Nicotinamide for Skin Cancer Chemoprevention

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To stem the ever-rising incidence of both melanoma and nonmelanoma skin cancers and help prevent recurrences, we urgently need effective, nontoxic and affordable chemopreventive options. Recent discoveries about nicotinamide, aka vitamin B3, offer a promising new possibility.

The Limitations of Current Chemopreventives

Nonmelanoma skin cancers, predominantly basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most common and thus the costliest cancers in fair-skinned populations. Despite public health campaigns to raise awareness of the need for sun protection, the incidence of skin cancer continues to increase in our aging populations, and even those with multiple previous skin cancers use sunscreen suboptimally. Oral retinoids such as acitretin are the current mainstay for chemoprevention in patients at extreme skin cancer risk, primarily those with multiple SCCs. Although retinoids can reduce skin cancer incidence, they carry significant side effects, potentially including liver dysfunction and lipid abnormalities, dry skin and eyes and teratogenicity. Nonsteroidal anti-inflammatory drugs may also effect some reduction in BCCs and SCCs, but confirming the nature and magnitude of their effects will require phase 3 randomized trials.

While great advances continue to be made in the treatment of skin cancer, prevention will always remain the best form of “cure.” With one in five Americans developing the disease, incidence still rising and often exorbitant costs involved in management (especially for advanced cancers), the need for effective chemopreventive agents has never been clearer.

Some of these agents, such as sunscreen ingredients, function as primary preventives, by blocking the DNA damage that can initiate carcinogenesis, while others inhibit, reverse or retard the progression of premalignant cells in which damage has already occurred. Ideally, they should be easy to administer, low-cost, have a proven mechanism of action and have few to no side effects.

To date, considerable research has focused on using vitamins and phytochemicals as antioxidants to combat oxidative stress. Vitamins E and C, polyphenols in green tea, silymarin in artichokes, curcumin in turmeric, lycopene in tomatoes, resveratrol in grapes, gingerol in ginger, genistein in soybeans and beta-carotene in yellow vegetables are all known antioxidants that may lower the risk of cancer development. The prevailing view is that by destroying free radicals (highly reactive, damaging cells generated by natural internal processes or external insults such as UV), antioxidants...
Nicotinamide’s Photoprotective Effects in Vitro and in Vivo

Both nicotinamide (niacinamide) and nicotinic acid (niacin) are forms of vitamin B3. The recommended daily intake is ~20 mg, readily obtainable from foods such as legumes, cereals, meat, fish, eggs, milk and yeast. Vitamin B3 deficiency (pellagra) is characterized by a striking photo-distributed dermatitis, diarrhea, dementia and, if untreated, death. Nicotinamide deficiency is now rare in developed countries, but is occasionally seen in the context of alcoholism, dietary restriction and malabsorption syndromes.6

 Whereas nicotinic acid causes a range of vasodilatory side effects such as headache, flushing and hypotension, nicotinamide lacks these adverse effects and has an established safety profile at doses up to 3 g daily.7 Nicotinamide has anti-inflammatory effects at pharmacological doses, and physicians use it at 1.5 g daily in the treatment of autoimmune blistering disorders such as bullous pemphigoid.8

 Ultraviolet (UV) radiation is the prime cause of both melanoma and nonmalignant skin cancer. If not correctly and promptly repaired, DNA photolesions in the skin can evolve into mutations. Both UVB (290-320 nm) and UVA (320-400 nm) cause cyclobutane pyrimidine dimers (CPDs) and oxidative DNA damage (8 oxoguanosine; 8oxoG), although UVB mainly causes CPDs and UVA predominantly causes oxidative photolesions.9 DNA repair efficiency declines with age,10 which may contribute to the increased incidence of skin cancer in older individuals. Oxidative DNA damage also occurs in unirradiated skin cells as a result of reactive oxygen species produced intracellularly in the course of normal cellular metabolism.11,12 Melanocytes are thought to have less efficient DNA repair mechanisms than keratinocytes,13 which may contribute to the higher basal levels of oxidative DNA damage in melanocytes.12

