

Skin Cancer Prevention: A Review of Current Oral Options Complementary to Sunscreens

Marie Stoddard MD,^a Alexis B. Lyons MD,^b Ronald L. Moy MD^c

^aDepartment of Dermatology, University of Michigan, Ann Arbor, MI

^bDepartment of Dermatology, Henry Ford Hospital, Detroit, MI

^cMoy, Fincher, Chipps Facial Plastics & Dermatology, Beverly Hills, CA

ABSTRACT

The incidence of non-melanoma skin cancer (NMSC) is dramatically increasing worldwide, despite the increased use of improved sunscreens. In 2014, the Surgeon General estimated that 2.2 to 5.0 million people are treated annually for NMSC.^{1,3} For decades, recommendations for sun protection have remained insufficient; subsequently, the numbers of newly diagnosed skin cancers continue to rise, and there is a need for additional preventative measures beyond sunscreens. The objective of this article is to review current oral prescription medications as well as supplements that may play an important role in skin cancer prevention.

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BACKGROUND

NMSC still remains the most common cancer in the United States,⁴ with its incidence increasing in both men and women under the age of 40.⁵ There is an estimated 3.5 million cases of NMSC diagnosed in 2 million people in the United States, which equates to a more than 300% increase in NMSC incidence from 1994 to 2015.^{4,7} More than 2.8 million new cases of basal cell carcinoma (BCC) and 1 million new cases of squamous cell carcinoma (SCC) are diagnosed annually in the United States,^{2,6} costing 8.1 billion healthcare dollars annually.⁴ Exposure to ultraviolet (UV) radiation remains the biggest risk factor for the development of skin cancer, and people are receiving more UV radiation today than ever before.^{7,9} Lifestyles where more time is spent outdoors, an eroding ozone layer, and a generally aging population with more cumulative sun damage have all contributed to this increased UV exposure.^{9,10}

Traditionally, skin cancer prevention has focused on sun protection, and recommendations have included wearing protective clothing, using sunscreens with a sun protective factor of 30 or higher, and avoiding the sun.¹¹ However, because skin cancer incidence continues to rise, additional preventative methods beyond photoprotection alone, more specifically, methods that repair past DNA damage, are needed. Through myriad mechanisms, non-prescription and prescription medications, administered orally, may play a role in skin cancer prevention (Table 1).

Decreasing DNA Damage Through Antioxidant Supplementation and Low-Fat Diet

Carotenoids

Free radicals produced from both by-products of cellular metabolism and environmental toxins damage DNA, and as

damage accumulates, cancers may develop. By neutralizing free radicals, carotenoids can assist in cancer prevention.¹²⁻¹⁴ Concerning skin cancer specifically, carotenoids like lutein and zeaxanthin have been shown, both in murine and human models, to provide significant protection against UV-induced skin injury by reducing mast cell infiltration, edema, and epidermal hyperplasia from UV exposure.^{14,15} Moreover, irradiated mice receiving dietary lutein and zeaxanthin grow fewer and smaller tumors and have increased tumor-free survival durations when compared to controls.¹⁴

The protective effects of oral antioxidants have been shown in human populations as well. In a cohort of Australian patients with a history of skin cancer, high dietary intake of lutein and zeaxanthin (2.9 mg/day) for 6 months in duration was associated with a more than 50% reduction in risk of SCC in 294 persons with a previous history of SCC (n=90), BCC (n=191), and unknown skin cancer (n=46) during an 8-year follow-up period.¹⁵ Analysis according to specific past history of SCC was not possible due to the small number of persons (n = 90) known to have a previous SCC before the initial skin examination. Further, after multivariate adjustment, the intake of lutein and zeaxanthin exhibited an inverse trend with SCC risk. In another study conducted in a similar population of 1,056 Australian adults, there was an inverse association between a 6-month period intake of green leafy vegetables (31g/day), a source of lutein and zeaxanthin, and risk of SCC over an 11-year follow-up period.¹⁶ Likewise, these results were only seen in those with a previous history of SCC. In both studies, no side effects were reported.^{15,16} While these studies suggest that oral antioxidants may be helpful for preventing SCCs, data for BCC prevention remains less clear. Some studies have shown decreased risk of BCCs, while others have shown the opposite.^{13,14} Additional

