that have developed characteristics suggesting progression to invasive squamous cell cancer—also rests on several assumptions about the natural history of AKs and SCC. One key assumption is that there are characteristics of AKs that predict progression to invasive SCC. Another is that early detection of invasive squamous cell cancers (rather than preventing them by removing AKs before they progress) will prevent the development of deeply invasive or metastatic cancer.

Methods

We searched MEDLINE from January 1966 to January 2001, the Cochrane Controlled Trials Registry, our own bibliographic databases of articles about skin cancer, and reference lists of published reviews and other studies to identify studies related to these questions. We abstracted information about the patient populations, interventions (when applicable), outcome

measures, and characteristics of the study design from 45 articles that contained data relevant to one or more key questions. We used criteria developed by the US Preventive Services Task Force to classify articles as good, fair, or poor for their study design category (for example, controlled trial or cohort study).

Results

Do different treatments or different methods of removal of the lesion lead to different outcomes?

In the short-term (3-4 months), initial courses of 5-fluorouracil (5-FU), photodynamic therapy, or a medium depth chemical peel with trichloroacetic acid (TCA) reduced the number of visible AKs by 75% to 80%. .For other topical treatments, short-term results are poorer (e.g. tretinoin diclofenac) or less well-studied, and long-term results are not available.For cryosurgery, in one fair-quality cohort study of 70 patients followed for 1 year to 8.5 years, only 12 of 1,018 AKs recurred. There is fair to good evidence 5-FU, chemical peels, dermabrasion, and extensive cryosurgery peeling with liquid nitrogen reduce the total number of visible AKs one or more years after treatment. For example, mean number of visible AKs per patient from 15 or 16 before treatment to 2 to 4 after treatment. The longest followup evaluation of 5-FU treatment was published in 1972; it reported that 25 percent of patients required retreatment for recurrent or new AKs within 2 years of treatment, and 50 percent within 3 years.

No studies reported on how different methods of treating AKs affect morbidity and mortality from SCC or the incidence of SCC. There are also no studies of the effect of different treatments on patients' quality of life in the long run.

In patients with actinic keratoses, what is the a) incidence and regression rate b) incidence of progression to invasive squamous cell carcinoma with and without removal of the lesion?

Over the course of a year, from 20 to 25 percent of AKs regress. In one good-quality study, AKs that were present on the first examination had a higher regression rate (74 percent) than those that were not present on the first examination but developed before a later visit (29

percent). It is unclear how often spontaneous regression is permanent. Over the course of a year, 15 percent of the prevalent AKs that regressed later reappeared.

Two good-quality, prospective, longitudinal studies suggest that the yearly rate of progression of an AK to an invasive SCC in an average-risk person in Australia is between 8 and 24 per 10,000. A high rate of progression (12 percent) over 5 years was observed in the SKICAP-AK study, a large, controlled trial of retinol supplementation conducted in Arizona.

Will reducing the incidence of SCC reduce morbidity and mortality?

Indirect evidence suggests that 2 percent of invasive SCCs arising from AK metastasize leading to significant morbidity and/or death, and that 7-12 percent recur. Accurate data on the morbidity associated with invasive SCC are lacking, and there is no direct evidence of the magnitude of benefit from reducing the incidence of invasive SCC.

A monitoring strategy assumes that metastasis or deep local invasion from a SCCoccurs long after an AK progesses to an invasive SCC. If metastasis or deep local invasion can occur soon after an AK progresses to invasive SCC, treatment of all AKs will reduce morbidity and mortality caused by invasive SCC more effectively than the monitoring strategy. Only one case series attempted to examine whether delay in treatment was related to the likelihood of metastasis. In that series three (2.5 percent) of 119 metastatic tumors had a diagnostic delay time of less than a month, and another 42 (35.3 percent) had a delay of 1 to 6 months.

Are there characteristics of actinic keratoses that can be used to identify lesions that are more likely to progress to invasive squamous cell carcinoma?

We found no studies that measured the ability of characteristics of AK to predict progression to invasive SCC.

Are there data to support a monitoring protocol that will allow detection and treatment of any squamous cell carcinoma at a sufficiently early stage?

In developing a monitoring protocol, one consideration is whether a high-risk group of patients can be identified prospectively. Good-quality epidemiologic studies clearly show that the number of AKs or the presence of AKs is a strong predictor of SCC. Among immonucompetent patients who have AKs, a prior history of skin cancer is the strongest

predictor of the development of invasive SCC. Gender, burning exposure, skin type, and age are also risk factors. A high-risk patient may have a 30 percent risk of developing SCC over 5 years. A small percentage of individuals with AKs had a major proportion of the burden of illness. In one prospective study, 9 of the 47 men (about 20 percent) had 73 percent of the AKs. Four of the 46 women (9 percent) had 67 percent of the AKs. This concentration of the burden of illness suggests that the risk of developing SCC is concentrated in patients with multiple AKs. This concentration does not affect the benefit of initial treatment for a particular AK, whether in a patient who has several or only one. It does mean that, over time, the overall effectiveness of a monitoring program will depend in large part on how frequently patients who have large numbers of AKs are seen and how aggressively they are managed.

There are no studies of the results of monitoring patients with AK to detect and treat invasive SCC when it arises. Available data are insufficient to determine whether immediate treatment of all AKs, or a strategy of selective treatment for AKs that develop suspicious characteristics, result in different outcomes.

For patients who have multiple, recurrent actinic keratoses, does the effectiveness of different management strategies differ?

No studies compared treatment of all AKs to selective treatment and monitoring.

Conclusions

Treatment with 5-FU eliminates up to 75 percent of AKs in the short-term.with cryosurgery having at least comporable short-term efficacy. Longer-term data are sparse and confounded by intervening treatments. Uncontrolled studies suggest that some treatments reduce the number of AKs up to 2 years. There are little or no data about patient preferences and quality of life related to different treatment approaches. This is a striking omission as patient preferences are often decisive in choosing among treatment modalities in clinical practice.

There is good evidence that progression rates are 1-2 per 1,000 AKs per year for average-risk persons in Australia. Indirect evidence suggests that 2 percent of invasive SCCs arising from AK metastasize, and that 7-12 percent recur. In good-quality prospective and cross-sectional studies, male sex, older age, prior history of skin cancer, continued sun exposure, and

the number of AKs are associated with a higher risk of developing malignancy. Patients with several of these risk factors (for example, multiple AKs and a prior history of skin cancer) have a 21-36 percent risk of developing invasive SCC over 5 years. However, there are no data linking characteristics of lesions themselves to the risk of progression to SCC in the future.

There are no data comparing the effect of different management strategies or different methods of removal of AKs on incidence, morbidity, or mortality from invasive SCC. We found no studies comparing immediate treatment of all AKs to selective treatment and monitoring. Little is known about the chance that an invasive SCC will metastasize early, before a monitoring protocol detects it.

Priorities for Future Research

The highest priorities for future research are:

- controlled trials of different strategies and comparative treatment modalities for the long-term management of patients who have actinic keratoses, especially those with multiple actinic keratoses.
- registry studies to assess morbidity and mortality associated with squamous cell cancer in the elderly population, assess the value of characteristics of AKs for predicting progression to invasive SCC, and to test hypotheses about geographic variation in incidence, prevalence, and practice patterns,
- patient-centered research on preferences for, and quality of life related to, different treatments.

Introduction

Squamous cell cancer of the skin (SCC) has the potential to metastasize and may account for up to 20 percent of deaths from skin cancer. In epidemiologic and pathologic studies, actinic keratoses (AKs), also known as solar keratoses or senile keratoses, are the precursors of at least 60 percent of squamous cell cancers.[1-3] AKs occur most frequently in the elderly, especially elderly men, who are also at highest risk for death or disfigurement from squamous cell cancer. Some experts argue that, because AKs are precancerous lesions, all of them should be removed immediately to prevent these complications of squamous cell cancer.[4-7] An alternative approach is to monitor patients who have multiple, recurrent AKs, removing only those lesions that persist, enlarge, or develop characteristics that suggest squamous cell cancer.[8]

In this paper, we examine evidence for the assumptions about the natural history and effectiveness of treatment that underlie different strategies for the management of AKs. Our assessment focuses on the choice of treatment for asymptomatic AKs in normal hosts, excluding those on the lip, ear, or eye. There is consensus that all AKs on the lip, ear, or eyelid should be removed surgically, because SCCs at these sites have a high rate of metastases.[9-11] For the same reason, there is also consensus that AKs should be removed routinely in immunocompromised patients, such as transplant patients,[12] patients with myelodysplasia, and patients undergoing chemotherapy, as well as patients with a history of multiple nonmelanoma skin cancers.

We specify "asymptomatic" patients because, in many cases, AKs are treated for reasons other than preventing progression to cancer. AKs may be painful or pruritic, or may have an adverse affect on appearance. As Marks, the most notable advocate of a conservative approach to managing AKs, wrote:

> …the question (is) whether or not treatment is justified in the prevention of morbidity and mortality due to squamous cell carcinoma. This discussion needs to be kept on that focus. It is not about whether or not AKs should be treated on the basis of symptoms, cosmetic appearance, or recent change, or merely because the patient does not want to have an abnormality. The treatment of AKs under these circumstances is justified and is part of overall patient care, not for preventing problems due to SCC.[8]

Burden of Illness and Epidemiology

Actinic keratoses. Destruction of AKs is the single most commonly performed dermatologic procedure in the outpatient setting.[13] In an analysis of data from the National Ambulatory Medical Care Survey, in 1993 and 1994 there were 3.7 million office visits and about 5.2 million procedures for actinic keratoses, more than 3 times the total for squamous cell cancer, basal cell cancer, and melanoma combined.[14] In an analysis of 1 year of claims from a Medicare HMO in Florida, 13,108 episodes of treatment for AK were recorded among 11,800 beneficiaries; there were approximately 10 times as many visits for AK than for squamous cell cancer and basal cell cancer combined.[15] Our own analysis of Medicare data found that, nationally, between 1 in 11 and 1 in 15 beneficiaries over 65 years of age were treated for AKs in the years 1991 to 1995.

Impressive as these numbers are, only a small proportion of individuals with AKs seek or receive treatment. In parts of Australia and the southern part of the United States, the lifetime risk of developing an AK is higher than 50 percent, and may reach 90 percent among those who live to be 80 years or older.[16, 17] In a good-quality, population-based survey of 978 white adults in 643 rural Tennessee households, 26.5 percent of men and 10.2 percent of women had at least one AK.[18] Among men 65-74 years of age, 51.5 percent had an AK; among men 75 years or

older, 63.6 percent did. A smaller survey in Texas found that 30 percent of paraquat workers and their unexposed friends had at least one AK.[19]

The prevalence of AK is lower in certain northern latitudes. For example, in a good-quality casefinding survey conducted in northwest England, the prevalence of AK in persons 70 years or older was 15.4 percent in men and 5.9 percent in women.[20] The prevalence in a Welsh study was 23 percent among 1,023 persons 60 years or older.[21]

Little has been published about the reasons patients seek care for AKs. In some epidemiologic studies, low rates of compliance with referrals for treatment of AK or SCC have been attributed to cultural attitudes that minimize the importance of these lesions and attribute them to "normal" aging.[18, 20] In one series of cases of metastatic SCC, one of every five patients had delayed more than 2 years before seeking care for a skin lesion.[22] Unfortunately, no study has explored how attitudes differ between those who seek timely treatment and those who do not.

Squamous cell carcinoma. Squamous cell carcinoma of the skin accounts for less than 0.1 percent of all cancer deaths. However, squamous cell cancer has the potential to metastasize and may account for up to 34 percent of deaths from skin cancer among persons 65 through 84 years of age, and 56 percent of deaths from skin cancer among persons 85 years and older.[23] A Finnish study of 2,927 individuals diagnosed to have SCC reported survival rates relative to that of the age-matched general population. Five-year survival was 87.7 percent of that of the general population in men and 84 percent of that in women; the relative survival rate ranged from 73.2 percent to 97.2 percent, depending on sex and the site of the cancer.[24] In contrast, survival rates for individuals diagnosed to have basal cell carcinoma were indistinguishable from those of the general population. These figures might reflect excess mortality from SCC, excess mortality from other diseases for which SCC is a marker, or both.

Most studies of the natural history of squamous cell cancer of the skin have been done in selected patients who have an elevated risk due to environmental exposures, such as UV–A radiation for psoriasis.[25, 26] Patients with these exposures may constitute a substantial proportion of all patients who die of metastatic squamous cell cancer.[27] Elderly men are also over-represented among patients who die of squamous cell cancer. While there is strong suspicion on clinical grounds that advanced locally invasive or metastatic nonmelanoma skin cancers results from medical neglect, careful studies of the rate of progress of SCCs and the consequences of delay are lacking.

