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# Skin Cancer Prevention: Recent Evidence from Randomized Controlled Trials

**Adèle C. Green · Catherine A. Harwood · John Lear · Charlotte Proby · Sudipta Sinnya · H. Peter Soyer**

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**Abstract** Despite the billions of health care dollars spent each year on treating skin cancer, there is a dearth of randomized controlled trials (RCTs) that have evaluated skin cancer prevention. RCTs published in the last 3 years that have directly assessed skin cancer prevention as their primary aim suggest that regular use of sunscreen is cost effective, but prolonged use of topical therapies such as tretinoin and 5-fluorouracil may not be. Sirolimus-based immunosuppression for secondary skin cancer prevention in long-term renal transplant recipients appears effective, but benefits may be offset by the adverse effects. Many RCTs using pre-invasive actinic keratoses (AKs) as endpoints are too small and/or too short to provide evidence on skin cancer prevention. Another stumbling block is the difficulty in reproducibly diagnosing and counting AKs in response to preventive agents. Longer term and better surveillance methods are urgently required to improve the quality of evidence from future RCTs.

**Keywords** Skin cancer · Prevention · Randomized controlled trials · RCTs · Clinical trials · Outcome measures · Interventions · Sunscreen · Topical treatment · Basal cell carcinoma · BCC · Squamous cell carcinoma · SCC · Actinic keratosis · AK · 5-fluorouracil · 5-FU · Digital photography · Dermoscopy

A. C. Green
Cancer and Population Studies Group, Queensland Institute of Medical Research,
300 Herston Rd.,
Brisbane, Queensland 4006, Australia

A. C. Green
University of Manchester,
Manchester Academic Health Sciences Centre,
Oxford Rd.,
Manchester M13 9PT, UK

A. C. Green (✉)
Queensland Institute of Medical Research,
PO Royal Brisbane Hospital,
Brisbane, Queensland 4029, Australia
e-mail: adele.green@qimr.edu.au

C. A. Harwood
Centre for Cutaneous Research, Blizard Institute,
Barts and the London School of Medicine and Dentistry,
Queen Mary University of London,
4 Newark St.,
London E1 2AT, UK
e-mail: caharwood@doctors.org.uk

J. Lear
Departments of Dermatology, Salford Royal NHS Foundation Trust and Manchester Royal Infirmary and University of Manchester,
Stott Ln.,
Salford M6 8HDUK
e-mail: john.lear@cmft.nhs.uk

C. Proby
Division of Cancer Research, Medical Research Institute,
University of Dundee, Ninewells Hospital & Medical School,
Dundee DD1 9SY ScotlandUK

S. Sinnya · H. P. Soyer
Dermatology Research Centre, The University of Queensland,
School of Medicine, Princess Alexandra Hospital,
Brisbane, QLD 4102Australia
e-mail: s.sinnya@uq.edu.au

H. P. Soyer
e-mail: p.soyer@uq.edu.au

## Introduction

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are by far the commonest cancers in white-skinned populations. It is estimated that in the United States alone in 2006, a total of 2,152,500 people were treated for around 3,507,700 such cancers [1]. Despite their relatively low mortality rates, such high-incidence rates mean that the associated health care costs impose a substantial financial burden on health care systems [2]. Cutaneous melanoma, the other major type of skin cancer, affected around 10,342 people in Australia in 2007 [3] and some 68,700 people in the United States in 2009, with around 8,600 deaths [4]. Collective management of these skin cancers drives an expenditure that exceeds the total amount spent on other major cancers combined [5–7]. In the United States, skin cancer treatments cost an estimated $2 billion each year [8••]. Beyond these are further billions—around $1.2 billion in the United States [9•]—expended treating the related and highly prevalent skin lesions, actinic keratoses (AKs). AKs affect 5 % to 25 % of people in the United Kingdom and United States and up to 60 % in Australia [10, 11], and are one of the strongest risk factors for skin cancer.