 Photodamaged DNA is rapidly repaired in the presence of normal DNA repair mechanisms, but this process is highly energy-intensive. UV radiation not only damages DNA, but also depletes cellular ATP at this time of greatest energy demand.14 As a precursor of nicotinamide adenine dinucleotide (NAD+), nicotinamide is an essential cofactor in ATP production. Nicotinamide replenishes cellular ATP levels in human keratinocytes after UV exposure, largely by enabling glycolysis14 to occur at a rate similar to that of unirradiated cells. This energy-replenishing effect is thought to be a key mechanism by which nicotinamide enhances DNA repair. It increases the rate of repair of both CPDs and 8oxoG in UV-irradiated human HaCaT keratinocytes,11 in normal human melanocytes15 and in ex vivo irradiated whole human skin (Figure 1).11 Nicotinamide has no discernible effect on expression of p53 or of HOGG1, a key enzyme in 8oxoG repair.11

 Along with their other deleterious effects, unrepaired DNA photolesions are a key trigger for the immunosuppressive effects of UV radiation.15 This UV-induced suppression of antitumor immunity enhances the progression of skin cancers. There is also evidence that individuals with a history of skin cancer are intrinsically more susceptible to the immunosuppressive effects of sunlight.16 Agents that enhance DNA repair, such as liposomes containing the DNA repair enzyme T4N5, have been shown to reduce the immunosuppressive effects of UV exposure.15 We found that nicotinamide, delivered either topically or orally to healthy human volunteers, reduced UV immunosuppression caused by suberythemal and minimally erythematous doses of solar-simulated UV radiation (UVB + UVA).17,18 Nicotinamide afforded equivalent immune protection against both shortwave UVB and longwave UVA radiation18 and was immunoprotective when administered either after or before UV exposure.19 Neither topical nor oral nicotinamide altered sunburn threshold (minimal erythemal dose) in our volunteers;17-19 hence, nicotinamide is not acting as a UV filter.

![Figure 1. Human skin irradiated ex vivo with low-dose solar-simulated UV radiation (4J/cm²) shows extensive epidermal cyclobutane pyrimidine dimers (immunohistochemistry using red chromogen staining) in the presence of vehicle lotion (a). Numbers of red-stained photolesions are reduced in skin pretreated with nicotinamide (b). Similarly, levels of oxidative DNA photolesions (8oxoG; red chromogen staining) in irradiated skin (c) are reduced to levels equivalent to those seen in unirradiated epidermis, when the irradiated skin has been pretreated with nicotinamide (d).11 All images taken at 45 minutes after UV irradiation.](image-url)
Rather, by preventing UV-induced energy depletion, nicotinamide attenuates two key pathways to carcinogenesis: DNA damage and UV-induced immunosuppression (Figure 2).

**Nicotinamide Reduces Actinic Keratoses**

We assessed the effect on premalignant actinic keratoses (AKs) of 1 percent nicotinamide lotion twice daily compared with base (placebo) lotion in 30 heavily sun-damaged Australians. Within three months we found a 21.8 ± 10 percent reduction in AKs in the nicotinamide group compared with a 10 ± 12 percent reduction in the placebo group (p=0.04). Further phase 2 studies using oral nicotinamide at doses of 500 mg once daily or twice daily found significant reductions in AK counts, 29 percent and 35 percent respectively compared to placebo, within four months, in groups of patients with an average of 30 to 35 AKs each at baseline. These studies strongly suggested that oral nicotinamide might also reduce nonmelanoma skin cancers; in the cohort of 74 participants in the two studies, 11 individuals in the placebo groups developed a total of 20 new skin cancers within four months, compared with only four new skin cancers in two participants in the nicotinamide arms. However, skin cancer prevention was not a primary endpoint of these early studies, so we designed a phase 3 multicenter, randomized controlled trial to address this question.

