

ORIGINAL ARTICLE

A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention

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ABSTRACT

BACKGROUND

Nonmelanoma skin cancers, such as basal-cell carcinoma and squamous-cell carcinoma, are common cancers that are caused principally by ultraviolet (UV) radiation. Nicotinamide (vitamin B₃) has been shown to have protective effects against damage caused by UV radiation and to reduce the rate of new premalignant actinic keratoses.

METHODS

In this phase 3, double-blind, randomized, controlled trial, we randomly assigned, in a 1:1 ratio, 386 participants who had had at least two nonmelanoma skin cancers in the previous 5 years to receive 500 mg of nicotinamide twice daily or placebo for 12 months. Participants were evaluated by dermatologists at 3-month intervals for 18 months. The primary end point was the number of new nonmelanoma skin cancers (i.e., basal-cell carcinomas plus squamous-cell carcinomas) during the 12-month intervention period. Secondary end points included the number of new squamous-cell carcinomas and basal-cell carcinomas and the number of actinic keratoses during the 12-month intervention period, the number of nonmelanoma skin cancers in the 6-month postintervention period, and the safety of nicotinamide.

RESULTS

At 12 months, the rate of new nonmelanoma skin cancers was lower by 23% (95% confidence interval [CI], 4 to 38) in the nicotinamide group than in the placebo group ($P=0.02$). Similar differences were found between the nicotinamide group and the placebo group with respect to new basal-cell carcinomas (20% [95% CI, -6 to 39] lower rate with nicotinamide, $P=0.12$) and new squamous-cell carcinomas (30% [95% CI, 0 to 51] lower rate, $P=0.05$). The number of actinic keratoses was 11% lower in the nicotinamide group than in the placebo group at 3 months ($P=0.01$), 14% lower at 6 months ($P<0.001$), 20% lower at 9 months ($P<0.001$), and 13% lower at 12 months ($P=0.001$). No noteworthy between-group differences were found with respect to the number or types of adverse events during the 12-month intervention period, and there was no evidence of benefit after nicotinamide was discontinued.

CONCLUSIONS

Oral nicotinamide was safe and effective in reducing the rates of new nonmelanoma skin cancers and actinic keratoses in high-risk patients. (Funded by the National Health and Medical Research Council; ONTRAC Australian New Zealand Clinical Trials Registry number, ACTRN12612000625875.)

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NONMELANOMA SKIN CANCERS, MAINLY basal-cell carcinomas and squamous-cell carcinomas, are the most common cancers in white populations.¹ In Australia, non-melanoma skin cancers are four times as common as all other cancers combined,^{2,3} and in the United States, the annual total cost of treating nonmelanoma skin cancers is estimated to be \$4.8 billion.⁴ Basal-cell carcinomas rarely metastasize but are locally invasive and can be disfiguring.⁵ Squamous-cell carcinomas, especially less well-differentiated tumors on the head and neck, have metastatic potential and may originate from premalignant actinic keratoses.⁶

Nonmelanoma skin cancers and actinic keratoses are caused primarily by exposure to ultraviolet (UV) radiation.⁷ The use of sunscreens can reduce the incidence of squamous-cell carcinoma⁸ and actinic keratosis⁹ and may also reduce the incidence of basal-cell carcinoma and melanoma after prolonged use.¹⁰ However, adherence to the application of sunscreens is often suboptimal, even among high-risk persons.¹¹ The increasing incidence of nonmelanoma skin cancer worldwide¹⁴ highlights the need for additional preventive measures.

UV radiation increases the risk of skin cancer by damaging DNA, suppressing cutaneous anti-tumor immunity,¹² and inhibiting DNA repair by depleting cellular ATP.¹³ Nicotinamide is an amide form of vitamin B₃ and the precursor of nicotinamide adenine dinucleotide (NAD⁺), an essential cofactor for ATP production. Nicotinamide prevents ATP depletion and glycolytic blockade induced by UV radiation,¹³ thereby boosting cellular energy and enhancing DNA repair.^{14,15} Nicotinamide also reduces the level of immunosuppression induced by UV radiation, which is triggered by DNA damage,¹⁶ without altering baseline immunity.^{17,18} Therapy with nicotinamide, administered orally in healthy volunteers at daily doses of 500 mg or 1500 mg, resulted in similar levels of protection against immunosuppression induced by UV radiation.¹⁸ Two phase 2, double-blind, randomized, placebo-controlled trials showed that among Australians with sun-damaged skin, the number of actinic keratoses at 4 months was 29% lower among those who received 500 mg of nicotinamide administered orally once daily and 35% lower among those who received 500 mg of nicotinamide twice daily than among those who received placebo.¹⁹ Given the activity of nicotin-

amide in these preclinical and early clinical studies, we conducted a multicenter, phase 3, double-blind, randomized, placebo-controlled trial (Oral Nicotinamide to Reduce Actinic Cancer [ONTRAC]) to assess the efficacy of oral nicotinamide for the chemoprevention of non-melanoma skin cancer in a high-risk population.