Exposure to solar UV radiation is the major environmental cause of skin cancer, and, recently—especially in temperate climates—exposure to artificial UV light such as sunbeds has contributed to carcinogenic exposure of the skin [12]. Theoretically, it should be straightforward to control a large proportion of skin cancers and their massive costs by implementing measures to decrease susceptible people's level of UV exposure. Adoption of sun-avoidance behaviors by fair-skinned people is an obvious and fundamental preventive measure. The U.S. Preventive Services Task Force has systematically reviewed all counseling measures aimed at preventing skin cancer [13•]. It found few rigorous counseling trials and concluded that, of all counseling strategies assessed, only those relevant to primary care settings increased skin-protective behaviors. Other diverse approaches to achieving skin-protective behavior changes have ranged from shade provision interventions in schools [14] to appearance-focused interventions based on decision-theoretical models of health behavior in young female indoor tanners [15]. A more direct interventional approach is to focus on skin cancer as the primary outcome, and trials that have taken this direct approach are the focus of this paper.

## Scope of This Review

Randomized controlled trials (RCTs) published in the last 3 years that followed up 100 or more patients and were conducted with the explicit primary aim of evaluating the effectiveness of preventive measures in decreasing the incidence of BCC, SCC, or melanoma have been reviewed. Intervention studies that aimed to prevent AKs in the long term (defined as at least 1 year) or, based on the premise that a proportion of AKs are premalignant SCC precursors, aimed to diminish AK burden as a long-term outcome and thus a means of achieving SCC prevention (although this was mostly implicit) have also been mentioned. Systematic reviews of relevant trials, including RCTs with outcomes assessed at less than 1 year given the high level of review evidence, have also been summarized.

We begin by briefly considering findings from prevention trials that were published prior to 2009 and then review the most recent substantive published evidence. We conclude by discussing the controversies regarding the natural history of AKs and the difficulties of assessing the prevalence of AKs in large-scale clinical settings.

## Pre-2009 Skin Cancer Prevention Trials and Systematic Reviews

RCTs published before April 2007 and conducted among people at high risk of developing keratinocyte cancer have been reviewed by the Cochrane Collaboration [16]. The authors noted that, because only 10 such studies had been conducted, data were very limited, and they summarized the results as follows. One trial that had assessed topical T4N5 liposome lotion containing DNA repair enzymes in patients with xeroderma pigmentosum, the rare inherited disorder [17], showed that annual rates of new AKs and BCCs were reduced, whereas annual rates of SCCs and melanomas were non-significantly raised in the intervention compared with placebo group. No significant adverse effects were seen. Six trials evaluated systemic retinoid therapies to prevent skin cancers in renal transplant recipients: half assessed acitretin and half other oral retinoids. Of the three that assessed acitretin, only one provided standard measures of outcome. It showed no difference in time to first skin cancer when 30 mg per day acitretin was compared to placebo over 6 months, but there was a reduction in number of new skin cancers in the first 12 months after intervention. All three acitretin trials reported frequent mucocutaneous side effects, and when adverse event data (evaluable in two of the trials) were pooled, an increased risk of having an adverse event (unspecified) with acitretin therapy could not be excluded (RR, 1.80; 95 % CI, 0.70–4.61) [16]. Among people with past keratinocyte cancer, results regarding new BCCs after oral retinoid or isoretinoin treatment were inconclusive, but risk of new SCC was raised in one trial and of adverse events in another [16]. In two trials of antioxidant supplements among people with a history of skin cancer, one found that selenium supplements significantly elevated the risk of a new SCC, whereas the other gave inconclusive evidence regarding

beta-carotene supplements. A trial of a reduced fat diet showed a trend toward fewer new keratinocyte cancers [16], although BCC and SCC endpoints could not be distinguished. The authors of this systematic review concluded that, although preventive treatments may benefit people at high risk of developing skin cancer, firm conclusions could not be drawn because of the very small number of trials addressing each type of intervention.

A systematic review and meta-analysis of five short-term RCTs (1293 patients) evaluated the efficacy and safety of an immune-response modifier, imiquimod 5 % cream, in the treatment of AKs and found that complete clearance occurred in 50 % of patients treated with imiquimod compared with 5 % treated with vehicle only [18]. The proportion of patients with any adverse event, most often erythema (27 %) and scabbing or crusting (21 %), was substantially higher with imiquimod than with the vehicle. The authors concluded that imiquimod 5 % cream was effective in the treatment of AK and thus may potentially prevent the development of SCC [18].