In Queensland, Australia, a good-quality epidemiologic study estimated that the prevalence of SCC was 2 per 1,000 among persons in their forties, 8 per 1,000 in their fifties, and 15 per 1,000 in their sixties.[28] The prevalence and incidence of squamous skin cancer in the United States are difficult to determine, since these cancers are not typically tracked by cancer registries and do not have a unique code in ICD-9. Based on indirect methods (extrapolation from population-based registries in British Columbia and in Portland, Oregon), the lifetime risk of developing squamous cell cancer has been estimated to be 9-14 percent in men and 4-9 percent in women in the U.S.[29] The US age-adjusted incidence of SCC was estimated to be 106 per 100,000 men and 29.8 per 100,000 women in 1986 (also calculated indirectly using population-based registry data from Kaiser Permanente in Portland, Oregon).[30] Rates vary geographically. A survey of one large health plan in Albuquerque, New Mexico found age-standardized incidence rates of 214 per 100,000 in nonhispanic white men and 50 per 100,000 in nonhispanic white women. A population-based study in Rochester, Minnesota covering the years 1976 to 1984 found age-standardized incidence rates of squamous cell cancer of 63.1 per 100,000 in men and 22.5 per 100,000 in women.[31] In a population-based study of non-

melanoma skin cancer in New Hampshire in 1993-1994, the age-adjusted incidence of squamous cell cancer was 97 per 100,000 men.[32]

Diagnosis and Treatment of Actinic Keratoses

AKs are circumscribed, irregularly scaly, slightly raised lesions appearing on a background of solar-damaged skin.[4, 33, 34] They are most often red, yellowish, or brown. Many are asymptomatic,[7] but some cause pruritis, burning, or a splinter-like sensation in the skin. Because they occur most frequently in sun-exposed areas (face, head, neck, forearms, and hands), individuals (or their family members) notice them and may seek medical care because of concern that they may be cancerous or because they adversely affect appearance.

Terminology

The term "actinic keratosis" was developed on the basis of clinical appearance and texture of these lesions without regard to histological appearance or pathogenesis. Histologically, AKs are a proliferation of atypical cells confined to the lower levels of the epidermis; criteria for the diagnosis of AK include parakeratosis, epidermal atrophy or thickening, and atypia. If microscopic examination reveals involvement of the dermis, the lesion is termed "invasive squamous cell carcinoma" (SCC); complete replacement of the epidermis by neoplastic cells without invasion of the dermis is called "squamous carcinoma-in-situ." Histologically, then, the difference between AK and SCC is the extent and location of atypical keratinocytes, including the cytologic and nuclear appearance of the cells. Genetically, there is also a continuum, with concentrations of the p53 gene increasing from AK through invasive SCC.[35]

For about 100 years, AKs have been considered to be precancerous lesions, meaning that, while they are not cancers, they can progress to squamous cell cancer. Throughout this time some have objected to the term "precancerous" and the implication that AKs undergo some kind of malignant transformation or progression to become "cancer."[36] Critics of the concept of "precancerosis" argue that AK is a true cancer because the abnormal cells that define it are indistinguishable from those in squamous cell carcinoma.[5, 37-40] They argue that, on the continuum from AK to carcinoma-in-situ to SCC, it is impossible to draw a meaningful distinction between what is and is not "cancer." They also point to molecular similarities between SCC and AK, particularly the frequency of a specific p53 gene mutation on chromosome 17p and the high frequency of loss of heterozygosity.[41] Therefore, they propose, the term "actinic keratosis" should be replaced by "keratinocytic intraepidermal neoplasia" or "incipient intraepidermal squamous cell carcinoma".[38, 42]

Proponents of the view that AKs are precancerous point out that AKs do not grow actively, frequently regress, and do not have the potential to metastasize. Consequently, such proponents support a definition of cancer based on the behavior of the neoplasm rather than on the appearance of the cells. They also point out that there are molecular similarities between AKs and sun-damaged skin without dysplasia,[43] and that the mechanism of malignant transformation is an area of intense molecular research that has not as yet settled the issue of whether or not AKs should be classified as cancers.

Diagnosis

Because of their characteristic appearance, AKs are usually diagnosed clinically, without confirmation by biopsy. In two small studies, the clinical diagnosis of AK was highly consistent with the histologic diagnosis. In one, a case series from one pathologist, dermatologists' clinical

diagnoses of AK were confirmed in 34 of 36 cases.[44] In a subsample from a prospective, population-based study of AKs, 20 of 22 AKs were consistent with the histologic diagnosis made by a single pathologist. In a third study, conducted as part of a randomized trial of sunscreen in Maryborough, Australia, 48 randomly selected lesions diagnosed clinically to be AKs were biopsied.[45] Of these, 39 (81 percent) were AKs histologically, using the criteria specified in the study (hyperkeratosis, epidermal thickening, and dysplasia). Six of the other nine lesions showed evidence of solar damage but lacked either hyperkeratosis or dysplasia, and the other three were lesions unrelated to AK.

The diagnosis of AK was less reliable in two studies of interobserver agreement, both by the same investigator and both using convenience samples from a dermatology clinic in a Veterans Affairs Medical Center. In one of these studies, two dermatologists examined 50 consecutive patients.[46] Their agreement on the diagnosis of single AKs was poor (kappa statistic 0.17 and 0.15) They were much more likely to agree on the diagnosis of multiple AKs (kappa statistic 0.62 and 0.55). In the other study, primary care clinicians' diagnoses were compared with that of a dermatologist.[47] Agreement was moderate as to whether a patient had single actinic keratosis (kappa, 0.36; 95 percent confidence interval [CI], 0.22-0.50), multiple actinic keratoses (kappa, 0.48; 95 percent CI, 0.34-0.61), or skin cancer (kappa, 0.48; 95 percent CI, 0.34-0.62).

The clinical diagnosis of squamous cell carcinoma of the skin is less reliable. In an Australian study of 1,292 skin cancers from 1986, dermatologists were correct in their clinical diagnosis of SCC 51 percent of the time, versus 35 percent for surgeons and 15 percent for general practitioners.[48] Other studies,[44, 46, 47] as well as a large, recent series of 2,058 tumors removed by surgeons,[49] confirm that the clinical diagnosis of skin cancer is imperfect.

Treatment

Various modalities are used to treat actinic keratoses. The options include, but are not limited to, destruction, topical therapy, resurfacing, excision, or combinations. The treatment options are described in detail in Appendix 1.[50-53]

Clinicians may take numerous factors into consideration when choosing the most appropriate treatment for a patient. These include the anatomical location, size, and extent of the lesion(s), changes in lesion growth pattern, previous treatment, medical stability of the patient, and patient preference of therapeutic options.

Key Questions

Key questions for this report were developed by the Agency for Healthcare Research and Quality (AHRQ) in consultation with the Health Care Finance Administration. After a draft of the questions was reviewed by representatives of dermatologic professional societies, AHRQ finalized the questions and assigned them to the Oregon Health Sciences University Evidence-based Practice Center. In consultation with AHRQ, OHSU refined the key questions, and used them to guide the literature search.

The key questions are listed in Table 1. These questions concern the logic underlying two strategies for management AKs: immediate treatment of all AKs versus monitoring plus selective removal of some AKs. The goal of immediate treatment is to prevent the development of invasive and metastatic cancer by destroying AKs before they can progress to SCC. This strategy assumes that, in the long run, periodic treatment of all AKs will reduce the number and duration of AKs. As a result, fewer squamous cell cancers will develop, and the reduced

incidence of SCC will prevent the longer-term consequences of deeply invasive or metastatic cancer.

The alternative approach—monitoring patients with AK and selectively removing lesions that have developed characteristics suggesting progression to squamous cell cancer—rests on several assumptions about the natural history of AKs and SCC. One key assumption is that there are characteristics of AKs that predict progression to SCC. Another is that early detection of squamous cell cancers (rather than preventing them by removing AKs before they progress) will prevent the development of deeply invasive or metastatic cancer.

Methods

Literature Search Strategy

We searched the topic of actinic keratosis in the MEDLINE database from 1966 to January 2001, and in the Cochrane Controlled Trials Registry, using the search terms *actinic keratosis*, *squamous cell carcinoma*, and *precancerous lesions*. We also searched an Endnotes library compiled for a recently completed assessment of skin cancer screening.[54] To identify additional relevant articles, we examined the reference lists of several review articles. In some cases we contacted experts, usually authors of cited unpublished manuscripts, to identify additional articles.

Working in pairs, the investigators reviewed abstracts and titles returned in the MEDLINE search. Titles and abstracts from the Cochrane Controlled Trials Registry that were not also retrieved from MEDLINE were reviewed by one of the authors (MH). We retrieved and read the full-text articles of 183 titles and abstracts that were judged relevant to one of the key questions. We also retrieved 90 articles identified by reference lists, the skin cancer screening

library, experts, and authors. Studies were included if they contained original data relevant to one of the key questions. Of 45 included studies, 23 addressed the treatment of AK, five addressed the incidence, progression, and regression of AK, three addressed the risk of metastasis, four addressed the accuracy of diagnosis of AK or SCC, and 10 addressed risk factors for AK or SCC. We reviewed and abstracted 23 articles on the efficacy of various modalities in the treatment of actinic keratoses. Three of these studies,[55-57] concerning pyruvic acid, topical colchicine, and Er:YAG laser, are not discussed further because they are not commonly used therapies.

Data Extraction and Synthesis

We abstracted information about the patient populations, interventions (when applicable), outcome measures, and characteristics of the study design from these 45 articles. We used criteria developed by the US Preventive Services Task Force (USPSTF)[58] to summarize information about the quality of included controlled trials of AK treatments and observational studies of the natural or treated history of AK and of risk factors for SCC. We used these criteria to classify articles as good, fair, or poor for their study design category (for example, controlled trial or cohort study) (Appendix 2).

Information about included prospective studies of AK incidence and progression, and about studies of various treatments for AK, was used to construct evidence tables. In addition, we constructed a simple mathematical model to synthesize information from studies of progression of AK to SCC and from one study of risk factors for SCC. The purpose of this analysis was to determine whether results of a previous model,[6] based on the results of two prospective studies,[1, 59] were consistent with the results of a more recent prospective study[60].

Analysis of Medicare data

We conducted an analysis to supplement published data about the prevalence and consequences of AKs in the Medicare population and to assess the usefulness of the data to obtain information about AKs and squamous cell cancer of the skin. The data source for this analysis was the Medicare 5-percent Sample Standard Analytical File (SAF) Part B from years 1991 through 2000 (first half).

Finder files were created using the Health Insurance Claim number (HIC), a unique beneficiary identification number. All beneficiaries with claims having any one of the HCFA Common Procedure Coding System (HCPCS) codes listed in Appendix 3, Table 1, were included in the finder files. Each beneficiary represented in the finder files was one that possibly had a removal procedure for a squamous cell carcinoma or actinic keratosis. The finder files were then used to retrieve all claims from each beneficiary.

We identified claims with an ICD-9-CM diagnosis code for actinic keratosis (702.0) or malignant skin neoplasia (173.x). Among these claims, we identified beneficiaries who had a relevant removal procedure (Appendix 3, Table 2) and a malignant skin neoplasia diagnosis. We determined whether or not these beneficiaries had an actinic keratosis diagnosis prior to the date of removal of the cancer. Among beneficiaries who had a previous diagnosis of AK, we determined whether an actinic keratosis removal procedure had been done. Results of the analyses were weighted to represent population estimates for Medicare beneficiaries 65 years of age or older.

Results

Key Question 1. Do different management strategies or different methods of removal of the lesion lead to different outcomes?

We examined the evidence for the effect of different management strategies on four outcomes: 1) morbidity and mortality from SCC; 2) incidence of SCC; 3) number and duration of AKs; and 4) quality of life related to side effects and complications of treatment.

Morbidity and mortality from SCC No studies examined how different methods of treatment of AKs affected morbidity and mortality from SCC.

Incidence of SCC. There are data from randomized trials about the effect of sun protection, diet, and chemoprevention on the course of AKs and the incidence of SCC. However, there are no comparable data on the efficacy of destruction, topical therapy, or other treatments to control AKs.

Sunscreen use and, probably, sun avoidance can reduce the incidence of AKs and increase the regression rate. In two randomized trials, one in Texas and one in Australia, daily use of sunscreen reduced the incidence of AK[45, 61, 62] The Texas trial, rated as poor quality, was small (53 patients with AK), had a 69 percent rate of completion of the 2-year followup period, and was not analyzed by intention-to-treat.[61] The first Australian study[45] enrolled 588 subjects who had from 1 to 30 AKs (mean 8 or 9 per patient). A total of 431 subjects (73 percent) completed the goal of 7 months of followup. This trial was rated fair-quality because the results were not analyzed by intention-to-treat. Among those who completed the trial, the mean number of AKs rose by one AK per patient in the placebo group and decreased by 0.6 AK per patient in the sunscreen group. The regression rates for AKs present at the first examination were 25 percent in the sunscreen group and 18 percent in the placebo group; for all AKs, the regression

rates were 28 percent (sunscreen group) versus 20 percent (placebo). In a subsequent, good-quality trial,[62] sunscreen reduced the incidence of SCC by 18 percent.