METHODS

STUDY DESIGN AND OVERSIGHT

The ONTRAC study was conducted at the Royal Prince Alfred and Westmead Hospitals in Sydney. The protocol of the study was approved by the human ethics committees of the University of Sydney and of each participating center, and all the study participants provided written informed consent. All the authors participated in the design of the study, collected the data, and contributed to the analysis or interpretation of the data (or both). All the authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the study to the protocol, which is available with the full text of this article at NEJM.org. The first author wrote the first draft of the manuscript; no one who was not an author contributed to the writing of the manuscript. The decision to submit the manuscript for publication was made by all the authors. There were no agreements regarding data confidentiality between the sponsor (University of Sydney) and the authors. The nicotinamide and placebo tablets used in the study were donated by the manufacturer (Blackmores), which had no role in the design of the study, in the accrual or analysis of data, in reviewing the manuscript, or in the decision to submit the manuscript for publication.

STUDY PARTICIPANTS

Eligible participants were 18 years of age or older and had had at least two histologically confirmed nonmelanoma skin cancers in the previous 5 years. Participants were ineligible if they were immunosuppressed; were pregnant or breastfeeding; had notably impaired liver or kidney function; had active peptic ulcer disease, a recent myocardial infarction, hypotension, a genetic skin-cancer syndrome, or large areas of confluent skin cancer (i.e., individual lesions that could not be counted); or had used nicotinamide supplements, oral retinoids, or field treatments for actinic keratosis, such as topical fluorouracil, in

the previous 4 weeks. Participants were also excluded if they had had metastatic cancer, invasive melanoma, or an internal malignant condition in the previous 5 years.

STUDY PROCEDURES

We randomly assigned participants in a 1:1 ratio to receive either 500 mg of nicotinamide (Inso-lar, Blackmores) twice daily or matched placebo. Randomization was performed centrally with stratification according to 5-year history of non-melanoma skin cancer (<6 vs ≥6 nonmelanoma skin cancers), sex, and study site. Nicotinamide and placebo were administered in identical coated tablets. Participants received either nicotinamide or placebo for 12 months, and adherence was monitored by two of the authors who counted the remaining tablets at each visit through 12 months. Skin-cancer checks were performed by dermatologists, who were unaware of the study-group assignments, at baseline and at visits at 3-month intervals (hereafter referred to as 3-month visits) for 18 months. Detected lesions that did not immediately warrant biopsy were monitored at subsequent visits, and if they were later found to be malignant on biopsy, the date of their initial detection was assigned as the date of detection for analyses. Actinic keratoses on the face, scalp, forearms, and hands were counted by means of palpation and observation at baseline and at the 3-month visits through 12 months by a single author at each site, who was unaware of the study-group assignments.

The histologic diagnosis of skin cancer was made by histopathologists at each site according to routine clinical practice. All new squamous lesions, including invasive squamous-cell carcinoma, keratoacanthomas, Bowen's disease (squamous-cell carcinoma in situ [full-thickness epidermal dysplasia]), and actinic keratoses (partial-thickness epidermal dysplasia),²⁰ and new high-risk subtypes of basal-cell carcinoma (morpheic, infiltrating, and micronodular)²⁰ were additionally reviewed by a single histopathologist, who was unaware of the study-group assignments, to ensure consistent classification of the types of squamous-cell carcinoma and subtypes of basal-cell carcinoma. New melanomas and severely dysplastic nevi were reviewed by a single histopathologist with subspecialty expertise in melanocytic neoplasms, who was unaware of the study-group assignments. Assessments for adverse events were performed over the course of

the entire 12-month intervention period and for 30 days thereafter. Blood samples were obtained at baseline and at 12 months for full blood counts and for assessment of electrolyte levels and renal and liver function.