**Oral Nicotinamide Reduces Nonmelanoma Skin Cancers In High-risk Patients**

Oral nicotinamide at 500 mg twice daily resulted in a slightly greater and more rapid reduction in AKs compared with 500 mg once daily in our phase 2 AK studies; in contrast, we observed that levels of protection against UV immunosuppression were not substantially greater with 500 mg thrice daily compared with 500 mg once daily. Hence, we designed a phase 3 multicenter double-blind randomized controlled trial for skin cancer chemoprevention, using nicotinamide at an intermediate dose of 500 mg twice daily. The ONTRAC study (Oral Nicotinamide to Reduce Actinic Cancer) recruited 386 immune-competent participants at two tertiary referral hospitals in Sydney, Australia. We selected high-risk individuals who had had at least two histologically confirmed nonmelanoma skin cancers in the previous five years. Participants were randomized 1:1 to receive nicotinamide 500 mg or matched placebo twice daily for 12 months, with dermatologist skin checks every three months during that period and for six months post-intervention. Secondary end points included AK counts checked every three months for 12 months, BCC and SCC counts during the intervention period and skin cancer incidence six months post-intervention. We found a 23 percent relative rate reduction in new nonmelanoma skin cancers (BCCs and SCCs) in the nicotinamide arm within the 12-month intervention period (p=0.02), after adjustment for the different research centers’ protocols and the patient’s number of previous skin cancers in the past five years (27 percent unadjusted relative rate reduction). There were similar magnitudes of reduction for BCCs and SCCs separately, with a trend to greater chemopreventive efficacy in individuals who had the highest number of previous skin cancers. We noted reductions in skin cancer counts as early as the first three-month visit, but the beneficial effect of nicotinamide was rapidly lost post-intervention; skin cancer rates in the six-month follow-up period were no different in the placebo and nicotinamide groups. We found that gender, age, number of AKs, statins and nonsteroidal anti-inflammatory drug

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**Figure 2.** UV radiation both damages DNA and depletes cells of the energy required for efficient DNA repair, thus increasing the likelihood of genetic mutations that can lead to skin cancer. Unrepaired DNA photolesions are also a trigger for the immunosuppressive effects of sunlight. By preventing UV-induced energy crisis in skin cells, nicotinamide both enhances DNA repair and attenuates UV immunosuppression.
use had no effect on nicotinamide efficacy. The only factor predicting efficacy was number of previous skin cancers; participants with the highest numbers of previous skin cancers showed greater relative reductions in skin cancers with nicotinamide.

Our ONTRAC cohort included a spectrum of patients ranging in age from 30 to 91 years (mean 66). Many of our patients had multiple medical comorbidities and were taking numerous concurrent medications. In this cohort, almost a quarter of patients experienced at least one hospitalization within the 12-month intervention period; there were 86 serious adverse event reports (some patients were hospitalized with multiple concurrent serious adverse events), with comparable numbers in the placebo and nicotinamide arms. In this medically diverse population, we found no increase in adverse events with nicotinamide compared with placebo. There were no notable differences in blood pressure, full blood count, renal function or hepatic function between the groups.

**Nicotinamide for Melanoma Chemoprevention**

DNA photodamage plays a central role in the genesis of melanoma as well as nonmelanoma skin cancer.22 The incidence of melanoma increases two- to seven-fold in immunosuppressed transplant recipients,23,24 and individuals with a history of melanoma also display greater susceptibility to UV immunosuppression than do controls.16 Hence, nicotinamide’s photoprotective actions in enhancing DNA repair and reducing the immunosuppressive effects of UV radiation may translate to chemopreventive efficacy against melanoma as well as nonmelanoma skin cancer.