One randomized trial evaluated the efficacy of a low-fat diet in controlling AKs.[63] In the trial, 133 patients with skin cancer were randomized to either a low-fat diet or usual care. In the first year of followup, the control group was diagnosed to have four times as many AKs as the low-fat group. Over 2 years of followup, patients in the low-fat group had a significant reduction in skin cancers. Rates of skin cancer began to diverge after 16 months; in the last 8 months of the followup period (months 17-24), the control group had 0.26 cancers per patient, versus only 0.02 in the intervention group. Using the USPSTF criteria for study quality, this trial was rated "poor-quality" because it did not describe the method of randomization or the comparability of the control and intervention groups at baseline, did not use intention-to-treat analysis, and did not describe the results in adequate detail to evaluate the appropriateness of the statistical methods.

Three randomized trials have evaluated dietary supplements containing retinol or beta-carotene to prevent SCC and reduce the incidence of AKs. In one good-quality trial, beta-carotene had no effect on the incidence of AK or SCC. A randomized trial of a daily oral retinol supplement showed no effect in patients at high risk of SCC, but in a similar trial in moderate-risk patients, retinol reduced the incidence of first new squamous cell skin cancers by 32 percent.[64, 65] Moderate-risk subjects had a history of at least 10 actinic keratoses and at most two prior skin cancers. Retinol was particularly effective in patients who were 63 years of age or older (19 percent vs. 13 percent, number-needed-to-treat [NNT]=17) and in those who had a history of one SCC in the past (21 percent vs. 12 percent, NNT=11).

Number and duration of AKs. Table 2 summarizes experimental and observational studies of the effect of treatment on the number and duration of AKs. Most of these studies recruited patients with multiple AKs from dermatologic referral clinics.

Cryosurgery. One frequently cited case series, conducted in a dermatology clinic based in a tertiary hospital in New Orleans, reported that, in 70 patients followed for 1 year to 8.5 years, only 12 of 1,018 AKs treated with cryosurgery recurred.[66]

Photodynamic Therapy. One pilot study and two multicenter phase 3 trials examined the efficacy of photodynamic therapy. In the pilot study, 40 patients undergoing photodynamic therapy, placebo (the vehicle) was compared with 10 percent, 20 percent, or 30 percent ALA for photosensitization.[67] Patients in all groups were exposed to the same light source after sensitization. In the group that received 30 percent ALA, 91 percent of AKs on the face or scalp responded completely (vs. 0 with placebo), and 45 percent of AKs on the trunk and extremities responded completely (versus 6 percent with placebo). In the group that received 20 percent ALA, 78 percent of AKs on the face and scalp and 38 percent of those on the trunk and extremities resolved completely. For those who received 10 percent ALA, 61 percent of AKs on the face and scalp, and 30 percent of those on the trunk and extremities, resolved completely.

Two multicenter phase 3 trials of 243 patients with 4 to 15 AKs compared one or two photodynamic treatments using a 20% ALA solution to placebo (vehicle).[68] ALA was applied to specific lesions on the face and scalp that were subsequently irradiated with blue light. By 3 months after initial treatment, 88 percent of ALA-treated patients had at least 75 percent clearance of their AKs, versus 20 percent in the placebo group.

Topical therapy. Five reports from four controlled trials [69-73] and two case series[53, 74] examined the efficacy of 5-FU. None of these compared 5-FU to a placebo. In these trials, 5-FU

eliminated 75-80 percent of AKs initially present. In one study,[74] the results of using 1 percent 5-FU and 5 percent 5-FU were similar. In some trials,[69, 74] a longer course of treatment was needed to treat AKs on the hand (where 5-FU is less efficacious) than on the face or scalp.

Two of these trials reported results at followup periods longer than 6 months.[71-73] The longest followup evaluation of 5-FU treatment was published in 1972;[74] it reported that 25 percent of patients had recurrent or new AKs within 2 years of treatment, and 50 percent within 3 years. In a trial of 15 patients performed in the 1990s, eight were available for evaluation 32 months after treatment with 5-FU on one side of the face and TCA peel on the other side.[71, 73] At 32 months, 5-FU reduced the mean number of AKs from 18 before treatment to 10. In one case series patients were treated with 5-FU 1-2 days a week for an average of 6.7 weeks. The first six of 11 patients reaching the 9-month post-treatment marker retained an 86 percent clearance of actinic keratoses.[53] In the second series, patients were treated with 1 percent 5-FU; at 2-year followup, 25 percent of one cohort and 40 percent of another required re-treatment with 5-FU for recurrence of AKs.[74]

A sixth report[75] examines a newer formulation of once daily 0.5% 5-FU cream. Two phase-3 trials described in an FDA document reported short-term results. One month after a 4-week course of treatment, 64% and 78% of patients had at least 75% fewer lesions on the face and anterior scalp.

Three controlled trials examined the efficacy of tretinoin in the treatment of AKs.[70, 76, 77] One study compared the efficacy of tretinoin and 5-FU vs. 5-FU alone on the upper extremity. The side treated with 5-FU plus tretinoin reduced the mean number of AKs per patient from 15.7 to 3.4.[70] In the other two studies, tretinoin reduced the number of AKs more effectively than placebo.[76, 77]

Clinical trials of diclofenac sodium gel were conducted by the manufacturer with data submitted for FDA approval[78] but not available in publication. A total of 427 patients who had 5 or more AKs per area of interest were treated with topical diclofenac for 30 to 90 days. Assessment at 30 days after completion of treatment revealed 39 percent of AKs on the forehead and 47 percent of AKs on the face were not visible, versus approximately 20 percent for the placebo group.

Resurfacing. Five controlled trials evaluated the efficacy of chemical peels.[71, 73, 79-81] In one controlled trial glycolic acid, which is a superficial chemical peel, reduced the mean number of AKs from 13.7 to 11.6 at 6-month followup.[79] In another trial comparing two medium-depth peels, independent investigators evaluated overall improvement of AKs at 2 months and assigned a clinical response score of "fair-good" to those who had a peel with TCA and glycolic acid and a score of "fair" to those who had a peel with TCA and Jessner's solution.[80] In one controlled trial of 15 patients, a medium-depth peel with TCA was as effective as initial treatment with 5-FU.[71] Nine of the 15 patients preferred the peel to 5-FU.[71]

In a case series conducted in a community-based practice in Florida, 373 patients with extensive AKs (a total of 34,604) were treated with extensive cryosurgery (“cryopeeling”) and re-examined 6 months or longer after treatment.[81] At 6 months, 336 patients (90 percent) were rechecked and there was a 4 percent recurrence rate of AK. A total of 167 patients (45 percent) were rechecked again between 6 and 12 months; these had a recurrence rate of 9 percent. By 12-18 months, when 124 patients (33 percent) were available for followup, there was a 12 percent rate of new or recurrent AK; at 2 years, this rate was 18 percent, but fewer than 25 percent of the original series was available for followup. Thirty-three patients developed SCC. Using an expected rate of progression of 1 per 1,000 AKs per year, or approximately 34 per year for the

entire sample, the author concludes that the observed rate of progression to SCC was lower than expected. However, the high rate of attrition and the lack of a control group make it impossible to determine whether or not this is true. The article did not use appropriate statistical methods to estimate the rate of development of SCC based on the size of the remaining sample when they occurred (that is, after appropriately censoring patients lost to followup). As a result, it is not possible to calculate an accurate rate of progression based on the data presented in the article. If the rate of SCC were less than expected, it is unclear whether this reduction was due to the initial cryopeeling; to subsequent monitoring to detect and remove new and recurrent AKs, or to the advice patients received to use sunscreen and retin-A.

In a case series of patients undergoing dermabrasion, 22 of 23 subjects had no AKs after 1 year and 19 of 23 had no AKs 2 years after treatment.[82] At 3 years, 15 of 19 (64 percent) patients available for followup had no AKs. No SCCs were found (5 BCCs seen after 4 years).

Quality of life related to side effects and complications of treatment. We described the patient experience and adverse effects of each treatment in Appendix 1. The adverse effects are generally well-known, and play a major role in management. Morbidity from treatments, primarily pain and short-term effects on appearance, can affect compliance and patient preferences among treatment alternatives. If these effects are strong, differences in efficacy (how well a treatment works under controlled, experimental conditions) may be overwhelmed by differences in effectiveness (how well a treatment works in actual practice).

Despite the major role adverse effects play, their effect on decision-making in practice has not been studied. As shown in Table 2, most of the treatment studies provided little or no information on the frequency or severity of adverse effects or on patients' preferences among

treatments; those that do did not use systematic methods to assess the frequency, duration, or severity of side effects. None of the studies used global or diseaes-specific measures to assess the impact of treatment on health-related quality of life.

Key Question 2. What is the natural history of actinic keratosis?

What is the incidence and regression rate of AKs? The incidence rate and spontaneous regression rate of AKs play a role in deciding how often to treat or monitor patients. For example, even if a course of treatment destroys all AKs present at the time, the patient will need to be treated again if new AKs develop rapidly. Also, the benefit of destroying a lesion is reduced if there is a high chance that the lesion would have regressed spontaneously if left alone.

Prospective, longitudinal studies of the incidence of AKs are summarized in Table 3. One of these was conducted in South Wales, Great Britain,[21], the others in Australia.[1, 16, 59, 83] All of these studies attempted to recruit samples representative of the general population in a particular community. In the study from Wales, the initial prevalence of AKs (23 percent); the number of AKs per subject initially (2); the overall incidence of AK in 1 year (12.6 percent); and the incidence among those who had no AKs initially (8.8 percent) were all lower than in the Australian studies. In the Australian studies, overall about 40 percent of subjects had new AKs during the followup period of approximately 1 year. Close to 20 percent of men and 7 percent of women who did not have an AK initially developed one or more during this period.

AKs can regress. In the first two studies in Table 3, the regression rates of AKs were 21 percent and 25.9 percent per year. In the second study, regression of AKs was strongly associated with outdoor work in patients age 40-49 years and 70-79 years, and 50 percent more

likely in those who "never burn, tan easily" compared with those who burn.[59] The third study, which is the most recent, reported rates for prevalent and incident AKs. This study used frequent followup visits to examine the natural history of AKs more thoroughly than other studies.[83] Subjects were a subset of participants in the Nambour randomized trial not assigned to the sunscreen arm of the trial (49 percent were receiving supplemental beta-carotene and 51 precent placebo). Patients were randomly assigned to examinations every 2 months or every 6 months. AKs that were present on the first examination (prevalent lesions) had a higher regression rate (74 percent) than those that were not present on the first examination but developed before a later visit (29 percent). Over the course of a year, 15 percent of the prevalent AKs that regressed were found to recur later. This finding raises the possibility that a lesion that "regresses" is still present, but is not visible on examination. It is unknown whether lesions that are not visible are still capable of progressing to SCC.

In patients with actinic keratoses, what is the expected incidence of progression to invasive squamous cell carcinoma with and without removal of the lesion? The rate at which AKs progress to squamous cell cancer is a key parameter in devising a strategy for treatment or monitoring. Confusion about the likelihood of progression, and about its timing, is longstanding, as these quotations from two textbooks published in 1983 and 1985 exhibit:

> Malignant change occurs in a small minority of cases, the developing squamous cell carcinoma being very slow growing, and with little tendency to metastasize. Such a change is only likely several years after the onset of the lesion. [84]

> Because they undergo malignant transformation to squamous cell carcinoma , in 20 percent of cases or more, they merit careful, thorough removal.[85](The 20 percent figure dates to a series of cases published in the 1930s.[86])

There are still very few sources of data to measure the rate at which AKs progress to SCC. Two publications from Marks[1, 59] report the rate of progression from AK to SCC, and Dodson[6] presents a mathematical model extending data from Marks' 1988 study to 10 years of followup. In the first study by Marks,[59] 1,040 Maryborough residents, 616 of whom had AKs, were followed for 1 year (see Table 3). Three of the 616 subjects with AKs underwent treatment during the year, but the other 613 subjects were re-examined 1 year later without intervening treatment. Ten of these 613 subjects (1.6 percent) developed SCCs during the year of followup. Among the 424 who did not have AKs initially, two developed SCC (0.47 percent). In this study, the authors did not attempt to link SCC to specific AKs. Assuming that, in the group that had AKs initially, all of the SCC arose from AKs, one in 429 AKs progressed to SCC in 1 year.