TABLE 1.

| Antioxidants, Dietary Supplementation, and Oral Prescription Medications Implicated in Skin Cancer Prevention | | | |
|---|---|--|------------------------|
| Oral Agent | Proposed Mechanism of Action | Sources | Dose Studied in Humans |
| Carotenoids (Lutein and Zeaxanthin) | An antioxidant that helps to prevent DNA damage | Kale, spinach, broccoli, egg, corn, romaine lettuce, paprika, cayenne pepper | 2.9mg/day |
| Polypodium Leucotomos | Photoprotective benefits and antioxidant properties | Dietary supplement | 480mg/day |
| Nicotinamide (Vitamin B3) | Boosts DNA repair | Tuna, chicken, salmon | 1000mg/day |
| Green Tea Polyphenols | A phytochemical that induces DNA repair via the induction of IL-12 in keratinocytes | Green tea | 1080mg/day* |
| Folic Acid | Provides precursor molecules for DNA repair and stabilizes DNA | Spinach, parsley, and romaine lettuce | 1.2mg/day |
| Oral Retinoids (Acitretin and Etretinate) | Initiates growth arrest in tumor cells, induces normal cellular differentiation, and immunomodulation | Oral prescription | 25-50mg/day |
| COX-2 Inhibitors (Celecoxib) | A non-steroidal anti-inflammatory drug that reduces inflammation-induced carcinogenesis | Oral prescription | 200mg/day |

*The results of this study were not statistically significant

research is needed to better elucidate the relationship between carotenoids and skin cancer prevention, but studies to date suggest an overall protective effect of oral antioxidants.

Polypodium Leucotomos

Derived from a tropical fern plant, polypodium leucotomos (PL) has been shown, both in vitro and in vivo, to decrease the prevalence of UVB-induced neoplasms of the skin.¹⁷⁻¹⁹ Its effects stem from its ability to enhance the activity of the endogenous antioxidant system that functions to block the formation of reactive oxygen species.²⁰ PL extract contains potent oxidation inhibitors caffeic and ferulic that may help achieve this. In irradiated mice supplemented with PL, histological cutaneous photodamage was less significant than in non-supplemented control mice.¹⁸ Specifically, treated mice showed increased dermal thickness and less dermal elastosis than controls.¹⁹ Further, fewer epidermal sunburn cells were detected in treated mice, and 12 out of 23 control mice developed SCCs, while just one treated mouse developed a single SCC tumor.¹⁹ In similar human studies, 9 patients who took oral PL (480mg/day) showed decreased skin erythema, edema, and post UV induced hyperpigmentation after UV exposure, without side effects.^{17-18, 20} Together, these results suggest that PL has the ability to mitigate UV radiation-associated skin damage and some skin cancers. These studies signify a potential beneficial role in skin cancer prevention.^{17, 22}

