Prevention of Non-Melanoma Skin Cancer

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Current Oncology Reports 2001, **3**:295–300
Current Science Inc. ISSN 1523-3790

Basal cell and squamous cell carcinomas comprise the majority of non-melanoma skin cancers. Whereas the incidence of skin cancer is equivalent to that of all other cancers combined, non-melanoma skin cancer receives a disproportionate share of attention because mortality is relatively low. However, the impact on public health is striking. This review is intended to update readers on the current findings in research on the prevention of these diseases. Topics covered include preventive strategies targeting high-risk populations, chemoprevention (including treatment of intraepithelial neoplasia), and an overview of recent and ongoing clinical and preclinical studies involving new chemopreventive agents.

Introduction

Non-melanoma skin cancer (NMSC) is the most common type of diagnosed malignancy. It has a tremendous impact on public health and health-care economics due to the sheer number of cases. Estimates for the United States in 2001 project almost as many cases of NMSC as all other cancers combined [1•]. Incidence of NMSC has risen in past years but may be leveling off; 900,000 new cases were expected in 1997 [2]. In 2000, 1.3 million new cases were expected [3], but only 1 million new cases are expected in 2001 [1•]. These estimates are probably all lower than the actual number of cases because many skin cancers are treated or removed in clinics without being reported to cancer registries. In spite of the tremendous number of cases of NMSC, mortality from this disease is relatively low. Death rates are less than 1.5 per 100,000 [4]. However, morbidity can be dramatic due to excision of lesions in cosmetically sensitive areas [5,6].

Almost all NMSC is keratinocytic and originates in the epidermis. Approximately 80% is basal cell carcinoma (BCC) [7]. These neoplasms, originally described by Jacob in 1827 [8], appear to originate from basal cells of the epidermis and occasionally those of the infundibular and outer root sheath of the hair follicles [5]. These slow-growing tumors are locally invasive and rarely metastasize. However, morbidity can be high because these tumors are often disfiguring and located in facial areas. Squamous cell carcinoma (SCC), the other major form of NMSC, originates in the keratinizing cells of the epidermis. These tumors are generally more aggressive than BCC and have a much higher potential for metastasizing. Mortality from NMSC is mainly due to SCC, with 1200 to 1500 deaths reported each year in the United States [6]. The death rate for SCC is approximately equivalent to that of Hodgkin disease or acute lymphocytic leukemia [1•].

Risk Factors

The predominant risk factors for NMSC are exposure to ultraviolet (UV) radiation and fair skin that is susceptible to sunburn. Increasing frequency of exposure, age, immune status, male gender, and DNA repair disorders such as xeroderma pigmentosum also contribute to increased risk [7]. The association between UV exposure and cancer is strong for SCC but less well-defined for BCC, as approximately one third of all BCC originates in anatomical sites receiving minimal UV exposure [5]. Skin temperature may also be a factor. Cultured immortalized human keratinocytes have been shown to spontaneously convert to a tumorigenic phenotype when incubated at elevated temperature [9]. Skin temperature may also play a role in the genesis of melanoma [10].

Some evidence indicates that human papilloma virus (HPV) infection may increase NMSC risk, although the relationship is not clear [11]. Strong evidence from studies of atomic bomb survivors and studies of radiotherapy patients suggests that exposure to ionizing radiation can cause BCC, but the evidence is weak for SCC [12].

Solid-organ transplant recipients are at extremely high risk for SCC. A comprehensive study of 5356 transplant recipients in Sweden showed that these patients experienced a 100-fold increase in relative risk of NMSC, almost exclusively in sun-exposed areas [13]. The increased frequency of SCC in these patients, especially in individuals with chronic actinic damage, is presumably caused by long-term immunosuppressive therapy [14], although non-immune mechanisms may play a role [15•].

Increases in NMSC incidence are expected as the population ages and larger amounts of UV radiation reach the surface of the earth due to depletion of the ozone layer [16]. Exposure to UV radiation can result in the formation of DNA thymine dimmers, which can lead to possible fixed mutations and the initiation of carcinogenesis. Whereas promotion of these initiated cells to a preneoplastic state may take 10 or more years, progression to carcinoma in situ may occur in 1 year or less. Thus, the best opportunity for intervention is during the promotion phase [17].

