CME

Skin Cancer Prevention: Current Modalities and Future Implications

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Clinicians know that skin cancer is often preventable. But they may not be aware that SPF is not the only criterion for choosing a sunscreen—or that other agents show promise for protecting against this common malignancy.

Fostering prevention of skin cancer is an important part of medical practice, for federal practitioners as well as those in the private sector. Skin cancer is exceedingly common, and the incidence of nonmelanoma skin cancer (NMSC) continues to rise among elderly adults.[1] A recent study suggests the same may be happening among younger populations.[1] Veterans may be at increased risk for skin cancer, not only due to their age but also because of chronic sun or chemical exposure related to their military service.

In 2009, there were an estimated 68,720 new cases of melanoma[2]—the type of skin cancer that accounts for the most deaths. NMSC, which mostly consists of squamous cell carcinoma, is responsible for about one fifth of cancer-related deaths.[3]

Yet skin cancer is highly preventable—chiefly, by limiting the time spent in sunlight and by using an effective sunscreen. Clinicians need to educate patients about the importance of these and other preventive measures. In order to do this effectively, they must stay abreast of changes in the ways in which sunscreens are evaluated as well as the latest research into emerging preventive modalities. This article aims to bring federal practitioners up to date on these issues.

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CONTINUING MEDICAL EDUCATION

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GOAL

To educate practitioners about the latest research on skin cancer prevention, enabling them to offer patients the best possible guidance.

LEARNING OBJECTIVES

After reading the article and taking the test, participants should be able to:

1. Explain to patients how skin cancer develops and outline the major risk factors.
2. Evaluate the relative effectiveness of available sunscreens and provide advice for patients on sunscreen selection and application.
3. Describe the latest findings in chemoprevention research.

INTENDED AUDIENCE

This CME activity is designed for physicians and other clinicians treating patients in the federal health care system.

ACCREDITATION

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom Inc. Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

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CME PEER REVIEW

This article has been peer reviewed and approved for CME credit by Michael Fisher, MD, clinical professor, department of medicine (dermatology) at Albert Einstein College of Medicine, Bronx, NY. Review date: April 2010.

CONFLICT OF INTEREST STATEMENTS

The Conflict of Interest Disclosure Policy of Albert Einstein College of Medicine requires that authors participating in any CME activity disclose to the audience any relationship(s) with a pharmaceutical or equipment company. No author whose disclosed relationships prove to create a conflict of interest, with regard to his or her contribution to the activity, is permitted to contribute. These policies also require that authors participating in any CME activity disclose to the audience any discussions of unlabeled or investigational use of any commercial product or device not yet approved for use in the United States. **The authors report no conflicts of interest. The article discusses investigational or off-label use of DNA repair enzyme creams and systemic and topical retinoids for skin cancer prevention.**

The CME reviewer, Dr. Fisher, reports no conflict of interest. The staff of Albert Einstein College of Medicine Center for CME have no conflicts of interest with commercial interest related directly or indirectly to this educational activity.