Finally, a single community-based skin cancer prevention trial was conducted in Australia [19]. The Nambour Skin Cancer Prevention Trial evaluated daily sunscreen use and beta-carotene supplementation in the prevention of BCC and SCC. The trial showed that, in comparison with people randomized to using sunscreen at their discretion, if at all, people randomized to daily use of a broad-spectrum SPF15+ sunscreen had no reduction in BCC but a 40 % reduction in SCC tumors at the conclusion of the trial [20]—a reduction maintained 8 years later [21]. Rate of acquisition of AKs was also reduced in the daily sunscreen group [22], as was the time to subsequent BCCs after the first BCC [23] in the trial period. There was no effect of beta-carotene supplementation on development of actinic tumors, malignant or benign [20, 22].

## Recent Skin Cancer Prevention Trials and Systematic Reviews

There continues to be a paucity of evidence from RCTs that have directly set out to assess skin cancer prevention, and most that are recently published or ongoing are secondary rather than primary prevention. Findings from three RCTs with at least 100 participants have been published recently: one, a pragmatic trial in an Australian community and two, secondary skin cancer prevention trials in renal transplant recipients and U.S. veterans, respectively (Table 1). There have been two systematic reviews published in the last 3 years of 5-fluorouracil (5-FU) and photodynamic therapy for treatment of AKs (Table 1).

### Community-Based Trial

Results of the long-term follow-up of participants of the aforementioned Nambour Skin Cancer Prevention Trial were recently published in relation to sunscreen allocation and prevention of new primary melanoma [24••]. It was shown that regular use of sunscreen by people in the high sun exposure setting of Queensland reduced the development of melanoma compared with discretionary sunscreen use. Investigation of the lifetime health costs and benefits of sunscreen promotion in the primary prevention of skin cancers, including melanoma, showed that routine sunscreen use by white populations residing in sunny settings is likely to be a highly cost-effective investment for governments and consumers over the long term [8••].

### Trial in Renal Transplant Patients

The CONVERT open-label, randomized, multicenter trial found keratinocyte skin cancer rates were reduced in long-term renal transplant recipients at 2 years after their conversion to sirolimus-based immunosuppression compared with continued calcineurin inhibitor immunotherapy [25••] (Table 1).

### Trial in Patients with Multiple Past Basal Cell Carcinomas and Squamous Cell Carcinomas

The Veterans Affairs Topical Tretinoin Chemoprevention Trial found no difference in times to first BCC or SCC and no difference in AK counts between patients treated with topical 0.1 % tretinoin compared with matching placebo over 1.5 to 5.5 years [26••].

### Systematic Reviews of Treatment of Multiple Prevalent Actinic Keratoses

A systematic review of 5-FU in the treatment of prevalent AKs found greater reduction in mean number AKs with both 5 % 5-FU and 0.5 % 5-FU compared with placebo, but not compared with laser resurfacing [27•]. However, two thirds of patients required retreatment after 1 year, and up to half of those treated were unable to complete treatment because of adverse effects. The systematic review of photodynamic therapy in the treatment of prevalent AKs found photodynamic therapy to be superior to placebo, but there was insufficient evidence regarding its comparison with other treatments [28•] (Table 1).

## Ongoing Skin Cancer Prevention Trials

The U.S. National Institutes of Health Clinical Trials registry [29] currently lists 66 RCTs of AK treatment. Of those that have recently updated information available, only two appear to have started in the last 5 years, with 100 or more patients followed-up for at least 12 months. In a phase II

**Table 1** Randomized controlled trials and systematic reviews of skin cancer prevention/treatment of AKs published since 2009