In the second Maryborough study,[1] 1,689 subjects from the general population (mean age 60.7 years) were invited to attend annual examinations for 5 years (see Table 3). For this study, in contrast to the earlier Maryborough study, the investigators used a grid map to record the location of AKs so that this could be correlated with the location of SCCs found on subsequent visits. As in the first study, the authors told the patients that they did not need to seek treatment for their AKs, but asked them to tell the investigators if they did. However, in this publication the authors did not report how many patients or lesions were treated. A total of 21,905 AKs were eligible for observation.

Over the course of followup, 28 SCCs in 26 people developed. Ten of these occurred at the site where an AK had been recorded 1 year earlier and seven on a site that was clinically normal a year earlier. In the other 11, the investigators could not determine whether the SCC arose from a preexisting lesion. If one assumes that the 11 doubtful cases all arose from AKs, the yearly rate of progression from AK to SCC was 1 in 1,042; a more conservative figure, assuming that 6 or 7 of the 11 originated in AKs, would be 1 in 1,333. For the entire sample, 1 in 152 subjects developed an SCC per year of observation. For the subset of subjects over 70 years of age, 1 in 100 developed an SCC per year of observation.

Another longitudinal study,[21] listed in Table 3, provides some additional support for the view that the annual rate of progression is relatively low. In that study, no SCCs developed over 557 person-years of followup without treatment of approximately 2,000 AKs. The authors calculated a confidence interval for the rate of progression of 0-11 per 1,000 AKs per year. No SCCs developed in the last study in Table 3,[83] but because the sample size was only 96, this study provides no additional evidence regarding the rate of progression.

Dodson used Marks' data to estimate the likelihood that an AK will progress over 10 years.[6] His calculation assumes that each AK has the same chance of progressing, and that the rate of progression is constant over many years. For example, consider a typical patient who has eight AKs. Based on a yearly rate of progression of 24 per 10,000—the rate from Marks' earlier study—over 10 years, the chance that one of these eight AKs would progress to SCC is 17 percent. For the first year only, 417 AKs would have to be treated to prevent one SCC (10,000/24 = 417). Over 10 years, however, treating the AKs in the first year in all patients would prevent one SCC in 10 years for every 46 AKs treated.

Dodson's analysis has several limitations. First, the high rate of regression of AKs makes it unlikely that the assumption of constant risk is accurate. Second, Dodson assumed that each subject had the mean number of AKs for the overall sample. The Nambour findings of the highly skewed distribution of AKs in the population,[83] calls this assumption into question.

Despite these limitations, Dodson's point—that a 1-year time frame makes the progression rate seem less significant clinically than it actually is—is well-taken. While a rate of 24 per 10,000 per year sounds low, it is similar to the annual risks associated with many conditions that we treat routinely. For example, the annual risk that a patient who has a 0.5 cm. colonic polyp will develop carcinoma is roughly of the same magnitude.

Higher rates of progression were observed in the SKICAP-AK study, a large, controlled trial of retinol supplementation conducted in Arizona.[60] In the placebo arm of that trial, 12 percent of 1,140 patients who had 10 or more AKs at baseline and no prior history of skin cancer developed an SCC within 5 years. Cumulative incidence rates of SCC were even higher (21-36 percent) among subjects who had a history of prior skin cancer.

Are the high rates of progression in the SKICAP-AK trial consistent with the frequently cited rate of approximately 1 per 1000 per year? To answer this question, we constructed Table 4, which extends the observations Dodson[6] used in his analysis of 10-year rates of progression.[1, 59] The first three columns of data replicate Dodson's analysis, except that we calculated 5-year progression rates instead of 10-year rates. The average number of AKs per patient is assumed to be 7.7, the same as it was in Marks' original study. The fourth column of data indicate the cumulative 5-year rates of progression to SCC if the yearly rate of progression for a single AK is 1 per 1,000 (0.1 percent). At this rate, over 5 years 3.8 percent of patients, or 1 in every 26, would develop a new SCC.

We then applied these assumptions to the Moon study, asking the question, How many AKs per patient would there have to be for the 5-year rate of developing a new SCC to be 12 percent (the rate observed in patients who did not have a history of a previous SCC)? As shown in the table, if the average number of AKs per patient was 25, the observed rate in the Moon study would be consistent with an average yearly rate of progression of 1 per 1,000 AKs. In fact, if the progression rate from the first Marks study (2.4 per 1,000) were used, the cumulative 5-year incidence of SCC would be 12 percent if the average patient had only 11 AKs (not shown). Moon's sample included only those patients who had 10 or more AKs. Because the distribution of AKs is highly skewed, with a small proportion of patients having most of the lesions, it is very plausible that the average number of AKs per patient in Moon's sample was this high.

These estimates do not address whether treating the AKs initially has any impact on the rate of developing SCC in the long run. Given the dynamic nature of AKs, and the high incidence of new lesions in patients who are prone to develop them, the risk of progression to SCC may be significant even in patients undergoing regular treatment. No studies compare observation alone, or promotion of sunscreen use and sun avoidance with selective removal of lesions, to aggressive treatment to remove AKs. Under these circumstances, the impact of a single treatment on 5-year or 10-year outcomes cannot be estimated meaningfully. Other critical issues are whether it is possible to focus on patients or lesions at higher risk of developing SCC; and whether there is sufficient evidence to conclude that an equivalent benefit can be achieved by monitoring patients, with selective removal of lesions that develop characteristics suggestive of progression. These issues are addressed in subsequent sections of this report.

Other studies have been cited as evidence about the rate of progression to SCC, but these studies have serious methodologic flaws. A recent summary by Glogau cites three additional

articles that reported the percentage of AKs progressing to SCC.[87] Of these three, two are unpublished manuscripts.[15, 88] One of the unpublished manuscripts[15] had no data about progression of AKs to SCC. The other unpublished manuscript[88] is a brief report of the results of a followup study of a series of 106 white adults in North Carolina who were diagnosed with AK. Of the 106, 26 (25 percent) were lost to followup. Of the remaining 80 patients, 36 (45 percent) had a history of skin cancer before entry into the study. Initially, 116 AKs were biopsied in these 80 patients. Over a median followup period of 39 months, 23 of the 80 patients (29 percent) developed at least one SCC. The SCCs had roughly the same distribution by body site as the original AKs. Methodologically, the study had serious flaws. The report does not describe how subjects for the study were selected, the reasons for dropouts, or how the AKs were treated. It is unclear whether lesions were biopsied for the purpose of the study, or whether they represent a subgroup of a larger group of patients and AKs selected for biopsy because their lesions had suspicious characteristics. It is also unclear whether these patients underwent destructive therapy for their AKs initially and what monitoring or therapy they underwent during the study period. If the AKs were treated initially and the patients did not undergo any subsequent followup for a median of 39 months, the study indicates that, especially in patients with a history of skin cancer, destruction of AKs does not provide protection against the subsequent development of SCC over 3 years. Because the study is uncontrolled, it is not clear whether the initial treatment was partially effective. Finally, the study provides no information on the likelihood that a particular AK will progress to SCC.

A third study cited in Glogau, published in 1976, reported that 12 percent of patients with AK develop “actinic keratosis with squamous cell carcinoma,” which is described by the author as “a nonaggressive lesion” that should be classified as “a separate entity distinct from malignant

squamous cell skin and mucocutaneous tumors, which do metastasize."[89] The article does not describe the sample size or design of the study that is the source of this estimate, but it is likely to be an earlier series based on specimens referred for to a pathology laboratory.[90] The article provides no information about the likelihood that AK will progress to "malignant" squamous cell carcinoma. The main point of the article is that patients who have "actinic keratosis with squamous cell carcinoma" are at high risk for developing internal or extracutaneous cancers and often die of them.

Key Question 3. Will reducing the incidence of SCC reduce morbidity and mortality?

The rationale for treating asymptomatic AKs is to prevent morbidity and mortality from SCC. Implicit in this rationale are the assumptions that SCC arising in AKs can cause significant morbidity and mortality, and that treatment of AKs would be more effective in preventing these consequences than treatment of SCC after it develops.

SCC can cause morbidity by invading deep structures of the skin (requiring extensive surgery), by recurring, and by metastasizing to local lymph nodes and distant organs. How often does SCC lead to these complications? In 25 studies over 6 decades, the incidence of metastases in SCC varied from 0.5-16 percent.[91] A review article, published in 1992, combined results from over 70 surgical and dermatologic case series, and estimated that 2.3 percent of SCCs in sun-exposed areas metastasized by 5 years, and 5.2 percent in series following patients for longer than 5 years.[11] Unfortunately, the methodology used in the studies on which these estimates were based was not considered in the review. Historically, the lack of registry data has made it difficult to measure the probability that an SCC will metastasize, or the time it takes to do so. In

the 1960s, two studies originating in dermatology practices found low rates of metastasis for SCCs that did not originate on the lip, ear, or eye, or in scars.[10, 92] The authors of both these studies wisely noted that referral bias was the probable explanation of the wide variation in reported rates of metastasis: patients with more extensive disease might be referred to surgeons or radiotherapists rather than to dermatologists. Other factors, including the efficacy of surgical procedures and prior exposure to ionizing radiation given as treatment for benign head and neck conditions—as well as the prevalence of arsenic poisoning, hematologic disorders, and immune compromise—might also cause results among studies done over several decades to differ.

Case reports and case series have demonstrated that squamous cell cancers that appear histologically to originate in AKs can metastasize.[3, 93] Data from clinical studies about the frequency with which this occurs conflict. An article by Lund published in 1965 is frequently cited to support the view that SCC arising in AK rarely metastasizes.[92] Lund's report, which was intended to provide a rough estimate of the frequency of metastasis, was not rigorous methodologically; it used an unreliable sampling methodology and relied heavily on extrapolation. The main strength of the study was that it attempted to sample SCCs that were encountered in community dermatologic practice. Lund sent a questionnaire to 45 dermatologists who sent skin biopsies to a pathology department in North Carolina. The dermatologists identified 17 cases of metastatic SCC from their practices. Lund also reviewed 1,000 skin biopsies. Of these, 82 revealed squamous cell tumors, 17 of which were clearly invasive. Based on this information, he estimated that one of every 200 clearly invasive squamous cell cancers metastasized. In a more detailed review, Lund concluded that, based on histology and clinical histories, only five of 12 cases of metastatic squamous cell cancers originated from actinic keratosis, and of these, two originated on the ear. Because this

proportion is lower than the proportion of SCC that originates in AKs, Lund concluded that metastasis occurs in far fewer than one in 200 cases of SCC originating from an AK (excluding those on the ear or lip).

In 1968, Epstein and colleagues estimated the frequency of metastasis using data from the California Tumor Registry, which included 6,900 squamous cell carcinomas of the skin diagnosed at 38 hospitals during the period 1942-1962.[22] Of these, 142 (2 percent) had metastasized to lymph nodes or distant organs by the time they were entered into the registry. The registry did not contain information about whether the tumors originated in AKs. Noting that nearly 70 percent of these occurred on the exposed areas of the body, Epstein and colleagues concluded that "one should not ignore the possibility of metastatic extension in malignancies presumably of solar causation." The main weakness of the study was that cases of SCC diagnosed in the hospital may not be representative of SCC generally.

An Australian study published in 1986 confirmed Epstein's report.[48] A series of 299 consecutive patients with SCC were identified from the records of a private pathology service. The referring physicians of 291 of the 299 patients responded to a questionnaire. Of 241 tumors that occurred on sun-exposed areas of the skin, 1.6 percent (4) had metastasized, and 7.5 percent (18) had recurred locally. In the subset of these patients who had been followed for 2 years or more, 2.1 percent had metastasized, and 7.4 percent had recurred locally. As expected, rates of metastases after 2 years or more of followup were higher for cancers that occurred on the lip (4 percent) and on non-sun-exposed areas (12.5 percent).

Key Question 4. Are there characteristics of actinic keratoses that can be used to identify lesions that are more likely to progress to invasive squamous cell carcinoma?

As stated earlier, AKs on the lip, ear, or eye are associated with a high risk of developing metastatic SCC. AKs in these locations were excluded from our analysis.

Some characteristics of lesions are commonly cited as signs that an AK is more likely to progress. These features are induration, erythema, bleeding, palpability, erosions, pain, hyperkeratosis, or increasing diameter. These characteristics may be indicators that a lesion has already progressed to SCC, but we found no studies of the probability of SCC when these features are present or absent. The diagnosis of AK is usually made clinically, but lesions that have these characteristics are not diagnosed clinically to be AK; they are biopsied. We found no prospective studies that measured the ability of characteristics of AK to predict progression to SCC.

Key Question 5a. Are there characteristics that can be used to identify a group of patients at higher risk of progression to invasive squamous cell carcinoma?