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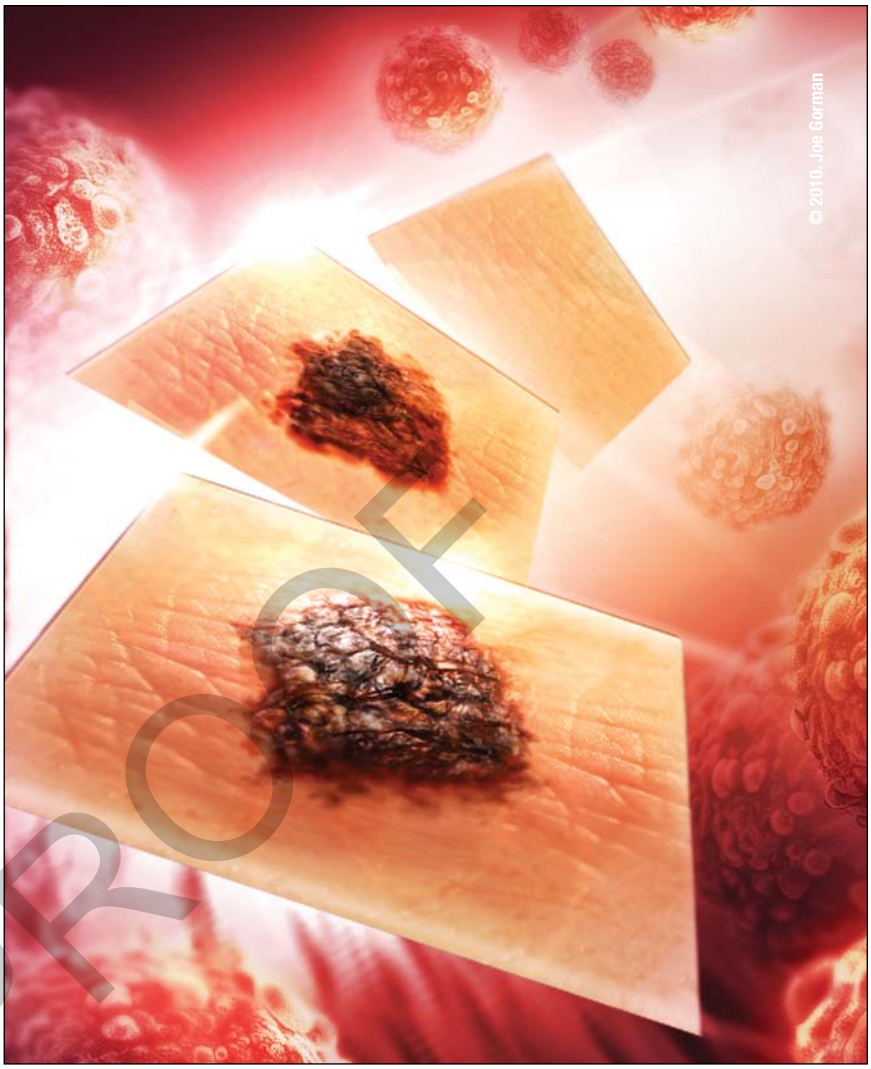
RISK FACTORS FOR SKIN CANCER

It is well known that exposure to ultraviolet (UV) light causes sunburn, resulting in DNA damage and immunologic alterations, which may lead to skin cancer.[4] Furthermore, UVA exposure generates reactive oxygen species, which damage DNA bases and other cellular molecules.[5] Chronic sun exposure is a major risk factor for development of both basal cell and squamous cell carcinoma of the skin, and intermittent intense sun exposure is correlated to risk for development of melanoma.[6]

Certain occupations may be associated with a higher risk for skin cancer. For instance, a 2004 study found an increased incidence of melanoma among white veterans exposed to dioxin-contaminated herbicides, such as Agent Orange, during the Vietnam War.[7] Other risk factors for development of skin cancer include fair skin or light hair, immunosuppression, genetic predisposition, ionizing radiation, and a history of multiple sunburns.[6] Aging also heightens risk because of its association with a significant decrease in the repair rates of both thymine dimers and photoproducts.[8]



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SUNSCREEN USE—SPF AND BEYOND

Sunscreens provide protection against damage to skin through absorption or reflection of UV radiation.[9] Compared with use of a placebo cream, sunscreen use has been associated with fewer new actinic keratoses and more remissions of existing lesions.[10] Furthermore, several studies have shown that sunscreens containing UVB and UVA filters provide better protection than sunscreens with UVB filters alone.[11] Additionally, daily photoprotection with a full–UV spectrum product significantly reduces solar-induced skin damage.[12] Although sunscreen's photoprotective effects are well established, its immunoprotective effects remain less clear.

A sunscreen's sun protection factor (SPF) is commonly used to indicate how well a particular product protects against sunburn and UV wavelengths, primarily UVB. SPF is likely a poor indicator, however, of how well a particular sunscreen protects against UVA-induced DNA damage and immunosuppression, especially after chronic exposure.[11,13] Indeed, even complete protection against sunburn may not prevent immunosuppression.[11,13] A study by Moyal and Fourtanier suggests that sunscreens with high UVA protection levels reduce UV-induced immunosuppression.[13] In light of these findings, the authors suggest that the labeling of each sunscreen product include its level of UVA protection.[13] Other authors have proposed that an immune protection factor (IPF) be developed as an alternative or adjunct to SPF.[14] To effect this recommendation, IPF parameters first would need to be standardized.