| Trial | Participants | Intervention and control groups | Outcomes | Comments |
|---|---|---|---|---|
| Nambour Skin Cancer Trial (Green et al. [24••]) | 1621 community members randomly selected; 44 % male | Daily application of sunscreen to head and arms vs discretionary sunscreen use; beta-carotene 30 mg vs placebo from 1992 to 1996 | Reduced new primary skin melanoma in daily sunscreen group from 1993 to 2006 (HR, 0.50; 95 % CI, 0.24–1.02); beta-carotene no effect | Melanomas histologically reviewed by two pathologists blinded to treatment allocation |
| CONVERT Trial (Alberu et al. [25••]) | 830 renal transplant patients; ages 25–75 y; 69 % male | Conversion to SRL-based vs continued CNI immunotherapy for 2 y | Lower keratinocyte skin cancer rates after SRL-based, CNI-free immunotherapy (1.2 vs 4.3, $P<0.001$) | Adverse events and withdrawal rates higher in SRL-based immunotherapy at 2 y (26 % vs 20 %, $P<0.07$) |
| VATTC Trial (Weinstock et al. [26••]) | 1131 U.S. veterans with 2 + BCC or SCC in past 5 y; 59 % ages> 70 y | Topical 0.1 % tretinoin vs matching placebo for 1.5–5.5 y | No difference in times to first BCC ($P=0.3$) or first SCC ($P=0.4$) between groups; no difference in AK counts | Worse symptoms in intervention group at 1 y |
| Systematic review of 5-FU and AKs (Askew et al. [27•]) | 13 studies involving 865 patients with multiple prevalent AKs | Topical 5 % 5-FU (5 % or 0.5 %) vs variety of treatments* for 4 w–12 m | Average reduction in mean number AK: 80 % (range, 59 %–100 %) (5 % 5-FU); 86 % (0.5 % 5-FU) vs 95 % (laser resurfacing); 28.0 % (placebo) | 66 % required retreatment after 1 y; up to 50 % unable to complete treatment because of adverse effects |
| Systematic review of photodynamic therapy and AKs (Fayter [28•]) | 28 studies involving 2611 patients with multiple prevalent AKs | PDT vs cryotherapy; placebo PDT (cream); cryotherapy; 5-FU; imiquimod; different PDT parameters for various durations | MAL-PDT superior to placebo (pooled odds of clearance at 3 m= OR, 8.05; 95 % CI, 5.50–11.79) | Insufficient evidence regarding PDT compared with other treatments |

*$CO_2$ laser or 30 % trichloroacetic acid peel; cryotherapy; imiquimod 5 % cream; diclofenac sodium 3 % gel; PDT; 5-FU augmented with tretinoin; placebo; 5-aminolevulinic acid PDT, activated with either blue or pulsed laser light

*5-FU* 5-fluorouracil; *AK* actinic keratosis; *AKs* actinic keratoses; *BCC* basal cell carcinoma; *CNI* calcineurin inhibitor; *HR* hazard ratio; *MAL* methyl aminolevulinate; *PDT* photodynamic therapy; *SCC* squamous cell carcinoma; *SRL* sirolimus

trial, the efficacy of afamelanotide (formerly CUV1647), a chemical analogue of alpha-melanocyte stimulating hormone, in reducing AKs and SCCs in around 200 organ transplant patients is being investigated (NCT00829192). Another RCT is studying the long-term effects of treatment of skin areas with 5 to 10 AKs with imiquimod 5 % cream versus diclofenac 3 % gel with respect to the risk of progression to in situ and invasive SCC at 3 years in around 250 immunocompetent patients (NCT01453179).

There are at least two other ongoing randomized controlled trials of skin cancer prevention, both in immunosuppressed patients ($N>100$), of which the authors are aware and/or directly involved. A multicenter-sponsored (Spirig Pharma Ltd., Switzerland) RCT examining the role of sunscreen in skin cancer prevention is currently in progress in Turkey and 11 countries across Europe. In this study, 300 organ transplant recipients at risk of skin cancer are being randomized to discretionary use of sunscreen in a galenically improved, dosable version of the liposomal sunscreen reported in a smaller study [30] of organ transplant recipients in Germany. This current 2-year study will examine reduction of AK and development of new skin cancers (as well as viral warts) as primary outcome measures (C. Ulrich, personal communication). The aims of another scheduled trial, the O3A Trial, are to evaluate omega-3 polyunsaturated fatty acid supplementation (4 g per day) versus placebo (double blind), in the prevention of BCC and SCC in 340 organ transplant patients in a 2-year intervention period. It is being conducted by a multicenter team, including some of the authors (A. C. Green, C. A. Harwood, J. Lear, and H. P. Soyer) in Australia and United Kingdom.