In addressing this question, we excluded immunocompromised patients, such as transplant patients, those with myelodysplasia, and those undergoing chemotherapy.

In other patients, several good-quality epidemiologic studies indicate that age,[20, 28, 83, 94-98] sex,[20, 28, 83, 94-98] skin type,[20, 28, 94] and various measures of sun exposure[20, 28, 94, 97-101] are risk factors for the development of both AK and SCC.

Good-quality epidemiologic studies clearly show that the number of AKs or the presence of AKs is a strong predictor of SCC. An Australian study,[98] the Nambour Trial, examined 2,095 people and then surveyed 1,770 of them 2 years later (response rate 84.5 percent) about any skin cancers treated by a doctor over the ensuing 2 years. Treating doctors were contacted to confirm the diagnosis. The number of AKs was more strongly associated with the development of SCC than was any other factor. The relative risk of SCC rose with the number of AK on the face. Adjusting for age and sex, for 1-5 AKs, the relative risk of SCC was 1.7 (0.4-6.5); for 6-20 AKs, the adjusted relative risk was 4.2 (1.1-16.1); and for more than 20 facial AKs, the adjusted relative risk was 11.0 (2.6-46.6). Other clinical signs of actinic damage, such as solar lentiges on the hands, telangiectasia of the face, and actinic elastosis of the neck, were also associated with a higher risk of both AK and SCC.[28]

A case-control study, also from Australia,[100]of people with and without SCC found that of all of the cutaneous indicators of solar damage measured, only the number of AKs had a stronger relationship with SCC than with BCC. A cross-sectional study in Maryborough, Australia[95] examined 2,113 patients over 1 week for the presence of skin cancer and AK. SCC occurred more frequently in people with AK, but the difference was not significant.

The presence of AK is a marker for the risk factors that predict SCC and is itself a powerful predictor for the development of SCC. Therefore, only studies that control for, or stratify by, the presence of AK, provide information about the existence of a high-risk group

among patients who already have AK. Among patients who have AKs, what factors are associated with a high risk of developing SCC?

One cross-sectional study[102] of 6,416 Australians examined risk factors for (prevalent) SCCs while controlling for AK. AKs were present on 2,643 people (41 percent), and 38 (0.6 percent) had an SCC. The presence or absence of an AK was the strongest predictor of SCC. Only one of the 38 patients with an SCC did not have a coexisting AK, and this patient was severely ill and had a history of several long courses of corticosteroids.

In a logistic regression analysis, the best combination of variables for predicting SCC was the presence or absence of an AK, age, sex, and burning exposure. None of the other variables considered in the logistic regression were significant after these were taken into account. Unfortunately, the investigators did not use the number of AKs or a history of SCC as potential risk factors. A formula based on this logistic regression illustrates the impact of several risk factors associated with SCC. Based on the formula, the probability of finding a SCC ranged from 0.12-5.71 percent. For example, a 40-year-old woman with a low propensity to sunburn has a probability of 0.12 percent of developing SCC, a 60-year old man with a moderate propensity to sunburn has a probability of 1.6 percent and a 70-year-old man who sunburns very easily has a 5.71 percent probability.

One large, good-quality prospective study,[60] discussed earlier, provides the best evidence about risk factors for SCC within a sample of patients with AKs. The subjects in this study were participants in the SKICAP-AK randomized trial of retinol to prevent skin cancer. All were Arizona residents whose median age was 63 (range 40 to 84) and who had, at least, 11 AKs and, at most, two prior confirmed squamous cell carcinomas or basal cell carcinomas (BCC). After 5 years, 249 subjects (10.8 percent) had developed a new SCC. The strongest risk factor for

developing SCC was a prior history of skin cancer. Nineteen percent (445/2,297) of the subjects had a prior skin cancer (numbers of prior basal and squamous cell cancers were not reported separately). In the placebo group, the risk of developing SCC for persons with no prior skin cancer was 0.12; for those with one prior skin cancer it was 0.21, and for those with two or more prior skin cancers, it was 0.36. Similarly, in the intervention group, the probabilities were 0.09, 0.12, and 0.24 for those with none, one, and two or more prior skin cancers, respectively. Other risk factors that predicted the development of SCC were male sex, age over 63 years, eight or more moles and freckles, skin that burns easily, and hours of sun exposure per week (0.16 for >10 hours vs. 0.12 for 0-10 hours). None of these factors was as strongly predictive as a prior history of skin cancer. If the average patient in this study had 15 to 25 AKs (see Table 4), the high rates of developing SCC in patients with a prior history of skin cancer are consistent with a yearly rate of progression for a single AK of 3-6 per 1,000.

In the context of these results, an important finding of the Nambour study[83] was that a small percentage of individuals with AKs had a major proportion of the burden of illness. Among the men in the study, nine of the 47 subjects (about 20 percent) had 73 percent of the AKs. Four of the 46 women (9 percent) had 67 percent of the AKs. This concentration of the burden of illness suggests that the risk of developing SCC is highly concentrated in patients with multiple AKs.

Key Question 5b. Are there data to support a monitoring protocol that will allow detection and treatment of any squamous cell carcinoma at a sufficiently early stage?

There are no studies of the results of monitoring patients with AK to detect and treat SCC when it arises. The safety of such a strategy has been inferred from the results of the prospective studies of observation listed in Table 3. Of these, the two studies by Marks and colleagues were the only ones in which any patients developed SCCs. Followup of the patients who developed SCC might have provided information on whether all of them were cured by initial treatment, but the authors did not report any followup results.

The study by Frost was a randomized trial of two different frequencies of followup visits for patients with AK. The number of new and persistent AKs was carefully measured every 6 months for 18 months in 1 group and every 2 months for 14 months in the other group.[83] The study was small (n=94) and no SCCs occurred during the trial.

A few other studies provide scant, indirect information about monitoring. A 32-month followup of eight patients who underwent 5-FU or chemical peel found that, 6 months after treatment, the number of AKs per patient was approximately one-fourth to one-fifth the number present before treatment (18 initially vs. three after 6 months for 5-FU, 20 initially vs. five after 6 months for peel).[73] After 32 months, patients had 10 AKs (in the 5-FU group) and 15 AKs (in the peel group).

A monitoring strategy assumes that metastasis or deep local invasion does not develop immediately after progression from AK to SCC. Conversely, one rationale that has been given for aggressive treatment of AKs is that SCC may metastasize early in its course, making a strategy of monitoring ineffective. Very little evidence supports either side of this issue. Only

one study, the California Tumor Registry study discussed earlier,[22] attempted to examine whether delay in treatment was related to the likelihood of metastasis. In that series of cases of metastatic SCC, the authors reported that, between the time a lesion was first noted by the patient and the time the patient was entered into the registry (the time of diagnosis), the median delay was 9.4 months. Three (2.5 percent) of the 119 metastatic tumors had a delay time less than a month. Another 42 (35.3 percent) had a delay of 1 to 6 months; 36 (30.2 percent) had a delay of 7-12 months; 13 (11 percent) had a delay of 13-24 months, and 25 (21 percent) had a delay of more than 2 years. The reliability of this information is difficult to assess, because the report did not say whether the delay was assessed by the patient's self-report or by review of the medical record.

Key Question 5c. For patients who have multiple, recurrent actinic keratoses, does the effectiveness of different management strategies differ?

We examined the effectiveness of immediate treatment of all AKs versus selective treatment of some AKs and monitoring for others, followed by selective treatment of those that persist, enlarge, or become suspected squamous cell cancers. By "effectiveness" we mean the impact on death, disfigurement, and major surgical procedures due to SCC, as well as the frequency and severity of complications of treatment.

Available data are insufficient to determine whether these strategies result in different outcomes. There are no data on the relative effects of immediate treatment of all AKs and selective treatment of some AKs on morbidity or mortality from SCC. In those studies of treatment of AKs that follow patients long enough for some SCCs to develop, it is not clear what

strategies were used during the followup period. The effects of the initial treatment cannot be distinguished by the effects of subsequent management because these are not adequately described.

Because a monitoring strategy might employ fewer treatments less often, it might result in lower short-term morbidity from the side effects of treatments, but this has not been studied directly. Moreover, as discussed earlier, patients seen in dermatologic practice may represent a subset of AK patients who are more motivated than others to have lesions removed or controlled; if this is the case, the utility of lower morbidity from treatment might be counterbalanced by the disutility of living with more lesions. Data about patient preferences for treatment versus no treatment are inadequate to assess this tradeoff.

Results of Additional Analysis of Medicare Claims Data

As mentioned in the Methods section, we conducted an analysis using the Medicare 5-percent Sample Standard Analytical File Part B to assess the usefulness of the data to obtain information about AK and SCC. For the period of 1991 through the first half of 2000, we found 4.35 million Medicare beneficiaries who had a malignant skin neoplasia diagnosis and a procedure to remove a possible squamous cell carcinoma (the average annual number of Medicare beneficiaries aged 65 or older during this period was 31.57 million). Of these, 2.82 million, or 64.7 percent, had a previous actinic keratosis diagnosis. Most of these, 2.33 million, or 82.5 percent, also had a removal procedure for actinic keratosis. More than one-third (35.3 percent) of the beneficiaries we found with a malignant skin neoplasia diagnosis and removal procedure did not have a previous diagnosis of actinic keratosis.

One caveat of this analysis is that the ICD-9-CM diagnosis code for malignant skin neoplasia (173.x) does not distinguish between squamous and basal cell carcinoma. Data external to the Medicare system on the ratio of squamous and basal cell carcinomas could be used to estimate prevalence of squamous cell carcinoma in the Medicare population.

Another issue is the possible overestimation of beneficiaries with malignant skin neoplasia without a previous actinic keratosis diagnosis. It is possible that an individual became eligible for Medicare after a diagnosis of actinic keratosis but before progression to squamous cell carcinoma. In such a scenario, we would not have captured their actinic keratosis diagnosis within the Medicare claims system.

Conclusions

Table 5 briefly summarizes the strengths and gaps in the evidence for each of the key questions.

Key Question 1. Do different management strategies or different methods of removal of the lesion lead to different outcomes?

There are no data comparing the effect of different management strategies or different methods of removal of AKs on incidence, morbidity, or mortality from squamous cell cancer. Among patients with AK, use of sunscreen prevents SCC. Treatment with 5-FU eliminates up to 75 percent of AKs in the short-term and some other treatments have equivalent short-term efficacy. Longer-term data are sparse and confounded by intervening treatments. Uncontrolled studies suggest that some treatments reduce the number of AKs up to 2 years. There are little or no data about patient preferences and quality of life related to different treatment approaches.

Key Question 2. What is the natural history of AK?

AKs are dynamic lesions; they often regress and recur. There is good evidence that rates of progression to SCC are 1-2 per 1,000 AKs for average-risk persons in Australia. Rates are higher in individuals with risk factors, including multiple AKs. The progression rate of clinically inapparent AKs (that is, those in "remission") has not been studied.

Key Question 3. Will reducing the incidence of SCC reduce morbidity and mortality?

Indirect evidence suggests that 2 percent of SCCs arising from AK metastasize, and that 7-12 percent recur. However, accurate data on the morbidity associated with SCC are lacking, and there is no direct evidence of the magnitude of benefit from reducing the incidence of SCC.

Key Question 4. Are there characteristics of actinic keratoses that can be used to identify lesions that are more likely to progress to invasive squamous cell carcinoma?

There are no data linking characteristics of lesions to the risk of progression to SCC in the future.

Key Question 5a. Are there characteristics that can be used to identify a group of patients at higher risk of progression to invasive squamous cell carcinoma?

In good-quality prospective and cross-sectional studies, male sex, older age, prior history of skin cancer, continued sun exposure, and the number of AKs are associated with a higher risk of developing malignancy.

Key Question 5b. Are there data to support a monitoring protocol that will allow detection and treatment of any squamous cell carcinoma at a sufficiently early stage?

There is no direct evidence, and too little is known about how often SCCs metastasize early to assess the effectiveness of monitoring to detect and treat SCC early in its course.

Key Question 5c. For patients who have multiple, recurrent actinic keratoses, does the effectiveness of different management strategies differ?

No studies compare immediate treatment of all AKs to selective treatment and monitoring.

Priorities for Future Research

Table 5 indicates that, for some key questions, no scientific evidence is available. Clinical research to address these information gaps is justified by several considerations. From 1 in 11 to 1 in 15 Medicare beneficiaries over 65 years of age have undergone treatment for AK at least once, and practice styles for the management of patients with AK are likely to vary considerably. Indirect evidence suggests that squamous cell cancer may cause significant morbidity and mortality in the elderly, especially elderly men.

The highest priorities for future research are

- controlled trials of different strategies for the long-term management of patients who have multiple, recurrent actinic keratoses,

- registry studies to assess morbidity and mortality related to squamous cell cancer in the elderly population, and to test hypotheses about geographic variation in incidence, prevalence, and practice patterns,
- patient-centered research on patients' preferences for, and quality of life related to, different treatments.