In August 2007, the FDA addressed this issue in a proposal to

regulate testing and labeling of sunscreens for UVA protection.[5] The proposed regulations use a categorical system to assess UVA protection as "low," "medium," "high," or "highest," similar to the star rating system already in use in Europe. Total UVA protection is determined by in vivo and in vitro testing. The in vivo method assesses persistent pigment darkening, while the in vitro method calculates the ratio of mean absorbance of UVA1 (which has wavelengths ranging from 340 to 400 nm) to mean total UV absorbance.[5]

Regardless of what labeling changes sunscreens undergo, patient counseling about proper use of sunscreen and photoprotection remains imperative. Many public health agencies recommend that patients reapply sunscreen every two to three hours. One study, however, found that more frequent reapplication enhanced protection.[15] The authors concluded that patients should apply sunscreen liberally to exposed areas 15 to 30 minutes before going out into sunlight, then reapply it 15 to 30 minutes later, if still exposed. Further reapplication is recommended after activities that could remove sunscreen, such as swimming, excessive sweating, or rubbing of the skin.[15] Whenever possible, patients also should wear clothing that shields the skin from the sun (such as hats, sunglasses, long-sleeved shirts, and pants) while outdoors. In addition, they should avoid UV radiation during peak sunlight hours (generally, from 10:00 AM to 4:00 PM).

Overall, sunscreen provides effective photoprotection and may provide immunoprotection, but it is unlikely to be effective once skin cell damage already has occurred. Nonetheless, there is a substantial need in the United States for sunscreen products with improved UVA protection.[5]

THE ROLE OF DIET

For decades, investigators have been studying possible associations between diet and skin cancer. It appears that dietary factors may sometimes influence the incidence of skin cancer. In the 1990s, Black and colleagues reported that a low fat diet was associated with reduced incidence of actinic keratosis and NMSCs in patients with a history of skin cancer.[16,17] In 2004, Middelkamp-Hup and colleagues demonstrated the photoprotective effects of the oral antioxidant *Polypodium leucotomos* (fern plant extract).[18] Following ultraviolet radiation, the group treated with the antioxidant had significantly less erythema than the untreated group.[18] Furthermore, histologic examination of the skin of treated subjects revealed a decrease in sunburn cells, cyclobutane pyrimidine dimers (CPDs), proliferating epidermal cells, and dermal mast cell infiltration.[18] Sunburn cells are evidence of DNA damage, CPDs and proliferating epidermal cells are predisposing factors for skin cancer, and dermal mast cell infiltration occurs as a result of skin immunosuppression and photoaging. This small study shows promising results for oral *Polypodium leucotomos* as a cancer chemophotoprotective agent, but additional research is needed.

Several studies also have addressed the benefits of isoflavones, flavonoids, and polyphenolic antioxidants as chemopreventive agents against cancer. Genistein (an isoflavone), silymarin (a mixture of flavonoids), epigallocatechin gallate (green tea extract), grape seed extract, lycopene (a carotenoid), and curcumin (a spice) have produced chemopreventive effects in murine models. Further investigations are necessary, however, to determine their efficacy in humans.[19] Vitamin E, beta carotene, and selenium previously were thought to protect against skin cancer, but subsequent research has demonstrated otherwise.[19]

ON THE HORIZON: CHEMOPREVENTION RESEARCH

Enzymatic therapy

DNA repair enzyme creams introduce DNA repair enzymes into human skin through topical application. Two common forms of these creams are T4 endonuclease V (T4N5), a bacterial enzyme, and photolyase, a xenogenic enzyme. These enzymes are encapsulated in liposomes, allowing them to be taken up by keratinocytes.[20] Within human skin cells, these enzymes reduce the quantity of CPDs.[9,20,21] This action is significant because CPDs, which form after UVB light exposure, have been linked to photocarcinogenesis in mammalian skin.[9] By decreasing CPDs, therefore, these enzymes may prevent both precancerous and cancerous skin lesions.[20,21]

To date, T4N5 has been used in the investigative setting to prevent skin cancer in patients with xeroderma pigmentosum, who have genetic defects in their DNA repair systems. In 2001, the Xeroderma Pigmentosum Study Group reported that topical T4N5 resulted in a 68% reduction in actinic keratoses and a 30% decrease in basal cell carcinomas in such patients.[22] In addition, the posttreatment rates of new lesions did not increase during the six months following therapy.[22]

Additionally, several studies have shown the effectiveness of T4N5 in patients without genetic defects. Yarosh and colleagues, for example, demonstrated that T4N5 liposomes enhance DNA repair in the keratinocytes of skin cancer patients.[23] And Gilchrest and colleagues reported that T4N5 treatment enhances UV-

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induced melanogenesis in human melanocytes, which decreases damage from subsequent sun exposure by increasing the amount of epidermal melanin.[24] In addition, Wolf and colleagues reported on the enzyme's immunoprotective effects after demonstrating that it almost completely prevented UV radiation–induced upregulation of interleukin-10 and tumor necrosis factor-α messenger RNA.[4] No significant effects on erythema response and microscopic sunburn cell formation, however, were seen. The chemopreventive properties of T4N5 in renal transplant recipients are currently under investigation.[19,25]