## Controversies Regarding Actinic Keratoses

Since the majority of skin cancer prevention trials have been aimed at secondary prevention of SCC, many RCTs have focused on the treatment of AKs as trial endpoint, since AKs are presumed to be surrogate biomarkers of SCC, as noted previously. This is a difficult area in many ways given the controversies surrounding the malignant potential of AKs and the assumption—but lack of conclusive evidence—that clearance of AK prevents SCC. In addition, even if the AK

intervention may be assumed to prevent SCC, it is not known whether complete clearance is required and/or whether persistent clearance or maintenance of clearance over an unknown period is required to achieve this. There are also controversies at the clinical level; that is, it is not known what type of AKs are most closely associated with SCC. For example, are small, barely palpable ones less of a risk than large, inflamed hyperkeratotic ones? The challenges around clinical diagnosis and quantification have not been addressed often in published studies but have important implications for interpreting study validity in terms of intervention agents' long-term efficacy in treating and/or preventing AK, as well as their putative role in SCC prevention.

## Definition

AKs are scaly skin lesions of variable size that are pink or red, often asymptomatic, and arising on the face, bald scalp, backs of hands and forearms, or other sites where cumulative UV light-induced changes have occurred. An early AK is flat, pink, and mildly scaly and is often appreciated more readily by palpation than visualization because of its distinctive roughened, sandpaper-like quality. As lesions progress, they become infiltrated, and the scaling may become increasingly more prominent, culminating in markedly hyperkeratotic AK and cutaneous horns. Adjacent AKs may merge into one another, thereby producing a field of abnormal skin. Such "field change" or "field cancerization" indicates severe photodamage (Fig. 1) and sites at which SCC preferentially develop. A proposed clinical grading of "mild," "moderate," and "severe" aims to reflect the progressive infiltration and hyperkeratosis of AK. Histopathologically, there is partial thickness dysplasia and loss of stratification of the epidermis such that histological grading systems have also been devised to reflect the extent of epidermal dysplasia—the so-called keratinocyte intraepithelial neoplasia grades I, II, and III [31, 32].

## Natural History and Rate of Malignant Transformation

The natural history of AK is poorly understood but is believed to involve turnover of prevalent individual lesions (regression and recurrence) as well as development of new lesions [10]. Although some AKs clearly evolve into SCCs, the majority do not and the risk of progression to invasive malignancy is unknown [33] but much debated. A systematic review of 15 studies showed estimated progression rates of between 0.025 % and 20 % per year, per lesion [34]. A more recent study from the United States that prospectively followed 169 patients with 7784 AKs found that the risk of progression for a specific AK was 2.57 % at 4 years, and that 65 % of all primary SCCs arose directly in lesions