Research Priority 1: Controlled Trials of Management Strategies

A small proportion of patients with multiple, recurrent actinic keratoses account for a much larger proportion of utilization and morbidity from AKs, and are also at higher risk of developing SCC in the longer term. Most studies of different methods of removal of AKs focus on short-term results related to specific lesions, but do not take into account the long-term consequences of the high incidence of new lesions and the frequency of regression among prevalent lesions. Studies of AK treatments are too small and, in most cases, of too short duration to measure outcomes related to the main goals of treatment, including cancer prevention, improvement in appearance, and reducing or eliminating symptoms.

Future studies should examine comprehensive, longer-term strategies for managing these patients. A comprehensive approach explicitly considers short-term and long-term morbidity related to lesions and to the choice of treatment as well as long-term outcomes related to the goals of treatment: prevention of cancer, improved appearance, and reduction or prevention of discomfort. A comprehensive approach is needed because symptomatic and asymptomatic lesions occur in the same patient, and treatment decisions for asymptomatic lesions may be influenced by the need to treat symptomatic ones in the same region.

At present, very few data are available to assess the short- and long-term advantages and disadvantages of different management strategies, such as immediate treatment of all AKs versus

selective treatment of some AKs, and monitoring for others. Because AKs have a high incidence and recurrence rate, both of these approaches require protocols for monitoring patients. In addition to their clinical impact, the choice of management strategies may have large resource implications, but these can be assessed only by studies that look beyond the initial approach to optimize the quality of care in the longer term.

Research Priority 2: Registry Studies

The results of this review lend support to the view, expressed by a National Cancer Institute panel, to develop a registry of patients with squamous cell cancer. The main goals of registry research would be to assess morbidity and mortality related to squamous cell cancer in the elderly population, to better measure the relation between SCC and actinic keratosis, and to test hypotheses about geographic variation and cost-effectiveness related to practice patterns. Because morbidity and mortality from AK and SCC are concentrated in the elderly, a key step in a population-based database about these conditions is to introduce a unique diagnostic (ICD) code for squamous cell cancer, since the current 173.x code does not discriminate SCC from BCC or other NMSC.

Research Priority 3: Measurement of Patient Preferences

Studies of treatments for AK provide little information about patients' preferences for, and quality of life related to, different treatments. Because most treatments for AK are associated with some discomfort and alteration of appearance, compliance and quality of life are likely to be important factors in the long-term effectiveness and costs of alternative treatments. Observational studies, surveys, and controlled trials using general and disease-specific instruments to measure these factors should be conducted.

References

1. Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma. Lancet 1988;1(8589):795-7.
2. 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(9):677-81.
3. Dinehart SM, Nelson-Adesokan P, Cockerell C, Russell S, Brown R. Metastatic cutaneous squamous cell carcinoma derived from actinic keratosis. Cancer 1997;79(5):920-3.
4. Callen JP, Bickers DR, Moy RL. Actinic keratoses. J Am Acad Dermatol 1997;36(4):650-3.
5. Cohn BA. From sunlight to actinic keratosis to squamous cell carcinoma. J Am Acad Dermatol 2000;42(1 Pt 1):143-4.
6. Dodson JM, DeSpain J, Hewett JE, Clark DP. Malignant potential of actinic keratoses and the controversy over treatment. A patient-oriented perspective. Arch Dermatol 1991;127(7):1029-31.
7. Schwartz RA. The actinic keratosis. A perspective and update. [Review]. Dermatol Surg 1997;23(11):1009-19; quiz 20-1.
8. Marks R. The role of treatment of actinic keratoses in the prevention of morbidity and mortality due to squamous cell carcinoma. Arch Dermatol 1991;127(7):1031-3.
9. Petrovich Z, Parker R, Luxton G. Carcinoma of the lip and selected sites of the head and neck and skin: a clinical study of 896 patients. Radiother Oncol 1987;8:11-17.

10. DeVries N. Metastasis of squamous cell carcinoma of the skin and lip. Dermatologica 1969;138:333-9.

11. Rowe D, Carroll R, Day C. Prognostic factors for local recurrence, metastasis and survival rates in squamis cell carcinoma of the skin, ear and lip. J Am Acad Dermatol 1992;26:976-90.

12. Otley CC, Pittelkow MR. Skin cancer in liver transplant recipients. [Review]. Liver Transpl Surg 2000;6(3):253-62.

13. Fleischer AB, Jr., Feldman SR, White RE, Leshin B, Byington R. Procedures for skin diseases performed by physicians in 1993 and 1994: analysis of data from the National Ambulatory Medical Care Survey. J Am Acad Dermatol 1997;37:719-24.

14. Smith ES, Feldman SR, Fleischer AB, Jr., Leshin B, McMichael A. Characteristics of office-based visits for skin cancer. Dermatologists have more experience than other physicians in managing malignant and premalignant skin conditions. Dermatol Surg 1998;24(9):981-5.

15. Nestor M. The incidence of nonmelanoma skin cancers and actinic keratoses in South Florida. Paper presented at: Annual Meeting of the Florida Society of Dermatology; June 6, 1997, 1997.

16. Marks R, Jolley D, Dorevitch A, Selwood T. The incidence of non-melatonic skin cancer in an Australian population: results of a five year prospective study. Med J Aust 1989;150:475-8.

17. Marks R, Selwood T. Solar keratoses: the association with erythemal ultraviolet radiation in Australia. Cancer 1985;56:2332-6.

18. Zagula-Mally Z, Rosenberg E, Kashagarian M. Frequency of skin cancer and solar keratoses in a rural southern county as determined by population sampling. Cancer 1974;34:349.

19. Cooper SP, Downs T, Burau K, Buffler PA, Tucker S, Whitehead L, et al. A survey of actinic keratoses among paraquat production workers and a nonexposed friend reference group. Am J Ind Med 1994;25(3):335-47.

20. Memon AA, Tomenson JA, Bothwell J, Friedmann PS. Prevalence of solar damage and actinic keratosis in a Merseyside population. Br J Dermatol 2000;142(6):1154-9.

21. Harvey I, Frankel S, Marks R. Non-melanoma skin cancer and solar keratoses: I. Methods and descriptive results of the South Wales Skin Cancer Study. Br J Cancer 1996;74:1302-7.

22. Epstein E, Epstein N, Bragg K. Metastases from squamous cell carcinomas of the skin. Arch Dermatol 1968;97:245-51.

23. Weinstock M. Deaths from skin cancer among the elderly: epidemeiological patterns. Arch Dermatol 1997;133:1207-9.

24. Karjalainen S, Salo H, Teppo L. Basal cell and squamous cell carcinoma of the skin in Finland: Site distribution and patient survival. Int J Dermatol 1989;28:445-50.

25. Preston DS, Stern RS. Nonmelanoma cancers of the skin. N Engl J Med 1992;327(23):1649-62.

26. Stern RS, Lunder EJ. Risk of squamous cell carcinoma and methoxsalen (psoralen) and UV-A radiation (PUVA). A meta-analysis. Arch Dermatol 1998;134(12):1582-5.

27. Osterlind A, Hjalgrim H, Kulinsky B, Frentz G. Skin cancer as a cause of death in Denmark. Br J Dermatol 1991;125(6):580-2.

28. Green A, Beardmore G, Hart V. Skin cancer in a Queensland population. J Am Acad Dermatol 1988;19:129-38.

29. Miller D, Weinstock M. Nonmelanoma skin cancer in the United States: incidence. J Am Acad Dermatol 1994;50:774-8.

30. Glass A, Hoover R. The emerging epidemic of melanoma and squamous cell skin cancer. JAMA 1989;262:2097-100.

31. Chuang TY, Popescu NA, Su WP, Chute CG. Squamous cell carcinoma. A population-based incidence study in Rochester, Minn. Arch Dermatol 1990;126(2):185-8.

32. Karagas MR, Greenberg ER, Spencer SK, Stukel TA, Mott LA. Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. New Hampshire Skin Cancer Study Group. Int J Cancer 1999;81(4):555-9.

33. Barnaby JW, Styles AR, Cockerell CJ. Actinic keratoses. Differential diagnosis and treatment. Drugs Aging 1997;11(3):186-205.

34. Frost CA, Green AC. Epidemiology of solar keratoses. Br J Dermatol 1994;131(4):455-64.

35. Leffell DJ, The scientific basis of skin cancer. J Am Acad Dermatol 2000;42:S18-22

36. Heaphy MR, Jr., Ackerman AB. The nature of solar keratosis: a critical review in historical perspective. J Am Acad Dermatol 2000;43(1 Pt 1):138-50.

37. Evans C, Cockerell CJ. Actinic keratosis: time to call a spade a spade. South Med J 2000;93(7):734-6.

38. Cockerell CJ. Histopathology of incipient intraepidermal squamous cell carcinoma ("actinic keratosis"). [Review]. J Am Acad Dermatol 2000;42(1 Pt 2):11-7.

39. Cohn BA. Squamous cell carcinoma: could it be the most common skin cancer? [letter; comment]. J Am Acad Dermatol 1998;39(1):134-6.

40. Lober BA, Lober CW. Actinic keratosis is squamous cell carcinoma. [Review]. South Med J 2000;93(7):650-5.

41. Rehman I, Quinn A, Healy E, Rees J. High frequency of loss of heterozygosity in actinic keratoses, a usually benign disease. Lancet 1994;344:788-89.

42. 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(1):3-14.

43. Einspahr J, Alberts DS, Aickin M, Welch K, Bozzo P, Grogan T, et al. Expression of p53 protein in actinic keratosis, adjacent, normal-appearing, and non-sun-exposed human skin. Cancer Epidemiol Biomarkers Prev 1997;6(8):583-7.

44. Ponsford M, Goodman G, Marks R. The prevalence and accuracy of diagnosis of non-melanotic skin cancer in Victoria. Australas J Dermatol 1983;24:79-82.

45. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. N Engl J Med 1993;329(16):1147-51.

46. Whited JD, Horner RD, Hall RP, Simel DL. The influence of history on interobserver agreement for diagnosing actinic keratoses and malignant skin lesions. J Am Acad Dermatol 1995;33(4):603-7.

47. Whited JD, Hall RP, Simel DL, Horner RD. Primary care clinicians' performance for detecting actinic keratoses and skin cancer [published erratum appears in Arch Intern Med 1997 Aug 11-25;157(15):1686]. Arch Intern Med 1997;157(9):985-90.

48. Nixon R, Dorevitch A, Marks R. Squamous cell carcinoma of the skin: accuracy of clinical diagnosis and outcome of followup in Australia. Med J Aust 1986;144:235-7.

49. Hallock GG, Lutz DA. Prospective study of the accuracy of the surgeon's diagnosis in 2000 excised skin tumors. Plast Reconstr Surg 1998;101(5):1255-61.

50. Feldman SR, Fleischer AB, Jr., Williford PM, Jorizzo JL. Destructive procedures are the standard of care for the treatment of actinic keratoses. J Am Acad Dermatol 1999;40:43-7.

51. Kurwa HA, Barlow RJ. The role of photodynamic therapy in dermatology. Clin Exp Dermatol 1999;24(3):143-8.

52. Dillaha CJ, Jansen G. T., Honeycutt W. M., Bradford, A. C. Selective cytotoxic effect of topical 5-fluorouracil. Arch Dermatol 1983;119:774-83.

53. Pearlman D. Weekly pulse dosing: effective and comfortable topical 5-fluorouracil treatment of multiple facial actinic keratoses. J Am Acad Dermatol 1991;25:665-7.

54. Helfand M, Mahon S, Eden K. Screening for skin cancer. Am J Prev Med 2001;20(3S):47-58.

55. Griffin TD, Van Scott EJ. Use of pyruvic acid in the treatment of actinic keratoses: a clinical and histopathologic study. Cutis 1991;47(5):325-9.

56. Jiang SB, Levine VJ, Nehal KS, Baldassano M, Kamino H, Ashinoff RA. Er:YAG laser for the treatment of actinic keratoses. Dermatol Surg 2000;26(5):437-40.

57. Grimaitre M, Etienne A, Fathi M, Piletta PA, Saurat JH. Topical colchicine therapy for actinic keratoses. Dermatology 2000;200:346-8.

58. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Methods of the third U.S. Preventive Services Task Force. Am J Prev Med 2001;20(3S):21-35.

59. Marks R, Foley P, Goodman G, Hage BH, Selwood TS. Spontaneous remission of solar keratoses: the case for conservative management. Br J Dermatol 1986;115(6):649-55.