Studies of the effects of photolyase have shown similar results. Stege and colleagues demonstrated that photolyase prevented UVB-induced immunosuppressive effects.[9] Unlike T4N5, however, photolyase also prevented erythema and sunburn cell formation. In addition, CPD repair by photolyase results in keratinocyte upregulation of cytokine-induced intercellular adhesion molecule-1 (ICAM-1) expression.[20] ICAM-1 stabilizes cell-to-cell interactions and facilitates leukocyte endothelial transmigration. Furthermore, photolyase is "photoreactive," meaning that it requires light to be activated; it therefore can be a useful adjunct to sunscreens.[25]

Two additional DNA repair enzymes are UV endonuclease, from a UV-resistant microbe, and 8-oxoguanine glycosylase 1 (OGG1), from the *Arabidopsis* mustard plant. Both enzymes also are encapsulated within liposomes and delivered into skin cells following topical application. UV endonuclease removes damaged DNA by stimulating the skin's natural process of DNA damage repair.[25] OGG1 enters both the nucleus and mitochondria, where it repairs oxidative DNA damage.[25] Several in vitro studies have shown that both enzymes enhance DNA repair.[26–28] Further investigations are needed, however, to determine the enzymes' chemopreventive efficacy.

None of these enzymes currently is approved by the FDA for skin cancer prevention in the general population. These agents may well be used in the future, however, to prevent premalignant and malignant skin lesions.

Retinoid therapy

Studies have demonstrated that systemic retinoid therapy can prevent skin cancer in patients with xeroderma pigmentosum and in organ transplant recipients.[29–31] The exact preventive mechanism is mostly unknown, but current evidence suggests that antiproliferative and proapoptotic signals may be involved.[32]

Of the topical retinoids, tretinoin is the most thoroughly studied. It is deemed effective in the treatment of photodamaged skin and is FDA approved for this indication.[33] Yet evidence regarding its use in skin cancer prevention remains unclear. Several studies of using topical tretinoin to treat dysplastic nevi, potential precursors of melanoma, have shown that the agent has beneficial effects, including clinical and histologic improvement.[34–36] Conversely, one study demonstrated that most treated nevi still met histologic criteria for atypia and that many nevi returned to their baseline appearance six months after treatment ended.[37] This study, however, applied tretinoin only once a week under occlusion, unlike previous studies that used more frequent applications not under occlusion. Not only are more extensive trials needed to better establish tretonin's efficacy in treating dysplastic nevi, but the agent's role in melanoma chemoprevention remains debatable.

Whether tretinoin can prevent premalignant lesions and NMSC also has been addressed. A few studies have reported that topical tretinoin can produce complete regression of actinic keratosis and basal cell carcinoma,[38–40] but subsequent data have shown recurrences among patients in whom lesions have regressed.[41] Some authors have concluded, therefore, that topical tretinoin is less effective than other existing methods of treating actinic keratoses and basal cell carcinomas (such as cryotherapy or 5-fluorouracil).[41] When used in conjunction with topical 5-fluorouracil, however, tretinoin typically has been successful at treating actinic keratosis.[42] It appears, therefore, that, while tretinoin may not be as efficacious as other modalities for chemoprevention of premalignant and malignant lesions when used alone, it may be a useful adjunct to current therapy.

A recent VA topical tretinoin chemoprevention trial evaluated whether topical application of tretinoin decreased risk of keratinocyte carcinoma. The trial was ended six months early because of increased mortality in the group treated with tretinoin. After adjusting for minor imbalances in age, comorbidity, and smoking status, the difference in mortality between the randomized groups remained statistically significant.[43] Ultimately, the authors concluded that, although topical tretinoin therapy was associated with death, no causal association could be inferred.[43] The authors have not yet reported their findings on the efficacy of topical tretinoin as a chemopreventive agent.

WHERE WE ARE, WHERE WE'RE GOING

Presently, basal cell and squamous cell carcinoma of the skin are the most common malignant lesions in

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the United States, with more than one million new cases annually.[43] Furthermore, with continued depletion of ozone, UV-induced cellular damage and the incidence of both melanoma and NMSC may increase. Practicing preventive measures, therefore, is imperative. Although sunscreen currently is the only agent with a well-established role in skin cancer prevention, DNA repair cream and tretinoin also may be of benefit in the future. At this time, however, patient counseling regarding sunscreen use, annual skin examinations for selected individuals, and avoidance of solar radiation during peak sunlight hours remain the essential weapons in the fight against skin cancer.

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