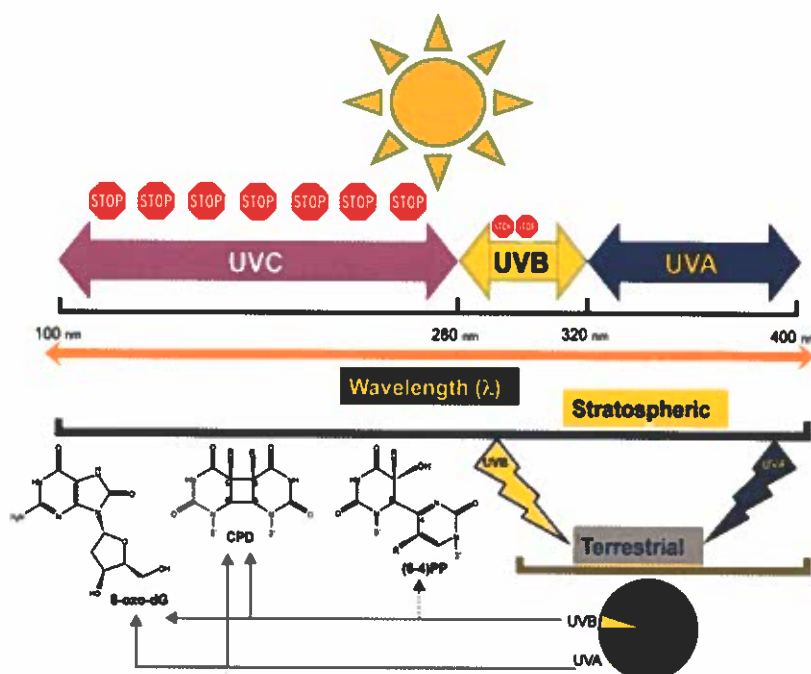
Low-Fat Diet

For decades, good nutrition has been correlated with cancer prevention, but there is conflicting data confirming that low-fat diets prevent skin cancer.²³⁻²⁶ Pertaining to the skin specifically,

a diet consisting of lean meats, fish, skinless poultry, and low-fat foods, has been shown to significantly decrease AKs and NMSC.²³ Black and colleagues found that within a 24-month period of 115 patients, the risk of developing new AKs in the low-fat diet group, consuming 21% of calories from fat, was 4.7 times less than the control group consuming 40% of calories from fat.²⁴ The mechanism behind this may relate to antioxidant production. Processing of ingested fat results in significant lipid peroxidation that generates free radicals. A low-fat diet that requires less lipid peroxidation may result in an overall decreased number of reactive oxygen species generated.^{23-24, 26-27} Because of this, low-fat diets, in theory, may be considered more "antioxidant" than higher fat diet diets and ultimately lead to less accumulated DNA damage. Further studies are needed to better expose the relationship between low-fat diet and skin cancer prevention, specifically.

Augmenting DNA Repair

Both the accumulation of DNA damage by UVA and UVB as well as the failure of DNA repair contribute to the development of NMSC. UV exposure alters DNA base-pairing, which results in either cyclobutane pyrimidine dimers, 6-pyrimidine-4-pyrimidone, or 8-Oxo-2'-deoxyguanosine photoproducts (Figure 1).¹⁰ Because accumulation of these photoproducts erodes genetic integrity and eventually contributes to skin cancer development, innate DNA repair systems exist to fix such UV-induced damage.¹⁰ While these systems are critically important, they are not perfect and may be overwhelmed. Thus, boosting these repair mechanisms with oral supplementation represents another way to enhance skin cancer prevention.

FIGURE 1. Major UVB- and UVA-induced DNA photoproducts at different wavelengths.¹⁰

Dietary supplements, including vitamins, minerals, amino acids, and enzymes, are products that contain ingredients intended to add further nutritional value to the regular diet. Supplements may be helpful in repairing damaged DNA, either directly or indirectly, by acting as biological cofactors.²⁸⁻²⁹ Evidence suggests that several key micronutrients including nicotinamide, green tea polyphenols, and folic acid are involved in the DNA repair process, which may act to help prevent skin damage.³⁰⁻³³ The deficiency of vitamins, like folic acid, mimic the effects of radiation by causing single- and double-stranded DNA breaks, oxidative stress, or both.³⁰

Nicotinamide

Functioning as a metabolic equivalent to nicotinic acid, nicotinamide, also known as niacinamide, is the active, water-soluble form of niacin (vitamin B3) that, unlike niacin, does not cause vasodilatory side effects such as flushing, hypotension, itching, and headaches.³¹ Foods rich in this essential vitamin include chicken, salmon, and tuna.^{31,35} Nicotinamide is vital to nicotinamide adenine dinucleotide (NAD), which is a coenzyme needed for cellular ATP production and a substrate for various DNA repair enzymes.^{31,35} Without nicotinamide, the cellular pool of NAD reduces, thus decreasing adenosine triphosphate (ATP) production needed for repair, and increasing the likelihood of DNA damage.³⁶⁻³⁹