Precancerous Lesions

Several precancerous dermatoses occur prior to development of epidermal malignancies. These include Bowen's disease, as well as radiation, tar, arsenical, thermal, and scar keratoses. Actinic keratosis (AK, also known as solar or senile keratosis) is by far the most common precancerous dermatosis and is attributable to UV radiation [17]. AK results from proliferation of transformed neoplastic keratinocytes confined to the epidermis and is characterized by thickened, cornified, scaly lesions that develop on the surface of the skin.

AK is an extremely common lesion, especially in older Caucasian populations. In the United States, an estimated 3.7 million physician office visits/year for AK were made in 1993 and 1994 [18]. In spite of these epidemic proportions of AK, there is little comprehensive epidemiologic data on its incidence in North American populations. These data are difficult to collect because of variability in diagnosis and treatment and lack of reporting. Based on limited available data, the best estimate for current prevalence of AK ranges from 5% to 14% in the United States [19]. In high-risk groups, prevalence may be as high as 26% [20]. In Australia, where skin cancer incidence is highest, prevalence of AK ranges from 40% to 60% in the adult population [21].

Targeting Intraepithelial Neoplasia

NMSC chemoprevention trials are difficult to conduct for the following reasons: 1) the rarity of cancer endpoints in the population as a whole; 2) the large population sizes required for adequate statistical power; and 3) the length of time required for carcinogenic progression. One approach to reducing sample size in chemoprevention trials is to develop strategies that do not depend on the cancer endpoint, but on treatment of the disease process (carcinogenesis) [22]. Because of the long latency of the promotion phase of carcinogenesis, intraepithelial neoplasia (IEN) serves as a reasonable target for preventive strategies. In SCC, AK is a clinically detectable IEN with regression that can be easily measured. Strategies that target IEN can reduce risk of full-blown cancer while providing direct clinical benefits such as reduced morbidity, delayed surgery, and longer surveillance intervals.

Evolving nomenclature of actinic keratosis

Many experts believe that the term "actinic keratosis" is outdated and that it does not convey the seriousness of the condition or the urgency for treatment, especially to third-party payors who may erroneously consider these procedures to be cosmetic [23]. This term refers only to clinical features and does not reflect the true pathobiology or histopathology of the lesion. Because the nomenclature used is inaccurate, it implies that these lesions are low-risk, when in fact they are not. Suggested terms for classification include "keratinocytic intraepidermal neoplasia" or "solar keratotic intraepidermal SCC" [24•]; or simply "SCC in situ" [25]. Recognized as such, SCC is probably more common than BCC [26].

Risk of progression

IEN lesions in skin can progress to metastatic disease, but most do not. Estimates of AK progression range from 0.1% to 14%. The lowest rates of conversion (<1%) were seen in the seminal studies by Marks *et al.* [27], which describe only the 1-year conversion rate. The higher rates seen in later studies were obtained over longer follow-up periods, taking into account multiple lesions, and are likely more accurate [7]. In a series of longitudinal studies conducted in Australia among moderate-risk AK patients [27,28], the estimated 10-year risk of malignant transformation for an average patient with AK ranged from 6.1% to 10.2%. An even higher rate of malignant transformation has been observed in southeastern Arizona, where among 1140 moderate-risk AK patients, the cumulative probability of developing a first new SCC was 14.1% over 5 years [29••]. Based on these data, the presence of AK should not be taken lightly because it indicates a significant risk for invasive NMSC.

Preventive Strategies

Primary preventive strategies are designed to reduce exposure to carcinogens. Because complete avoidance of sunlight is impossible (and undesirable), secondary chemopreventive strategies are designed to circumvent the promotion or progression of initiated precancerous cells using non-cytotoxic nutrients or pharmacologic agents. Secondary chemopreventive strategies are particularly necessary for individuals at increased risk of NMSC. Ultimately, a combination of primary and secondary preventive strategies should bring the best outcome for high-risk patients.