STUDY END POINTS

The primary end point was the number of new, histologically confirmed nonmelanoma skin cancers (i.e., basal-cell carcinomas plus squamous-cell carcinomas, including invasive and in situ squamous-cell carcinoma) through the end of the 12-month intervention period. Secondary end points included the number of new basal-cell carcinomas, new squamous-cell carcinomas, and actinic keratoses during the 12-month intervention period, the number of new nonmelanoma skin cancers in the 6-month postintervention period, and the safety of nicotinamide as assessed by the numbers and types of adverse events. Because previous studies have suggested a benefit from nicotinamide^{21,22} with respect to cognitive function and transepidermal water loss, these variables were also prespecified as secondary end points, but the results are not presented here.

STATISTICAL ANALYSIS

We estimated that with a sample size of 386, the study would have 90% power to detect a 33% lower rate of new nonmelanoma skin cancers with nicotinamide than with placebo at 12 months at a 5% level of significance, assuming that non-melanoma skin cancer counts would follow a Poisson distribution and that a mean of 1.0 new nonmelanoma skin cancers per person would be detected in the placebo group, and allowing for an average rate of nonadherence of up to 10%. Analyses were prespecified in a statistical analysis plan (see the protocol) and were performed according to the intention-to-treat principle. In accordance with the provision specified in the statistical analysis plan, a negative binomial model was used for the analysis of data on non-melanoma skin cancer because of overdispersion that rendered the Poisson model inappropriate. Models included an offset term to account for variation in the duration of follow-up. The primary analysis of nonmelanoma skin cancers included center and 5-year nonmelanoma skin cancer history as covariates; these covariates were omitted in a secondary sensitivity analysis. The same approach was used for the analysis of

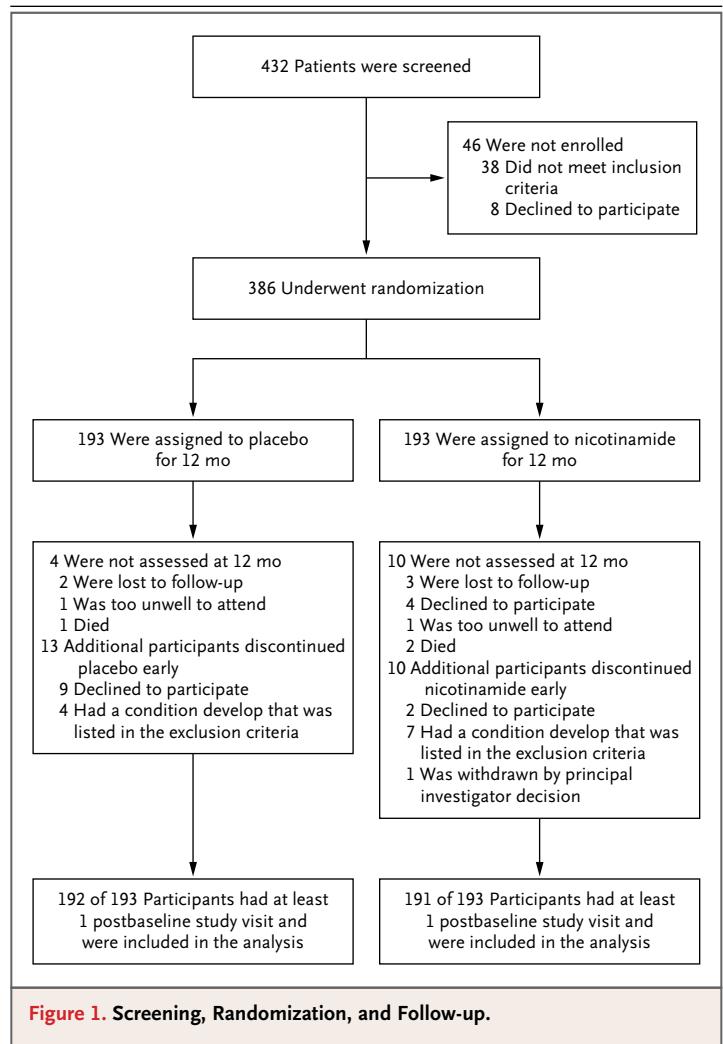
basal-cell carcinomas and squamous-cell carcinomas.