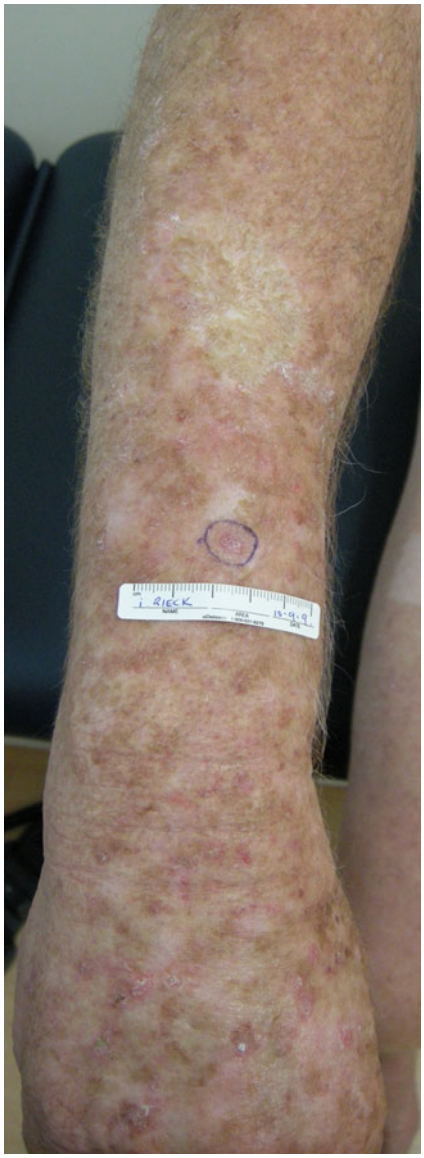

**Fig. 1** Multiple AKs merge with widespread field changes in severely photodamaged skin

previously diagnosed as AKs [35]. Cited rates of transformation into SCC are almost certainly overestimates, since even the most conservative have been based on successive clinical counts of AK of subjects' skin at widely varying intervals, using counting techniques of uncertain reliability and validity [30]. Indeed, there remains lack of agreement among histopathologists regarding the diagnosis of SCC and AK [36••] because of the continuous clinicopathologic spectrum from benign atypical keratotic lesions to invasive malignant lesions [2].

## Monitoring Actinic Keratoses

Evaluating the efficacy of AK therapies requires quantification of AK burden before and after treatment. For the purposes

of clinical studies, distinguishing features for AK have not been well established. In immunosuppressed organ transplant recipients, the clinical picture is further complicated by the increased prevalence of verrucokeratotic lesions, most of them viral warts, which are often present in areas of field cancerization and are clinically (or sometimes histologically) indistinguishable from AK [37]. Many studies have validated clinical diagnosis of AK by biopsying lesions, but how target lesions were selected has not been stated often. Diagnosis of discrete, clinically typical AK is relatively easy, but in patients with multiple and atypical lesions—particularly where lesions merge to give a field of skin abnormality (Fig. 1)—diagnosis and counting of AKs is far from straightforward and may be almost impossible [36••].

Previous studies of treatment and natural history of AK have usually quantified lesions by counting alone, yet counting of AK as a technique for evaluating therapeutic efficacy may be unreliable, even when performed by experienced dermatologists, since interobserver reproducibility is poor [26••] and may inadequately account for spontaneous regression of AK [30]. Joint discussion of discrepancies by observers may enhance the reliability of these counts, although substantial variation remains [38]. The importance of developing and validating techniques to enhance reliability of AK assessment has been highlighted, but the problem remains unresolved [30, 38].

### Role of Digital Photography and Dermoscopy for Imaging of Actinic Keratoses

Standard photographic evaluation, blinded, has been suggested as perhaps the most reliable technique, but this is also untested [30]. More recently, digital photography of regions of the body such as the face, scalp, and dorsa of hands and forearms has been advocated for early detection and surveillance of keratinocyte skin cancer. Advantages of imaging AKs with digital photographs over counting AKs, especially on severely photodamaged skin (Fig. 1), are the relative ease and speed that an established imaging protocol can be carried out. Digital photography also allows clinicians to detect smaller or nonspecific lesions, which may otherwise be missed or passed over, especially in a busy outpatient clinic. Digital images can be stored for successive comparisons during repeated follow-up, as in clinical trials, using similar protocols to those now established for naevus surveillance [39].

On the other hand, the role of dermoscopy in assessing large number of AKs over time is not established. To date, most of the dermoscopic literature on AK has focused on differentiating pigmented AKs from lentigo maligna [40], although recently a progression model of facial AK has been proposed based on a large series of dermoscopic images of AKs developing into invasive SCCs [41]. However, the added value of dermoscopic examination of individual AKs among some thousands of AKs being followed during large skin cancer prevention trials seems quite low, and even lower for confocal microscopy. Ultimately, it is hoped that high-definition regional photography in combination with available image-analysis tools will enhance clinical examination to achieve accurate and reproducible counts and assessments of AKs.

## Conclusion

The number of recently published skin cancer prevention trials is small in inverse proportion to the need for them to better control the vast health costs associated with skin cancer treatment. Sunscreen emerges as a cost-effective preventive agent for people living in sunny places. There is inconsistent evidence regarding the long-term efficacy of topical treatments such as retinoids and 5-FU, and AK clearance in the short term is often associated with side effects. Several skin cancer prevention trials evaluating a range of possible preventive agents in immunosuppressed patients are currently underway, but the lack of validity and reproducibility of standard clinical and histopathological assessment of AK as a trial endpoint is an ongoing limitation. There is an urgent need to address these methodological challenges of diagnosis, quantification, and surveillance of AK burden as well as a need for future adequately powered, well-designed, long-term RCTs for strengthened evidence regarding skin cancer prevention.

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