Primary prevention

Obviously, decreasing exposure to sunlight is the best way to lower risk of NMSC. However, the realities of sun exposure and active outdoor lifestyles make it difficult to avoid this risk. Common-sense behavioral changes include avoidance of peak hours of sunlight, wearing protective clothing,

educating children to the dangers of overexposure, avoiding deliberate sun tanning, and regular skin examination. Reduction of AK by regular sunscreen use is well documented [30]. Public awareness campaigns appear to be reducing the incidence of skin cancer in Australia [31]. Screening programs utilizing low-cost digital imaging systems to monitor appearance of skin lesions may be a useful public health tool for reducing NMSC incidence [32].

Secondary prevention

Because we cannot eliminate harmful UV radiation exposure to our skin, nor can we go back in time to reverse the significant exposure most of us have already accrued, development of secondary preventive strategies is warranted to halt or reverse skin carcinogenesis. In the past decade, several large randomized, placebo-controlled phase III intervention trials of chemopreventive agents have been performed in groups at high risk for the development of new NMSC (Table 1). These trials all used daily oral dosing regimens. In one of the first chemoprevention trials conducted by the Skin Cancer Prevention Study Group, 1805 patients with recent NMSC received a 50-mg dose of β-carotene daily for up to 5 years with no significant effect on the incidence of first new NMSC despite an 8.5-fold increase in median plasma β-carotene levels [33].

In the Nutritional Prevention of Cancer Study Group trial, 1312 patients with a history of NMSC were treated with 200 μg of selenium in brewer's yeast, or placebo for 4.5 ± 2.8 years with 6.4 ± 2.0 years of follow-up. Selenium had no effect on the incidence of BCC or SCC in these patients [34].

In the Southwest Skin Cancer Prevention Study Group trial, 2297 patients with a history of greater than 10 AK and less than or equal to 2 SCC or BCC were treated with 25,000 IU of retinol or placebo for up to 5 years with a median follow-up of 3.8 years. No effect was seen on the incidence of BCC in this trial. However, oral vitamin A significantly reduced the 5-year probability of developing a new SCC [29••]. This result marks the first positive phase III chemoprevention trial in any cancer.

Recently, the results of additional β-carotene trials have been published. In an Australian study, 30 mg of daily β-carotene and daily sunscreen use were analyzed using a two-by-two factorial design. Beta-carotene with or without sunscreen use had no effect on the incidence of SCC or BCC after 4.5 years of follow-up [35]. In an extended follow-up to the Physicians' Health Study, 50 mg of daily β-carotene had no effect on the incidence of new NMSC after 12 years of intervention in presumably healthy male subjects [36].

Current trials

Both small-scale and large-scale trials of chemopreventive agents have recently been completed or are currently underway (Table 2). These trials include topical, parenteral, and oral agents. In a Swiss study, use of topical colchicine (1% gel) resulted in complete regression of recurrent AK in 7 of 10 subjects in a double-blinded, placebo-controlled phase II study [37]. Topical diclofenac (Solaraze; SkyePharma, San Diego, CA) was recently approved in the United States for treatment of AK. Approval was based on studies in patients with five or more AK in major body areas. The primary endpoint was complete clearance of AK 30 days after completion of treatment. Ninety days of diclofenac treatment resulted in a 47% clearance, versus 19% in vehicle control subjects ($P<0.001$). A second 60-day study showed a 31% clearance in treated patients versus 10% in control subjects ($P=0.021$). When stratified for location, significant clearance of AK lesions was seen only in the forehead and facial regions.

In a phase IIb study by Alberts *et al.* [38], 48 patients with at least 10 AK on their forearms received topical difluoromethylornithine (DFMO) on either the left or the right forearm and placebo ointment on the other forearm twice daily for 6 months. DFMO caused a 23.5% reduction in the number of AK on treated forearms. Levels of spermidine in biopsy samples were used as a biomarker of DFMO activity, and spermidine suppression was directly related to AK reduction. However, inflammatory reactions were seen in some of the DFMO-treated arms. A follow-up phase IIb study ($n=150$) is ongoing at the University of Arizona. This study, in patients with moderate to heavy AK (three or more AK/forearm), is designed to assess additional biomarker endpoints and potentially confirm the results of the published trial. This study will also determine whether the irritation reported by patients in the previous DFMO study can be reduced or eliminated by concurrent use of a topical corticosteroid.