The consistency of the treatment effect with respect to the primary end point was investigated by means of a series of prespecified subgroup analyses that tested for an interaction between study-group assignment and age, sex, 5-year nonmelanoma skin cancer history, actinic keratosis count at baseline, smoking, nonsteroidal antiinflammatory drug use at baseline,²³ and statin use at baseline.²⁴ With an assumption of independence among the seven tests of interaction, there was a 30% probability that at least one P value would be less than 0.05 by chance alone. We explored the consistency of the treatment effect on the rate of nonmelanoma skin cancer over time by using generalized estimating equations to fit a negative binomial model for repeated measures to the data on nonmelanoma skin cancer collected at the 3-month visits. The data on actinic keratosis counts collected at the 3-month visits were analyzed with the use of a mixed-effects model for repeated measures. Models for repeated measures included study group, center, baseline value, time point, and the interaction between time and study group as covariates. No formal adjustment for multiple comparisons was made to P values from secondary analyses.

RESULTS

PATIENT CHARACTERISTICS

During the period from July 2, 2012, to June 14, 2014, we evaluated 432 patients (321 at the Royal Prince Alfred Hospital and 111 at the Westmead Hospital in Sydney) to determine eligibility for enrollment. We randomly assigned, in a 1:1 ratio, 386 of these patients (292 at the Royal Prince Alfred Hospital and 94 at the Westmead Hospital) to receive either nicotinamide or placebo (193 patients in each study group) (Fig. 1). The baseline characteristics were similar in the two groups (Table 1). The median rate of adherence to the nicotinamide or placebo regimen over the 12-month intervention period was 96% (mean, 88%) in the placebo group and 94% (mean, 89%) in the nicotinamide group, with no between-group differences in adherence at any of the 3-month visits (Table S1 in the Supplementary Appendix, available at NEJM.org). Follow-up rates were high, and skin assessments after baseline were available for all but 3 participants (Fig. 1).



OUTCOMES OF NONMELANOMA SKIN CANCERS AND ACTINIC KERATOSES

Figure 2 shows the results for the development of new nonmelanoma skin cancers, basal-cell carcinomas, and squamous-cell carcinomas. The mean number of new nonmelanoma skin cancers per person through the 12-month intervention period was significantly lower in the nicotinamide group than in the placebo group (1.8 [total of 336 cancers] vs. 2.4 [total of 463 cancers]), representing a rate that was lower by an estimated 23% (95% confidence interval [CI], 4 to 38) with nicotinamide after adjustment for center and 5-year nonmelanoma skin-cancer history ($P=0.02$) and by an estimated 27% (95% CI, 5 to 44) with no adjustment ($P=0.02$). At each 3-month visit during the 12-month intervention period, the estimated rate of new nonmelanoma skin cancers was lower in the nicotinamide group than in the

Table 1. Baseline Characteristics.*

Characteristic	Placebo (N=193)	Nicotinamide (N=193)
Age — yr		
Mean	66.4±11.8	66.4±11.8
Range	30–91	30–89
Sex — no. (%)		
Male	121 (63)	122 (63)
Female	72 (37)	71 (37)
Never smoked — no. (%)	88 (46)	92 (48)
Skin cancers in previous 5 years — no.		
Nonmelanoma skin cancers		
Mean	8.2±7.4	7.9±8.0
Range	2–52	2–61
Basal-cell carcinomas		
Mean	6.1±7.0	5.7±6.9
Range	0–49	0–59
Squamous-cell carcinomas		
Mean	2.1±3.2	2.1±3.5
Range	0–23	0–31
Actinic keratoses at baseline		
Mean	46.2±42.9	47.7±43.2
Range	0–214	0–205
Medical history — no. (%)		
Hypertension	84 (44)	86 (45)
Hypercholesterolemia	82 (42)	79 (41)
Asthma	21 (11)	37 (19)
Ischemic heart disease	23 (12)	32 (17)
Osteoporosis	20 (10)	19 (10)
Diabetes	15 (8)	16 (8)
Cancer other than skin	10 (5)	14 (7)
Stroke or transient ischemic attack	13 (7)	5 (3)
Sunscreen use in the past week — no. (%)	98 (51)	90 (47)
Statin use — no. (%)	71 (37)	75 (39)
Nonsteroidal antiinflammatory drug use — no. (%)	48 (25)	53 (27)

* Plus-minus values are means ±SD. There were no significant differences between the groups at baseline except for a more frequent history of asthma ($P=0.03$) in the nicotinamide group.

placebo group: relative difference, 25% (95% CI, –7 to 48) at 3 months ($P=0.11$), 27% (95% CI, –5 to 50) at 6 months ($P=0.09$), 18% (95% CI, –18 to 43) at 9 months ($P=0.29$), and 29% (95% CI, –6 to 52) at 12 months ($P=0.09$).