It has been hypothesized that by boosting DNA repair, supplementation with nicotinamide after UV damage may help prevent the development of skin cancers. Indeed, oral nicotinamide has

been shown to both significantly decrease UV-induced immunosuppression and decrease skin cancer incidence in human populations.^{36,39} In a recent 2018 study, it was concluded that oral supplementation of 1000mg of vitamin B3 daily increased NAD⁺ bioavailability in the blood by 60%, when compared to the placebo group.⁴⁰ This finding provides further evidence on the vitamin's ability to potentiate DNA repair. In another report, 386 patients taking 500 mg of nicotinamide twice daily experienced a 23% decrease in skin cancer development over a 12-month treatment period compared to controls.³⁹ However, once the supplement was discontinued, its protective effect diminished. Study participants reported no side-effects, and the vitamin was well-tolerated. Although more research is needed, oral nicotinamide appears promising as the most effective skin cancer prevention supplement.

Green Tea Polyphenols

Green tea is derived from the *Camellia sinensis* species of the Theaceae family, and contains several polyphenols including epigallocatechin-3-gallate (EGCG), which is considered a major green tea polyphenol (GTP). Several studies have implicated GTP as an anti-carcinogenic agent that can prevent the development of UV-induced skin cancer.³²⁻³³ In vitro studies by Schwarz et al. showed that the treatment of normal human keratinocytes with GTP reduced UVB-induced DNA damage.⁴¹ It is hypothesized that such effects are mediated by the secretion of interleukin (IL)-12 by keratinocytes, which was previously shown to induce DNA repair.⁴¹ In a murine study, oral supplementation with 6mg GTP daily decreased tumorigenesis; specifically, 85%

of mice who were irradiated and supplemented with GTP developed skin tumors, while 100% of non-supplemented mice developed tumors.⁴¹ Further, the latent period prior to the onset of the first tumor was prolonged in the treatment group by two weeks.⁴¹ In another study, Mantena et al. showed that oral administration of 2g/L GTP to UVB-exposed mice decreased tumor incidence by 35%, when compared to placebo.⁴² In addition, tumor multiplicity and growth were reduced by 63% and 55%, respectively.⁴² Thus, administration of oral GTP may prevent skin cancers. Such a conclusion is yet to be determined in the human population, as there are conflicting data pertaining the inability of 1080mg GTP to reduce skin erythema or leukocyte infiltration in response to UV radiation, despite evidence showing their bioavailability in skin.⁴³⁻⁴⁴ Further studies are needed to explain the relationship between GTP and skin cancer prevention, specifically.

Folic Acid

Folic acid plays a role in skin cancer prevention by providing precursor molecules for DNA repair and by stabilizing DNA via its donation of methyl groups.⁴⁵ Folate deficiency results in increased chromosomal breaks and a subsequent increase in epithelial cancers.³⁰ Likewise, when cancer cells are folate-deprived, there is a significant increase in incidence of tumor development in mice.⁴⁶ Although specific human trials have not been performed in regards to its role in preventing skin cancer, it is possible that either increasing intake of foods rich in folic acid like spinach, parsley, and romaine lettuce,^{45,46} or taking a folic acid supplement (1.2mg/day) may help prevent skin cancer development by assisting in DNA repair.³⁰

Regulating Gene Transcription

Retinoids

Retinoids are vitamin A analogues that interact with nuclear receptors to influence transcription of specific genes. Proposed mechanisms by which they either inhibit or decrease skin cancer development include initiation of growth arrest or apoptosis of tumor cells, induction of normal cellular differentiation, and immunomodulation.^{8,47} The role of high dose systemic retinoids in skin cancer chemoprevention was first recognized in patients with xeroderma pigmentosum. Kraemer et al. demonstrated that 2mg/kg/day oral isotretinoin can be used for preventing premalignant AKs as well as NMSCs.⁴⁸ Specifically, treatment with oral isotretinoin resulted in a mean reduction of NMSCs by 63%. Oral retinoids have also decreased development of NMSCs in patients with a history of prior skin cancers.⁴⁹ Kelly et al. showed the efficacy of etretinate at decreasing the rate of new SCCs in renal transplant recipients.⁵⁰ A 50 mg per day dose for 12 months reduced tumors from 23 to 6 in four subjects. Similar results with other oral retinoids have been reported by numerous investigators.⁴⁹⁻⁵¹ In a prospective randomized control trial, George et al. demonstrated that patients supplemented with 25mg/day oral acitretin developed significantly

fewer SCCs than those in the drugfree group.⁵² A similar, yet not significant, trend was observed for BCCs.