A unique agent in human trials is Melanotan-I, a superpotent melanotropic peptide originally developed at the University of Arizona. In a recent trial, normal volunteers received 10 daily subcutaneous injections of Melanotan-1. Significant increases in Melanotan-1–induced tanning were seen in the forehead, cheek, and neck regions. Tanning was associated with a statistically significant increase in eumelanin levels of forearm skin biopsies [39•].

Several other NCI-sponsored NMSC prevention trials are ongoing (Table 2). A phase II randomized double-blinded, placebo-controlled trial at the University of California, Irvine (UCI), is studying topical green tea extract (Polyphenon E) in patients with at least two clinically and histologically confirmed AK on each arm. This study is designed to determine the ability of Polyphenon E to cause complete regression of AK, as well as effects on biomarkers and treatment duration. At the University of Maryland, the effect of oral fenretinide on clinical AK is being studied in a phase II randomized, double-blinded trial with parallel group design. This dose-finding trial is powered to determine if fenretinide can decrease the number of clinical AK by at least 80% in patients with at least 15 AK. This study will also evaluate biomarkers as well as the pharmacokinetics of oral fenretinide. The University of Alabama Comprehensive Cancer Center is coordinating a phase II/III randomized, placebo-controlled, double-blinded multicenter study of the effect of oral celecoxib on AK prevention/regression. This trial is expected to accrue 300 patients.

Table 1. Results of large (*n* >1000) randomized, controlled trials of NMSC chemoprevention

Population (*n*)	Intervention	Target	Risk ratio (95% CI)	Study
Previous NMSC (1805)	50 mg of β-carotene	NMSC	1.05 (0.91–1.22)	Greenberg *et al.* [33]
Recent NMSC (1312)	200 μg of selenium	BCC	1.10 (0.95–1.28)	Clark *et al.* [34]
		SCC	1.14 (0.93–1.39)	
Previous AK, <2 NMSC (2297)	25,000 IU of retinol	BCC	1.06 (0.86–1.32)	Moon *et al.* [29••]
		SCC	0.74 (0.56–0.99)*	
Queensland, Australia (1621)	30 mg of β-carotene	BCC	1.04 (0.73–1.27)	Green *et al.* [35]
		SCC	1.35 (0.84–2.19)	
Healthy males (22,071)	50 mg of β-carotene	NMSC	0.98 (0.92–1.05)	Frieling *et al.* [36]

*Statistically significant result.
AK—actinic keratosis; BCC—basal cell carcinoma; NMSC—non-melanoma skin cancer; SCC—squamous cell carcinoma.

Table 2. Recent and ongoing clinical studies of new NMSC chemopreventive agents

Agent	Phase	Results/objectives	Study and notes
Melanotan-I	I	Injections induced skin tanning and increased eumelanin content	Dorr *et al.* [39•]
Topical colchicine	II	Induced complete regression of AK in 70% of subjects	Grimaitre *et al.* [37]
Topical diclofenac	III	Induced significant reduction in AK burden	Approved October 2000
Topical DFMO	IIb	Induced significant reduction in AK burden and skin polyamines	Alberts *et al.* [38]
Topical DFMO	IIb	Analyzing efficacy in AK, biomarkers, and ability of triamcinolone to reduce DFMO-induced skin irritation	Ongoing, University of Arizona
Topical EGCG	Iia	Analyzing sun protection factor, safety	Ongoing, University of Arizona
Topical Polyphenon E	II	Analyzing efficacy in AK and biomarkers	Ongoing, UCI
Oral fenretinide	II	Analyzing efficacy in AK and biomarkers	Ongoing, University of Maryland
Oral celecoxib	II/III	Analyzing regression/prevention of AK and biomarkers	Planned, University of Alabama
Oral acitretin	II/III	Analyzing rate of NMSC and biomarkers in solid-organ transplant recipients with previous NMSC	Ongoing, NCCTG
Oral DFMO	III	Analyzing rate of new NMSC and biomarkers	Ongoing, UWCCC

AK—actinic keratosis; DFMO—difluoromethylornithine; EGCG—epigallocatechin gallate; NCCTG—North Central Cancer Treatment Group; NMSC—non-melanoma skin cancer; UCI—University of California, Irvine; UWCCC—University of Wisconsin Comprehensive Cancer Center.