The effect of nicotinamide on nonmelanoma skin cancers was not maintained into the 6-month

follow-up period after the drug was discontinued (relative difference, nicotinamide vs. placebo, –17%; 95% CI, –59 to 14; $P=0.33$) or modified by age, baseline actinic keratosis count, sex, smoking status, nonsteroidal antiinflammatory drug use, or statin use (Fig. S1 in the Supplementary Appendix). There was a trend toward greater effectiveness of nicotinamide among patients who had had a higher number of non-melanoma skin cancers in the 5 years before baseline. The interaction term was significant ($P=0.02$) when the nonmelanoma skin cancer count in the previous 5 years was treated as a continuous covariate, but was not significant ($P=0.18$) when 5-year history of nonmelanoma skin cancer was treated as a categorical covariate (i.e., <6 vs. ≥6 nonmelanoma skin cancers). There was no significant difference between the groups in the number of recurrent nonmelanoma skin cancers (13 in the placebo group and 17 in the nicotinamide group).

The mean number of basal-cell carcinomas per person through the 12-month intervention period was 1.3 in the nicotinamide group (total of 239 cancers) and 1.7 in the placebo group (total of 327 cancers), representing a rate that was lower by an estimated 20% (95% CI, –6 to 39) with nicotinamide after adjustment for center and 5-year basal-cell carcinoma history ($P=0.12$). This relative difference with respect to basal-cell carcinomas appeared to be associated primarily with a lower number of superficial basal-cell carcinomas in the nicotinamide group than in the placebo group (Table 2). The number of basal-cell carcinomas was similar in the two groups in the 6-month postintervention period (relative difference, nicotinamide vs. placebo, –6%; 95% CI, –53 to 26; $P=0.73$).

The mean number of squamous-cell carcinomas per person through the 12-month intervention period was 0.5 in the nicotinamide group (total of 97 cancers) and 0.7 in the placebo group (total of 136 cancers), representing a rate that was lower by an estimated 30% (95% CI, 0 to 51) with nicotinamide after adjustment for center and 5-year squamous-cell carcinoma history ($P=0.05$). The effect of nicotinamide appeared to be independent of the differentiation of squamous-cell carcinoma (well differentiated, moderately differentiated, or poorly differentiated) (Table 2). There was a nonsignificant trend toward the development of more squamous-cell carcinomas in the nicotinamide group than in

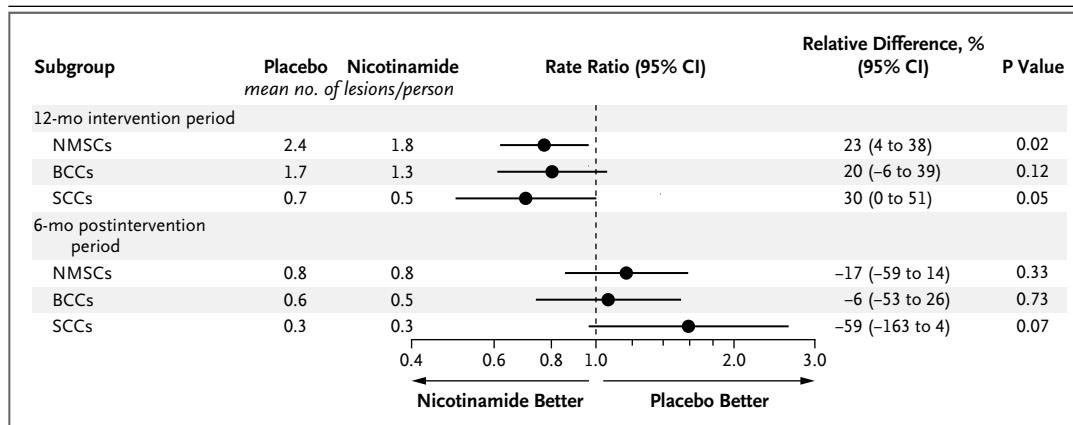


Figure 2. Incidence of New Nonmelanoma Skin Cancers, Basal-Cell Carcinomas, and Squamous-Cell Carcinomas.