Preclinical studies have shown that the photoprotective effects of nicotinamide in melanocytes are similar to those in keratinocytes. Normal human melanocytes irradiated with solar-simulated UV radiation demonstrated enhanced repair of both CPDs and oxidative DNA damage when cultured with nicotinamide.12 We found increased rates of unscheduled DNA synthesis (indicative of DNA repair) after UV exposure in the presence of nicotinamide, as well as reduced levels of DNA photolesions across the time course of DNA repair.12 We saw similar effectiveness in cell lines that were predominantly pheomelanin-producing or predominantly eumelanin-producing.12 Reactive oxygen species generated in the course of normal cellular metabolism produce a basal level of oxidative DNA damage; we found that this basal 8oxoG was higher in human melanocytes than in keratinocytes,12 consistent with previous findings that DNA repair mechanisms may be less effective in melanocytes.13 Interestingly, nicotinamide reduced levels of basal oxidative DNA damage in unirradiated cells as well as levels of UV-induced DNA damage.12

Given the findings of the ONTRAC study in nonmelanoma skin cancer, the similar carcinogenic pathways of melanoma and nonmelanoma skin cancer and the initial in vitro findings of enhanced DNA repair in melanocytes, clinical trials of nicotinamide for melanoma chemoprevention are now indicated. The ONTRAC study recruited participants at high risk of developing nonmelanoma skin cancer during the study; as anticipated, only a small number of melanomas arose during the 12-month intervention period (six melanomas in situ and four invasive melanomas, which were evenly distributed between the nicotinamide and placebo arms).2 A melanoma chemoprevention study would require a larger cohort comprising individuals selected for their high melanoma risk, such as those with previous melanoma, strong family history of melanoma and atypical nevus syndrome.

**Nicotinamide in Practice**

The ONTRAC study found that oral nicotinamide reduced nonmelanoma skin cancer by a quarter in a high-risk group, with comparable efficacy against both BCC and SCC. There was a trend to greater relative reduction in new skin cancers in those at highest skin cancer risk, possibly reflecting a greater susceptibility of these extreme-risk individuals to UV-induced immunosuppression and DNA damage.25 At this time, there is no evidence for the efficacy or appropriateness of nicotinamide chemoprevention in the broader population. Instead, physicians should consider it for chemoprevention in individuals with multiple previous nonmelanoma skin cancers. The lack of interaction of nicotinamide with most prescription and over-the-counter medications and its excellent safety profile over a large number of clinical trials make it worthy of consideration for this patient group. It is essential to ensure that patients take nicotinamide and not nicotinic acid, and maintain sunscreen use and regular skin checks in this high-risk group.

**What Next?**

Nonmelanoma skin cancer incidence is 50- to 80-fold higher in transplant recipients,24 and is highly elevated in immunosuppressed patients with hematological malignancies such as chronic lymphocytic leukemia.26 Melanoma is at least twice as likely to occur in transplant recipients.23 We now need data on nicotinamide’s chemopreventive efficacy and safety in immunosuppressed individuals, as well as assessment of nicotinamide’s efficacy in melanoma prevention.

**References**


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can help to prevent mutations leading to cancer. Despite all the research, however, the effectiveness of antioxidants has not been definitively proven.

New forms of chemoprevention have emerged. For example, certain chemicals such as oral retinoids, derivatives of vitamin A, are now believed to help prevent skin cancer by defusing proliferation through cellular differentiation. The treatment can entail serious side effects, however.

Yet another intriguing new method of chemoprevention, one with a good safety profile and few side effects, involves enhancing the body’s ability to repair UV-induced DNA damage. The first significant examples of this kind of chemopreventive were liposomes containing the DNA repair enzyme T4N5, shown to reduce the immunosuppressive effects of UV exposure. And in the past year, research led by Dr. Diona Damian in Australia has revealed that nicotinamide, a version of vitamin B3 and an essential cofactor containing the DNA repair enzyme T4N5, shown to reduce the immunosuppressive effects of UVB radiation on induction of contact hypersensitivity as a risk factor for skin cancer. J Invest Dermatol 1990; 95:530-6.


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