Although oral retinoids offer clear chemopreventative benefits, these prescription medications are difficult to maintain long term, given their numerous side effects, including increased serum triglycerides, abnormal liver-function tests, and arthralgias.^{48,53,54} Moreover, once these medications are discontinued, some patients experience a rebound effect, and tumor development can accelerate.^{53,54} Patients are often committed to long-term use of these agents, which can be challenging. Thus, although oral retinoids can prevent skin cancers, they are often reserved for the highest risk patients where their benefit outweighs their high cost of substantial toxicity.

Decreasing Inflammation

Cyclooxygenase-2 Inhibitors

Inflammation has been linked to carcinogenesis, and studies have shown that cyclooxygenase-2 inhibitors (COX-2) are overexpressed in multiple neoplasms, including NMSC and precursor AK lesions.^{55,56} COX-2 inhibitors may therefore play a role in preventing cutaneous malignancies. Elmetts and colleagues assessed the efficacy and safety of 200mg/day celecoxib, an oral selective COX-2 inhibitor, as a chemopreventive agent for AKs.⁵⁷ Although there was not a significant difference in number of AKs developed during the treatment period, fewer NMSC were found in those patients taking COX-2 inhibitors, with 84% of participants reporting at least one adverse event including infections, gastrointestinal disorders, and skin rashes.⁵⁷ This preferential effect of celecoxib targeting later stages of tumor growth is consistent with findings of colorectal adenoma trials using celecoxib.^{58,59} Although the precise mechanism for these unexpected results is not known, it is proposed that it may be due to mechanisms by which celecoxib could inhibit the progression of premalignant keratinocytes to invasive malignancies.⁵⁷ Because this is a single study, repeated trials should investigate the potential of COX-2 inhibitors as skin cancer chemo preventative agents.⁵⁷ Most recently Johannesdottir and colleagues examined the use of aspirin, nonselective NSAIDs, and selective COX-2 inhibitors in 1,974 cases of SCC, 13,316 cases of BCC, and 3,242 cases of MM from 1991-2009 in northern Denmark. They found that overall, use of greater than 2 NSAIDs was associated with a decreased risk of SCC and MM, especially for seven years or longer.⁶⁰ Similarly, researchers the United Kingdom looked at 65,398 patients with BCC and 7,864 patients with SCC between 1995-2013. They compared prior NSAID use between cases and controls and found no association between NSAID use and BCC, but a suggested reduction of BCC risk in regular users of aspirin and ibuprofen, specifically. The risk of SCC was slightly decreased in regular users of any NSAIDs. These findings demonstrate patients predisposed to NMSC might benefit from NSAID chemoprevention.⁶¹

CONCLUSION

Skin cancer is a major and growing public health concern. As its incidence increases, additional attention must focus on skin cancer prevention. An improved preventative strategy can not only begin to lower skin cancer incidence, but also decrease morbidity, mortality, and healthcare dollars spent on treatment. Current clinical studies on oral antioxidants, dietary supplements involved in DNA repair, retinoids, and COX-2 inhibitors all show promise as agents that will not only prevent skin cancer, but also save valued healthcare dollars. In addition, the possibility of combining such oral preparations, like PL or oral nicotinamide, may offer additional benefits and enhance UV protection. Currently, the evidence that exists demonstrates that 500mg oral nicotinamide, twice daily, along with polypodium leucotomos, are the best oral supplements that prevent non-melanoma skin cancer.

DISCLOSURE

The authors have no relevant conflicts of interest to report.

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AUTHOR CORRESPONDENCE

Alexis Lyons MD

E-mail:..... alexisblyons@gmail.com



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