The mean numbers of lesions per participant reflect simple averages, whereas the rate ratios (the ratio of the estimated rates in the two study groups), relative differences (1 minus the rate ratio, multiplied by 100), and P values are estimated from a model that includes center and skin cancer count in the previous 5 years as covariates. When the covariates of center and 5-year nonmelanoma skin cancer history were omitted from the models in secondary analyses, the conclusions remained unchanged and the estimates corresponded directly to the ratio of mean numbers per participant in the two groups. The rate of new nonmelanoma skin cancers (NMSCs) during the 12-month intervention period was significantly lower with nicotinamide than with placebo (relative difference, 23%; $P=0.02$), with similar relative differences observed for both basal-cell carcinomas (BCCs) and squamous-cell carcinomas (SCCs). This benefit with nicotinamide was not observed during the 6-month postintervention period. Because of rounding, the mean number of SCCs per patient appears identical in the two study groups; the actual values are 0.250 for the placebo group and 0.325 for the nicotinamide group. Although the between-group comparison for the postintervention period is unbiased, the annualized rates for this period cannot be compared directly with those from the 12-month intervention period because of variance in the duration of surveillance of detected lesions that did not immediately warrant biopsy (e.g., a lesion identified at month 3 could be monitored for many months before being confirmed as a nonmelanoma skin cancer on biopsy, whereas a lesion identified at month 18 could not be monitored for many months).

the placebo group in the 6-month postintervention period (relative difference, nicotinamide vs. placebo, -59% ; 95% CI, -163 to 4 ; $P=0.07$).

The number of actinic keratoses was 11% lower in the nicotinamide group than in the placebo group at 3 months ($P=0.01$), 14% lower at 6 months ($P<0.001$), 20% lower at 9 months ($P<0.001$), and 13% lower at 12 months ($P=0.001$). This equated to 3 to 5 fewer actinic keratoses, on average, from the baseline count in the nicotinamide group than in the placebo group (Fig. 3). The rate of sunscreen use in the week before baseline and at the 3-month visits through 12 months was lower in the nicotinamide group than in the placebo group (Table S2 in the Supplementary Appendix).

SAFETY

No clinically significant between-group differences were found with respect to the number or types of adverse events that occurred in the study groups (Table S3 in the Supplementary Appendix). The terms for the most common seri-

ous adverse events, reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, that occurred in the two groups combined included neoplasm (12 patients), cardiac chest pain (9 patients), fall (7 patients), lung infection (6 patients), atrial fibrillation (6 patients), injury (6 patients), heart failure (5 patients), and hematoma (5 patients). Two internal cancers were diagnosed in the placebo group (duodenal carcinoma diagnosed at month 1 of the study and lung cancer at month 3) and five internal cancers were diagnosed in the nicotinamide group (non-Hodgkin's lymphoma diagnosed at month 1 of the study, colorectal cancer at month 2, lung cancer at month 2, prostate cancer at month 7, and bladder cancer at month 9). Four new invasive melanomas and six new melanomas in situ were diagnosed during the 12-month intervention period and were evenly distributed between the two groups. A microcystic adnexal carcinoma developed as a collision tumor (two originally separate tumors that have developed in close

Table 2. Subtypes of Basal-Cell Carcinoma and Differentiation of Squamous-Cell Carcinoma at 12 Months.

Variable	Placebo (N=193)	Nicotinamide (N=193)
	<i>number</i>	
Basal-cell carcinoma		
Total	327	239
Subtype		
Superficial	181	98
Nodular	128	115
Micronodular	6	6
Infiltrating	12	18
Morpheic	0	2
Squamous-cell carcinoma		
Total	136	97
Differentiation		
Bowen's disease (squamous-cell carcinoma in situ)	69	47
Well differentiated	43	31
Moderately differentiated	24	16
Poorly differentiated	0	3

proximity) with a squamous-cell carcinoma in a patient receiving nicotinamide. There were no clinically or statistically significant differences between the study groups with respect to changes in weight, blood pressure, hemoglobin, white-cell count, platelet count, or levels of creatinine, alkaline phosphatase, γ -glutamyl transferase, alanine aminotransferase, or aspartate aminotransferase.