Although most current chemoprevention studies are targeting IEN, at least two ongoing phase III studies are designed to determine the effect of chemopreventive agents on frank NMSC. Following positive phase II results [40], a North Central Cancer Treatment Group (NCCTG) phase II/III randomized, placebo-controlled study of acitretin is underway in solid-organ transplant patients with multiple prior NMSC. This study is expected to accrue 110 patients and will evaluate HPV as a possible etiologic factor. Treatment is expected to last 2 years, with patients followed every 6 months. The other trial is a randomized study of oral DFMO in patients with previously treated stage 0, I, or II BCC or SCC. This University of Wisconsin Comprehensive Cancer Center (UWCCC) study is expected to accrue 334 patients. Patients are followed every 6 months, and treatment is expected to extend for 3 to 5 years.

The Future: New Agents and Molecular Targets

Analysis of new agents and their mechanisms of action is a hot area in skin cancer prevention research. Advances in human genome research and the advent of new technologies for gene analysis add an exciting dimension to this field. As selective agents are developed for specific molecular targets, individual tailoring of preventive strategies based on genetic analysis may become possible [41••,42••]. Preclinical reports on new agents appear regularly in the literature. Molecular targets include cell-cycle and apoptosis regulators such as p53; second messenger systems linked to cell proliferation such as the mitogen-activated protein kinases (MAPK) and activator protein-1 (AP-1) complexes; and inflammatory mediators such as cyclooxygenase (COX). An understanding of mechanisms of action is crucial in clinical trial design and development of selective agents. Several promising new agents and their molecular targets are shown in Table 3.

Table 3. Mechanisms of selected potential new NMSC chemopreventive agents

Agent	Source	Target/mechanism
Apigenin	Chamomile	Stimulation of p53-p21/waf1
Celecoxib	NSAID	COX-2 inhibitor
EGCG	Green tea	Blocks p38 MAPK activation, antioxidant
Green tea extracts	Green tea	Antioxidant, various
Indomethacin	NSAID	Nonspecific COX inhibitor
Isothiocyanates	Cruciferous vegetables	Induction of phase II enzymes
Perillyl alcohol	Plant essential oils	Blocks AP-1 activation
Salicylates	NSAID	Blocks AP-1 activation
Silymarin	Milk thistle, artichoke	Inhibition of MAPK pathways, antioxidant

AP-1—activator protein-1; COX—cylcooxygenase; EGCG—epigallocatechin gallate; MAPK—mitogen-activated protein kinase; NSAID—nonsteroidal anti-inflammatory drug.

Apigenin, derived from chamomile, inhibits ornithine decarboxylase and stimulates the p53-p21/waf1 response pathway in mouse keratinocytes. This compound has been shown to inhibit UV-induced skin tumorigenesis when it is applied topically to mice [43]. Chemopreventive nonsteroidal anti-inflammatory drugs (NSAIDs) exert their activity mainly through inhibition of COX. The COX-2 selective inhibitor celecoxib, as well as the nonselective COX inhibitor indomethacin, have also been shown to reduce UV-induced skin carcinogenesis in a mouse skin model [44]. Green tea polyphenols, including epigallocatechin gallate (EGCG), are some of the most heavily studied chemopreventive compounds [45]. Topically applied EGCG has been shown to inhibit UV-induced skin carcinogenesis in a mouse skin model [46]. In this study, EGCG was applied topically to the backs of mice following UV irradiation. The mechanism of photocarcinogenesis inhibition by EGCG was distinct from a simple sunscreen effect or inhibition of photoimmunosuppression. In support of this finding, Chen *et al*. [47] have shown that EGCG blocks AP-1 activation by inhibiting phosphorylation of p38 MAPK, an important step in UV-induced skin carcinogenesis. Other agents that appear to block these pathways include perillyl alcohol [48], silymarin [49], and salicylates such as aspirin [50].

Conclusions

Research in non-melanoma skin cancer prevention is advancing. A combination of primary preventive strategies (reduced UV radiation exposure) and secondary preventive strategies (chemoprevention and treatment of IEN) offers the best hope for radically reducing incidence. Discovery of selective new agents with specific molecular targets, combined with new tools for genetic analysis, means that individually tailored strategies for NMSC prevention may soon be a reality.

Acknowledgments

This work has been supported by National Institutes of Health grants CA27502 and CA87991.

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