

## Nicotinamide Found to Reduce the Rate of Nonmelanoma Skin Cancers in High-Risk Patients

A recent study has shown that taking daily oral nicotinamide reduced the incidence of non-melanoma skin cancers and actinic keratoses in individuals at high risk (*N Engl J Med.* 2015;373:1618-1626). Nonmelanoma skin cancers are the most common type of cancer, with an estimated 3.5 million tumors diagnosed per year (American Cancer Society. *Cancer Facts & Figures 2015.* Atlanta, GA: American Cancer Society; 2015). In addition, it is estimated that 58 million Americans have been diagnosed with actinic keratosis, a premalignant lesion. Furthermore, the incidence of both non-melanoma skin cancer and actinic keratoses are on the rise worldwide.

Because nonmelanoma skin cancers and actinic keratoses are primarily caused by ultraviolet (UV) light exposure, sunscreen is the main recommendation for prevention. However, compliance with sunscreen use has proven to be challenging, and with the high prevalence and increasing incidence of these entities, researchers set out to investigate pharmacologic prevention.

Nicotinamide, an amide form of vitamin B3 believed to work by enhancing DNA repair and protecting the skin's immune system from UV light exposure, has been shown in preclinical studies and early clinical trials to

be active in attenuating UV-induced skin damage and decreasing the development of actinic keratoses, prompting this randomized clinical trial of nicotinamide for the prevention of nonmelanoma skin cancers.

Researchers at the Royal Prince Alfred and Westmead hospitals in Sydney, New South Wales, Australia, recruited patients who were aged 18 years or older and had been diagnosed with at least 2 nonmelanoma skin cancers within the previous 5 years. Patients diagnosed with invasive melanoma within the last 5 years were excluded. A total of 386 patients were randomized 1:1 to receive either 500 mg of nicotinamide or placebo twice daily for 12 months. Skin cancer checks were performed every 3 months for 18 months by dermatologists blinded to study treatment at baseline. The primary endpoint was the number of new nonmelanoma skin cancers, confirmed by pathological examination, through 12 months. Secondary endpoints were the development of new basal cell carcinoma, new squamous cell carcinoma, and actinic keratosis counts during the 12-month intervention; the number of new nonmelanoma skin cancers in the 6 months after the intervention; and the safety of nicotinamide.

### Study Results

There were a total of 463 non-melanoma cancers diagnosed in the placebo group and 336 in the intervention group over the 12-month intervention period. During this time, the mean number of cancers per person was significantly lower for the intervention group versus the placebo group (1.8 and 2.4, respectively). This

### KEY POINTS

- Daily nicotinamide significantly reduced the incidence of nonmelanoma skin cancers in high-risk individuals.
- It is reasonable to recommend nicotinamide in high-risk individuals along with continued sunscreen use and regular skin checks in motivated patients.
- Further studies including longer follow-up and a wider population of patients to assess for any unforeseen safety issues as well as efficacy are indicated.

represents a rate that was lower by an estimated 23% with the use of nicotinamide after adjustment for study center and nonmelanoma skin cancer history, and a reduction of 27% without adjustment ( $P = .02$ ). The rate of new nonmelanoma skin cancers was lower in the nicotinamide group at each 3-month visit during the 12 months that the drug was administered; however, the effect dissipated at the 6-month follow-up after nicotinamide was discontinued.

The reduction in the rate of new basal cell carcinomas specifically was an estimated 20% after adjustment ( $P = .12$ ), and the reduction was 30% for the development of new squamous cell carcinomas ( $P = .05$ ). At the 6-month follow-up after treatment with nicotinamide was stopped, there were no significant differences noted with regard to either rate.



Photo credit: Courtesy of American Cancer Society, Atlanta, GA.

The number of actinic keratoses specifically also was found to be significantly reduced, with an average of 3 to 5 fewer actinic keratoses observed from the baseline count in the nicotinamide group compared with the placebo group. Despite the fact that study participants were a high-risk population, only approximately one-half used sunscreen within the week before the study and the rate of sunscreen use in the nicotinamide group was lower throughout the study period compared with the placebo group. No differences in the number or type of adverse events were noted between groups.

“For patients who have already had a number of skin cancers, we believe nicotinamide should be considered as one part of their cancer prevention strategy,” says corresponding author Diona Damian, PhD, a professor in the department of dermatology at the University of Sydney and Royal Prince Alfred Hospital. “It’s important that patients take nicotinamide (niacinamide) and not the nicotinic acid (niacin) form of vitamin B3. Nicotinic acid causes vasodilatory side effects like headaches, hypotension, and flushing. We did not find these side effects with nicotinamide.”

Kenneth Tsai, MD, PhD, associate professor in the department of dermatology and department of translational molecular pathology at The University of Texas MD Anderson Cancer Center in Houston, raised some concerns about the patient population. “The spread in terms of [the] number of nonmelanoma skin cancers in the past 5 years was huge (2-61), so the effect may be dominated by specific subgroups,” says Dr. Tsai. “Also, one major high-risk group was excluded: the immunocompromised. A larger and longer randomized, placebo-controlled trial with a comparison arm to something like topical 5-fluorouracil or imiquimod would be important to do in a population that includes immunosuppressed individuals,” he adds.

### Clinical Implications

Nicotinamide reduced the development of basal cell carcinomas, squamous cell carcinomas, and actinic keratoses throughout a 12-month study period. The effects were observed as early as after 3 months of treatment, but no protection was evident 6 months after the drug was discontinued. With nicotinamide’s excellent safety profile, inexpensive cost, and wide availability, the authors conclude it is a worthwhile

intervention that can be easily translated into clinical practice.

“For high-risk patients, we are recommending that nicotinamide be considered now as a chemoprevention option together with ongoing sunscreen use and regular skin checks. Further studies in lower-risk individuals are needed before it is considered for the broader population,” says Dr. Damian. “The strength of our study was that our population mirrored what we see in our daily practice: our patients ranged in age from 30 to 90 years old, many had multiple comorbidities, and all had a history of multiple skin cancers. The main shortcoming was length of intervention and follow-up. Future studies could examine whether the beneficial effects of nicotinamide are maintained over longer time frames,” she says.

“Given it is safe, I do not see much of a downside for a motivated, high-risk patient as defined in the trial who can afford it. It’s cheap, but it’s not free,” says Dr. Tsai. “However, I do not think it is a practice-changer at this point, and current surveillance and preventive measures remain standard. Longer study to assess for unforeseen safety issues is absolutely required.”

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