60. Moon TE, Levine N, Cartreel B, Bangert JL, Rodney S, Dong Q, et al. Effect of retinol in preventing squamous cell skin cancer in moderate- risk subjects: A randomized, double-blind, controlled trial. Cancer Epidemiol Biomarkers Prev 1997;6(11):949-56.

61. Naylor MF, Boyd A, Smith DW, Cameron GS, Hubbard D, Neldner KH. High sun protection factor sunscreens in the suppression of actinic neoplasia. Arch Dermatol 1995;131(2):170-5.

62. Green A, Battistutta D, Hart V, Leslie D, Marks G, Williams G, et al. The Nambour Skin Cancer and Actinic Eye Disease Prevention Trial: design and baseline characteristics of participants. Control Clin Trials 1994;15:512-22.

63. Black H. Influence of dietary factors on actinically-induced skin cancer. Mutat Res 1998;422:185-90.

64. Moon TE, Levine N, Cartmel B, Bangert JL. Retinoids in prevention of skin cancer. Cancer Lett 1997;114(1-2):203-05.

65. Moon TE, N L, B C, J B, S R, M S, et al. Design and recruitment for retinoid skin cancer prevention (SKICAP) trials. Cancer Epidemiol Biomarkers Prev 1995;4:661-69.

66. Lubritz RR, Smolewski SA. Cryosurgery cure rate of actinic keratoses. J Am Acad Dermatol 1982;7(5):631-2.

67. Jeffes EW, McCullough J. L., Weinstein G. D., Fergin P. E., Nelson J. S., Shull T. F., Simpson K. R., Bukaty L. M., Hoffman W. L., Fong, N. L. Photodynamic therapy of actinic keratosis with topical 5-aminolevulinic acid. A pilot dose-ranging study. Arch Dermatol 1997;133:727-32.

68. Omrod D, Jarvis B. Topical Aminolevulinic Acid HCl Photodynamic Therapy. Am J Clin Dermatol 2000;1(2):133-39.

69. Kurwa HA, Yong-Gee SA, Seed PT, Markey AC, Barlow RJ. A randomized paired comparison of photodynamic therapy and topical 5-fluorouracil in the treatment of actinic keratoses. J Am Acad Dermatol 1999;41:414-8.

70. Bercovitch L. Topical chemotherapy of actinic keratoses of the upper extremity with tretinoin and 5-fluorouracil: a double-blind controlled study. Br J Dermatol 1987;116(4):549-52.

71. Lawrence N, Cox SE, Cockerell CJ, Freeman RG, Cruz PD, Jr. A comparison of the efficacy and safety of Jessner's solution and 35% trichloroacetic acid vs 5% fluorouracil in the treatment of widespread facial actinic keratoses. Arch Dermatol 1995;131(2):176-81.

72. Simmonds WL. Double-Blind Investigation Comparing a 1%-vs-5% 5-Fluorouracil Topical Cream in Patients with Multiple Actinic Keratoses. Cutis 1973;12:615-7.

73. Witheiler DD, Lawrence N., Cox S. E., Cruz C., Cockerell C. J., Freemen R. G., Brody H. J. Long-term efficacy and safety of Jessner's solution and 35% trichloroacetic acid vs 5% fluorouracil in the treatment of widespread facial actinic keratoses. Dermatol Surg 1997;23:191-96.

74. Simmonds WL. Topical management of actinic keratoses with 5-fluorouracil: results of a 6-year follow-up study. Cutis 1972;10:737-41.

75. Anonymous. Carac Cream 0.5%: FDA; 2000.

76. Alirezai M, Dupuy P, Amblard P, Kalis B, Souteyrand P, Frappaz A, et al. Clinical evaluation of topical isotretinoin in the treatment of actinic keratoses. J Am Acad Dermatol 1994;30:447-51.

77. Misiewicz J, Sendagorta E, Golebiowska A, Lorenc B, Czarnetzki BM, Jablonska S. Topical treatment of multiple actinic keratoses of the face with arotinoid methyl sulfone (Ro 14-9706) cream versus tretinoin cream: a double-blind, comparative study. J Am Acad Dermatol 1991;24:448-51.

78. Anonymous. Solaraze: FDA; 2000.

79. Marrero GM, Katz BE. The new fluor-hydroxy pulse peel. A combination of 5-fluorouracil and glycolic acid. Dermatol Surg 1998;24:973-8.

80. Tse Y, Ostad A, Lee HS, Levine VJ, Koenig K, Kamino H, et al. A clinical and histologic evaluation of two medium-depth peels. Glycolic acid versus Jessner's trichloroacetic acid. Dermatol Surg 1996;22(9):781-6.

81. Chiarello SE. Cryopeeling (extensive cryosurgery) for treatment of actinic keratoses: an update and comparison. Dermatol Surg 2000;26(8):728-32.

82. Coleman WP, 3rd, Yarborough JM, Mandy SH. Dermabrasion for prophylaxis and treatment of actinic keratoses. Dermatol Surg 1996;22(1):17-21.

83. Frost C, Williams G, Green A. High incidence and regression rates of solar keratoses in a queensland community. J Invest Dermatol 2000;115(2):273-7.

84. Solomons B. Lecture notes in dermatology. 5th ed. Oxford: Blackwell; 1983.

85. Sauer GC. Manual of skin diseases. Fifth ed. Philadelphia: Lippincott; 1985.

86. Montgomery MH, Dorffel J. Verruca senilis und Keratoma senile. Arch Dermat Syphil (Berlin) 1932;166:286-97.

87. Glogau RG. The risk of progression to invasive disease. J Am Acad Dermatol 2000;42(1 Pt 2):23-4.

88. Graham JH, Graham GF. Solar keratosis and skin cancer. Paper presented at: Annual Meeting, North American Clinical Dermatologic Society, 2000; St. Petersburg, Russia.

89. Graham J. Precancerous lesions of the skin. Prim Care 1976;2:699-716.

90. Bendl BJ, Graham JH. New concepts on the origin of squamous cell carcinomas of the skin: solar (senile) keratosis with squamous cell carcinoma--a clinicopathologic and histochemical study. Proc Natl Cancer Conf 1971;6:471-88.

91. Dinehart SM, Pollack S. Metastases from squamous cell carcinoma of the skin. J Am Acad Dermatol 1989;21:241-8.

92. Lund H. How often does squamous cell carcinoma of the skin metastasize? Arch Dermatol 1965;92:635-7.

93. Fukamizu H, Inoue K, Matsumoto K. Metastatic squamous cell carcinomas derived from solar keratosis. J Dermatol Surg Oncol 1985;11:518-22.

94. Silverstone H, Searle J. The epidemiology of skin cancer in Queensland: the influence of phenotype and environment. Br J Cancer 1970;24:235-52.

95. Marks R, Ponsford M, Selwood T. Non melanomatic skin cancer and solar keratoses in Victoria. Med J Aust 1983;2:619-22.

96. Marks R, Staples M, Giles G. Trends in non-melanoma skin cancer treated in Australia: the second national survey. Int J Cancer 1993;53:585-90.

97. Giles G, Marks R, Foley P. Incidence of non-melanocytic skin cancer treated in Australia. BMJ 1988;296:13-7.

98. Green A, Battistutta D. Incidence and determinants of skin cancer in a high risk Australian population. Int J Cancer 1990;15:356-61.

99. Marks R, Jolley D, Lecastas S. The role of childhood sunlight exposure in the development of solar keratoses and non melanoma skin cancer. Med J Aust 1990;152:62-5.

100. English D, Armstrong B, Kricker A. Demogr aphic characteristics, pigmentary and cutaneous risk factors for squamous cell carncinoma of the skin: a case control study. Int J Cancer 1998;76:628-34.

101. Vitasa B, Taylor H, Strickland P. Association on non-melanoma skin cancer and actinic keratosis with cumulative solar ultraviolet exposure in Maryland watermen. Cancer 1990;65:2811-7.

102. Marks R, Rennie G, Selwood T. The relationship of basal cell carcinomas and squamous cell carcinomas to solar keratoses. Arch Dermatol 1988;124(7):1039-42.

Table 1. Key questions

1. Do different management strategies or different methods of removal of the lesion lead to
    a) different morbidity and mortality from SCC?
    b) different incidence of SCC?
    c) different number and duration of AKs?
    d) different quality of life related to side effects and complications of treatment?

2. What is the natural history of actinic keratosis?
    a) What is the incidence and regression rate of AKs?
    b) In patients with actinic keratoses, what is the expected incidence of progression to invasive squamous cell carcinoma with and without removal of the lesion?

3. Will reducing the incidence of SCC reduce morbidity and mortality?
    a) How often does SCC cause disfigurement or death, excluding immunocompromised patients and those with SCC originating on the lip,ear, or eye?
    b) What proportion of disfiguring or lethal SCCs arise from AKs and are potentially preventable?

4. *Risk assessment.* Are there characteristics of actinic keratoses that can be used to identify lesions that are more likely to progress to invasive squamous cell carcinoma?

5a. Are there characteristics that can be used to identify a group of patients at higher risk of progression to invasive squamous cell carcinoma?

5b. Are there data to support a monitoring protocol that will allow detection and treatment of any squamous cell carcinoma at a sufficiently early stage?

5c. For patients who have multiple, recurrent actinic keratoses, do the effectiveness of the following management strategies differ:

--immediate treatment of all AK's

--selective treatment of some AK's, and watchful waiting for others, followed by selective treatment of those that persist, enlarge, or become suspected squamous cell cancers? By "effectiveness" we mean the impact on death, disfigurement and major surgical procedures due to SCC?

Table 2. Efficacy of treatment for actinic keratoses

Treatment	Study design (Author, Year)	Design features	Patients	Baseline risk factors	Treatments	Co-interventions	3-4 months
5-FU	*Controlled trials*						
	Bercovitch, 1987	Randomized to arm, double-blinded	Convenience sample of 20 patients, probably from a referral clinic	15 AKs per arm, 8 of 20 had a history of SCC	5-FU vs. 5-FU plus tretinoin	Not specified	Reduced AKs per patient from 15.3 to 4.2
	Kurwa, 1999	Randomized to hand, not blinded	Convenience sample of 17 patients from a referral clinic	Long history of AKs	5-FU vs. PDT	Not specified	70% reduction in mean lesional area
	Lawrence, 1995	Not randomized, face, not blinded	Convenience sample of 15 patients, probably from a referral clinic	15 AKs on each side of face	5-FU vs. peel	Additional treatments throughout the study period	Reduced AKs per patient from 15.3 to 3
	Witheiler, 1997	Not randomized, face, not blinded	Followup of 8 available patients from Lawrence study	18 AKs on each side of the face	5-FU vs. peel	Additional treatments given at 1 and 6 months	N/A
	Simmonds, 1973	Not randomized, face, double-blinded	Convenience sample of 16 patients from private clinic	Presence of AKs on face	5-FU 1% vs 5%	Not specified	Patients at < 1 mo. Judged to have equal treatment effects to each side of face
	Case series						
	Simmonds, 1972	Face, scalp, hands	Series of 134 patients from a referral clinic	Not stated	1% 5-FU BID	Not specified	N/A
	Pearlman, 1991	Face	Convenience sample of 11 patients, probably from a referral clinic	20+ AKs on face	Pulse 5FU BID 1-2 days per week for up to 9 weeks (AV 6.7wks).	Not specified	98% reduct at end of rx (max 9 weeks)

Table 2. Efficacy of treatment for actinic keratoses

Treatment	*Study design* (Author, Year)	Design features	Patients	Baseline risk factors	Treatments	Co-interventions	3-4 months
Tretinoin	*Controlled trials* Alirezai, 1994	Randomized, double-blinded	Multicenter study of 100 patients, France	9.2 AKs on face, 8.1 on scalp, 5.9 on arm	Tretinoin vs. vehicle cream	Not specified	Face: 65% in tretonion group had 30-100% clearance compared with 45% in placebo group
	Bercovitch, 1987	Randomized to arm, double-blinded	Convenience sample of 20 patients, probably from a referral clinic	15 AKs per arm, 8 of 20 had a history of SCC	5-FU vs. 5-FU plus tretinoin	Not specified	Reduced AKs per patient from 15.7 to 3.4
	Misiewicz, 1991	Randomized to face, double-blinded	Convenience sample of 26 patients, from a referral clinic	8 AKs per side of face	RO 9706 vs tretinoin	Not specified	Reduced AKs per patient from 8 to <6 at 4 months
Cryotherapy	*Case series* Lubritz, 1982	Retrospective review, lesion focused treatment	Convenience sample of 70 patients with a total of 1018 AKs	Most patients with obvious actinic-damaged skin	Cryotherapy	Not specified	N/A
Peels	*Controlled trials* Lawrence, 1995	Not randomized, face, not blinded	Convenience sample of 15 patients, probably from a referral clinic	15 AKs on each side of face	5-FU vs. medium depth peel	Additional treatments throughout the study period	Reduced AKs per patient from 16 to 3
	Witheiler, 1997	Not randomized, face, not blinded	Followup of 8 available patients from Lawrence study	20 AKs on each side of the face	5-FU vs. medium depth peel	Additional treatments given at 1 and 6 months	N/A
	Marrero, 1998	Randomized to side of face, not blinded	Convenience sample of 18 patients, probably from a referral clinic	13-14 AKs on each side of face	8 weekly treatments with glycolic acid+5FU vs. glycolic acid alone (superficial peel)	Not specified	N/A
	Tse, 1996	Not randomized, face, not blinded	Convenience sample of 13 male patients at 2 referral clinics	Not stated	Glycolic Acid plus TCA peel vs Jessners plus TCA peel	2 weeks of pretreatment with nightly tretonoin	At 2 months, "clinical response score" for GA+TCA was fair-good, versus, fair for TCA+Jessner's