DISCUSSION

The rate of new nonmelanoma skin cancers was lower in the nicotinamide group than in the placebo group (relative difference, 23%; $P=0.02$), with similar differences in the rates of new basal-cell carcinomas and new squamous-cell carcinomas. There was a trend toward increasing effectiveness of nicotinamide among patients who had had higher numbers of nonmelanoma skin cancers in the preceding 5 years; however, the statistical evidence was limited, given the multiple tests performed, and is insufficient to warrant restricting treatment to a particular subgroup of high-risk patients, particularly in light of the favorable safety profile and low cost of

nicotinamide. The possible increased efficacy among participants with higher numbers of nonmelanoma skin cancers may reflect the immunoprotective effects of nicotinamide.¹⁸ Patients with previous skin cancers have a greater susceptibility to the immunosuppressive effects of sunlight,¹⁸ and it may be that this susceptibility is more pronounced in patients with higher numbers of nonmelanoma skin cancers, who thus may have a greater potential to benefit from nicotinamide.

Sunscreen is effective in reducing the number of actinic keratoses and the incidence of squamous-cell carcinoma,⁸ but even in our high-risk study population, only half the patients had used sunscreen in the week before baseline. Hence, potential exists for oral chemopreventive agents to become an effective component in the prevention of skin cancers. By chance, there was a lower rate of sunscreen use from baseline to 12 months in the nicotinamide group than in the placebo group. The lower number of new nonmelanoma skin cancers with nicotinamide treatment than with placebo observed in our study is therefore not attributable to chance differences in sunscreen use. Other agents with evidence of clinical efficacy for the prevention of nonmelanoma skin cancer include oral retinoids, topical DNA repair enzymes, and oral nonsteroidal antiinflammatory drugs. In a randomized, controlled trial involving 2297 participants, the risk of new squamous-cell carcinomas was lower among those who received oral administration of 25,000 IU of retinol daily than among those who received placebo (hazard ratio, 0.74; $P=0.04$), but the risk of basal-cell carcinomas was not lower with retinol (hazard ratio, 1.06; $P=0.36$).²⁵ A number of smaller studies showed that oral retinoids such as acitretin and isotretinoin significantly reduced the risk of new nonmelanoma skin cancers,²⁶⁻²⁹ although these agents are associated with substantial adverse effects including dry skin, increased lipid levels, hepatotoxic effects, and teratogenicity.³⁰ Treatment with topical DNA repair enzymes was associated with a lower rate of new actinic keratoses and basal-cell carcinomas than was placebo in patients with xeroderma pigmentosum,³¹ but the usefulness of these DNA repair enzymes in the broader population is limited by cost and availability. A randomized, controlled trial involving 240 patients showed that treatment with

the nonsteroidal antiinflammatory drug celecoxib was associated with a significantly lower rate of new nonmelanoma skin cancers than was placebo, but this was not a primary or secondary end point of the trial.²³

Nicotinamide was significantly associated with lower actinic keratosis counts than those with placebo as early as the first 3-month visit and at each subsequent 3-month visit up to 12 months, a finding that is consistent with the results from our previous phase 2 studies.¹⁹ Similarly, there was a relatively constant, although nonsignificant, trend toward lower rates of new nonmelanoma skin cancers in the nicotinamide group than in the placebo group at each 3-month visit during the 12-month intervention period. This benefit was not maintained in the postintervention period. The trend toward lower rates of new nonmelanoma skin cancers with nicotinamide than with placebo starting from 3 months after the start of intervention suggests that nicotinamide suppresses the progression of nascent, preexisting cancers. The chemopreventive effect of nicotinamide was lost shortly after discontinuation, a finding that was also seen with respect to oral retinoids in other studies.^{26-28,32}

Nicotinamide appeared to reduce the incidence of new superficial basal-cell carcinomas more than that of other subtypes, whereas it had a relatively constant effect across strata of differentiation of squamous-cell carcinoma. However, interpretation was limited by small numbers of high-risk subtypes of basal-cell carcinoma (micronodular, infiltrating, and morpheic) and of poorly differentiated squamous-cell carcinomas. The characteristics of superficial basal-cell carcinomas differ from those of nodular basal-cell carcinomas at the molecular level,³³ and superficial basal-cell carcinomas are proportionally more common in immunosuppressed transplant recipients,³⁴ which suggests that different biologic pathways underlie the pathogenesis of superficial basal-cell carcinomas and may enable them to be more readily prevented by nicotinamide.