Table 2. Efficacy of treatment for actinic keratoses

Treatment	*Study design* (Author, Year)	Design features	Patients	Baseline risk factors	Treatments	Co-interventions	3-4 months
	Chiarello, 2000	Face, scalp, arms, hands	Convenience sample of 373 patients from a private clinic	Extensive AKs	Cryopeeling (extensive cryosurgery)	Retin-A and sun protection after treatment	N/A
Dermabrasion	*Case series* Coleman, 1996	Face, head and scalp, nose, or upper lip	23 patients from 2(?) referral clinics, Florida	"chronic recalcitrant AKs who failed other treatments		No (personal communication, author)	N/A
Photodynamic therapy	*Controlled trial* Ormrod, 2000	Randomized on face, scalp, double-blinded	Sample of 243 patients in 2 multicentered trials	4-15 AKs per patients	Placebo vs. 20% ALA solution	Not specified	88% of patients had >= 75% reduction in AKs at 12 weeks
	Kurwa, 1999	Randomized to hand, not blinded	Convenience sample of 17 patients from a referral clinic	Long history of AKs	5-FU vs. PDT	Not specified	70% reduction in mean lesional area
	Jeffes, 1997	Face, scalp, trunk, and extremities	Pilot study of 40 patients from a referral clinic	6 AKs per patient	Placebo vs. 20% or 30% ALA	Not specified	Overall, 50% of AKs had a complete response, vs. 3% with placebo. 91% of AKs on face or scalp had CR (45% on trunk and extremities).

Notes. (1) Treatment not randomized to side of face, or uncertain whether randomization was used. (2) Low or uncertain followup rates. (3) unequal co-interventions in compared groups (4) assessment not masked or other problem with masking (5) no mention of number of lesions or standard for retreatment

Table 2. Efficacy of treatment for actinic keratoses

Treatment	*Study design* (Author, Year)	Efficacy		Adverse Effects	Study Quality (reasons)
		6-11 months	1 year or more		
5-FU	*Controlled trials*				
	Bercovitch, 1987	N/A	N/A	Not specified	Good
	Kurwa, 1999	N/A	N/A	11/14 filled out "adverse effects". No dif b/t PDT and 5-FU	Good minus (4)
	Lawrence, 1995	Reduced AKs to 2	Reduced AKs to 2 by 1 year.	2 pts had impetiginized eczematous rxn. Chem Peel in 9/15 pts was "preferred rx".	Fair Minus (1, 3)
	Witheiler, 1997	N/A	At 32 months, 5-FU reduced mean number of AKs from 18 before treatment to 10.	Not specified	Fair Minus (1, 3)
	Simmonds, 1973	N/A	N/A	Not specified	Fair
	Case series				
	Simmonds, 1972	N/A	At 24 months 25% of one cohort, and 40% of another, required retreatment.	Not specified	Fair (5)
	Pearlman, 1991	At 9mo first 6 pts to reach this marker had 86% clearing.	N/A	Minimal, none with swelling, oozing or ulceration.	Fair

Table 2. Efficacy of treatment for actinic keratoses

Treatment	*Study design* (Author, Year)	Efficacy		Adverse Effects	Study Quality (reasons)
		6-11 months	1 year or more		
Tretinoin	*Controlled trials* Alirezai, 1994	N/A	N/A	mod-severe 68% rx vs 24% placebo by authors	Good Minus (2)
	Bercovitch, 1987	N/A	N/A	Not specified	Good
	Misiewicz, 1991	N/A	N/A	Not specified	Good minus (4)
Cryotherapy	*Case series* Lubritz, 1982	N/A	Patients evaluated from 1-8.5 years after initial treatment with 12/1018 recurrences of AKs	Not specified	Fair (retrospective, 3)
Peels	*Controlled trials* Lawrence, 1995	Reduced AKs to 3	Reduced AKs to 2 by 1 year.	Erythema for 3 mo in 1 patient.Chem Peel in 9/15 pts was "preferred rx".	Fair Minus (1, 3)
	Witheiler, 1997	N/A	At 32 months, TCA reduced the mean number of AKs from 20 before treatment to 10.	Not specified	Fair Minus (1, 3)
	Marrero, 1998	5FU+glycolic acid reduced AKs, from 13 to 0.9; glycolic acid alone reduced AKs from 13.7 to 11.6.	N/A	Not specified	Good
	Tse, 1996	N/A	N/A	Not specified	Fair (1)

Table 2. Efficacy of treatment for actinic keratoses

Treatment	*Study design* (Author, Year)	Efficacy		Adverse Effects	Study Quality (reasons)
		6-11 months	1 year or more		
	Chiarello, 2000	At 6 mos. 336/373 with 4% recurrence rate (rr) At 6-12 mos. 167/373 with 9% rr	At 12-18 mos.,124/373 with 12% rr At 18-24 mos., 92/373 with 16% rr At 24-30 mos., 71/373 with 22% rr At 30-36 mos., 64/373 with 22% rr At 36-42 mos., 50/373 with 40% rr	Not specified	Fair (2)
Dermabrasion	*Case series*				
	Coleman, 1996	N/A	At 1 yr, 22/23 with no AK (96%), at 2 yr 19/23 no AK's (83%), at 3 yrs 15/19 available had no AKs (64%) 13/23 at 5 yrs 7/13 with no AK(54%). No SCCs were found (5 BCCs seen after 4 yrs.)	Not specified	Fair Minus (2)
Photodynamic therapy	*Controlled trial*				
	Ormrod, 2000	N/A	N/A	Erythema, scaling in most patients.	Good
	Kurwa, 1999	N/A	N/A	11/14 filled out "adverse effects". No dif b/t PDT and 5-FU	Good
	Jeffes, 1997	N/A	N/A	"Minimal"	Fair (1, 4)

Notes. (1) Treatment not randomized to side of face, or uncertain whether randomization was used. (2) Low or uncertain followup rates. (3) unequal co-interventions in compared groups (4) assessment not masked or other problem with masking (5) no mention of number of lesions or standard for retreatment

Table 3. Incidence of actinic keratosis

Author, Year	Study sample and setting	Instruments	Length of followup	Followup rates	Initial prevalence of AK	Initial AKs per person	Incidence of new AKs during followup		Regression rate	Squamous cell cancer		
						mean (range)	*all subjects*	*newly affected subjects*	*% of lesions (rate per 1k/yr)*	*preva-lence*	*incidence*	
											overall	*in those with AK*
Harvey, 1996	Random sample of 1034 subjects age 60 years or older, South Glamorgan, Wales.	Detailed questionnaire and examination of face, head, neck, arms, and legs (below the knee)	1-2 years	70.7% of eligible subjects were seen at visit 1; of these, 79.3% of eligible subjects were seen at visit 2.	23.0%	2 (1-17)	12.6%	8.8%	21% (111-188/1000)	0.002	0.0%	0.0%
Marks, 1986	1040 people age 40 years or older, Maryborough, Australia	Questionnaire and examination of face, head, neck, hands, and forearms.	1 year	100% (presumably only those who completed followup were reported); 3 patients who had treatment for 11 AKs were excluded.	59.2%	7.7	43.4%	19.1%	25.9%	NR	NR	1.6%
Marks, 1988; Marks, 1989	Population-based sample of 2,669 people over 40 (mean age 60.7), Maryborough, Australia	Demographic variables and examination of face, head, neck, hands, and forearms.	1-5 years	81% of eligible subjects were seen at visit 1; 74% of these were seen at visit 2 or higher.	61.1%	8.4	NR	NR	NR	0.004	overall: 0.66% age >70:1%	
Frost, 2000	96 adults 30-69 years, population-based, Nambour, Australia	Demographic variables and examination of face, head, neck, hands, and forearms.	14-18 months	93% of scheduled visits were completed; 7 patients had treatment for 93 Aks (6% of total AKs in the study). Treatment of 2 men accounted for 73 of these.	46% (83% in men 60-69)	5 (1-50 or more)	39.3%	15% (men) 7% (women)	74% for prevalent AKs; 29% for incident AKs.	NR	0.0%	0.0%

AK--actinic keratosis, NR--not reported

Table 4. Hypothetical rate of progression over 10 and 5 years

	1st Marks study	2nd Marks study	Dodson	Base rate of 1 per 1000	Moon (hypothetical)
Yearly rate of progression	0.24%	0.08%	0.14%	0.10%	0.10%
Average number of AKs per patient	7.7	7.7	7.7	7.7	25
Not transform	99.8%	99.9%	99.9%	99.9%	99.9%
None transform in 1 year	98.2%	99.4%	98.9%	99.2%	97.5%
At least 1 transform in 1 year	1.8%	0.6%	1.1%	0.8%	2.5%
none transform in 10 years	83.1%	94.4%	89.8%	92.6%	77.9%
at least 1 transform in 10 years	16.9%	5.6%	10.2%	7.4%	22.1%
none transform in 10 years	91.2%	97.2%	94.7%	96.2%	88.2%
At least 1 transform in 5 years	8.8%	2.8%	5.3%	3.8%	11.8%
NNT in 1 year	417	1333	714	1000	1000
NNT in 5 years	11	35	19	26	9

NNT=number needed to treat. This is the minimum number of AKs that would have to be destroyed to prevent 1 cancer in the specified number of years of followup.

Table 5. Summary of evidence for each key question

Key Question	Quality of Evidence	Comment
1. Do different management strategies or different methods of removal of the lesion lead to		
a) different morbidity and mortality from SCC?	Poor	No data.
b) different incidence of SCC?	Good (sunscreen, beta carotene, retinol); Poor (other agents)	Among patients with AKs, use of sunscreen prevents SCC. Use of oral vitamin A may also prevent SCC, and beta-carotene does not. There are no data for other agents.
c) different number and duration of AKs?	Fair-Poor	5-FU eliminates up to 75% of AKs in the short-term and some other treatments have equivalent short-term efficacy. One long-term followup study suggests that cryosurgery eliminates over 95% of AK's. Longer-term data is sparse and confounded by intervening treatments. Uncontrolled studies suggest that some treatments reduce the number of AK's up to 2 years.
d) different quality of life related to side effects and complications of treatment?	Poor	Little or no data about patient preferences and quality of life related to different treatment approaches.
2. In patients with actinic keratoses, what is the incidence, regression rate,and expected incidence of progression to invasive squamous cell carcinoma with and without removal of the lesion?	Good (without removal) Poor (with removal)	AKs are dynamic lesions; they frequently regress and recur spontaneously. Progression rates are 1-2 per 1,000 for average-risk persons in Australia. Rates are higher in individuals with risk factors (see below). It is not known whether clinically inapparent AKs can progress.
3. Will reducing the incidence of SCC reduce morbidity and mortality?	Fair-Poor	Indirect evidence suggest that 2% of SCCs arising from AKs metastasize, and 7-12% recur. However, accurate data on the morbidity associated with SCC are lacking, and there is no direct evidence of the magnitude of benefit from reducing the incidence of SCC.
4. Risk assessment. Are there characteristics of actinic keratoses that can be used to identify lesions that are more likely to progress to invasive squamous cell carcinoma?	Poor	There are no data linking characteristics of lesions to the risk of progression to SCC in the future.
5a. Are there characteristics that can be used to identify a group of patients at higher risk of progression to invasive squamous cell carcinoma?	Good	In good-quality prospective and cross-sectional studies, male sex, older age, prior history of skin cancer, continued sun exposure, and the number of AKs are associated with a higher risk of developing malignancy.
5b. Are there data to support a monitoring protocol that will allow detection and treatment of any squamous cell carcinoma at a sufficiently early stage?	Poor	There is no direct evidence, and too little is known about how often SCCs metastasize early to assess the effectiveness of monitoring to detect and treat SCC early in its course.
5c. For patients who have multiple, recurrent actinic keratoses, does the effectiveness of management strategies differ?	Poor	There are no studies comparing immediate treatment of all AKs to selective treatment and monitoring.