We found that nicotinamide had a good safety profile. Nicotinamide has been used at pharmacologic doses (up to 3 g daily) over many years with minimal side effects³⁵ and is used clinically to treat autoimmune blistering disorders such as bullous pemphigoid, usually at doses of 1.5 g daily.³⁶ Unlike nicotinic acid (niacin),

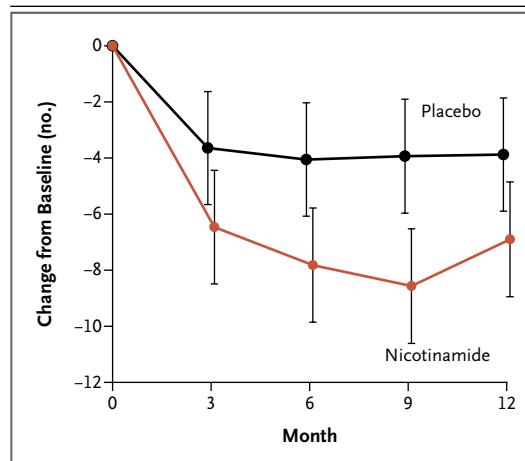


Figure 3. Change from Baseline to Month 12 in Number of Actinic Keratoses.

The change from baseline in the number of actinic keratoses was adjusted for center and number of actinic keratoses at baseline. The number of actinic keratoses was 11% lower in the nicotinamide group than in the placebo group at 3 months ($P=0.01$), 14% lower at 6 months ($P<0.001$), 20% lower at 9 months ($P<0.001$), and 13% lower at 12 months ($P=0.001$).

nicotinamide does not cause vasodilatory side effects such as flushing, itching, hypotension, and headaches.³⁷ Our decision to use a dose of 1000 mg daily was based on the results of our phase 2 studies that showed a reduction in actinic keratosis counts at this dose.¹⁹ Previous studies on immunosuppression induced by UV radiation suggested that there is no greater efficacy with 1500 mg than with 500 mg daily,¹⁸ but the minimum and maximum effective chemopreventive doses are as yet unknown.

In conclusion, among high-risk patients, nicotinamide was associated with a lower rate of new nonmelanoma skin cancers than was placebo and had an acceptable safety profile. Nicotinamide is widely accessible as an inexpensive over-the-counter vitamin supplement and presents a new opportunity for the chemoprevention of nonmelanoma skin cancers that is readily translatable into clinical practice.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES

- Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. *Br J Dermatol* 2012;166:1069-80.
- Fransen M, Karahalios A, Sharma N, English DR, Giles GG, Sinclair RD. Non-melanoma skin cancer in Australia. *Med J Aust* 2012;197:565-8.
- Cancer in Australia: an overview, 2006. Canberra, ACT: Australian Institute of Health and Welfare, 2007.
- Guy GP Jr, Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and costs of skin cancer treatment in the U.S., 2002-2006 and 2007-2011. *Am J Prev Med* 2015;48:183-7.
- Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. *N Engl J Med* 2005;353:2262-9.
- Alam M, Ratner D. Cutaneous squamous-cell carcinoma. *N Engl J Med* 2001;344:975-83.
- Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. *J Photochem Photobiol B* 2001;63:8-18.
- Green A, Williams G, Neale R, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet* 1999;354:723-9.
- Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. *N Engl J Med* 1993;329:1147-51.
- Green AC, Williams GM, Logan V, Strutton GM. Reduced melanoma after regular sunscreen use: randomized trial follow-up. *J Clin Oncol* 2011;29:257-63.
- Ismail F, Mitchell L, Casabonne D, et al. Specialist dermatology clinics for organ transplant recipients significantly improve compliance with photoprotection and levels of skin cancer awareness. *Br J Dermatol* 2006;155:916-25.
- Yarosh DB. DNA repair, immunosuppression, and skin cancer. *Cutis* 2004;74:Suppl:10-3.
- Park J, Halliday GM, Surjana D, Damian DL. Nicotinamide prevents ultraviolet radiation-induced cellular energy loss. *Photochem Photobiol* 2010;86:942-8.
- Surjana D, Halliday GM, Damian DL. Nicotinamide enhances repair of ultraviolet radiation-induced DNA damage in human keratinocytes and ex vivo skin. *Carcinogenesis* 2013;34:1144-9.
- Thompson BC, Surjana D, Halliday GM, Damian DL. Nicotinamide enhances repair of ultraviolet radiation-induced DNA damage in primary melanocytes. *Exp Dermatol* 2014;23:509-11.
- Kuchel JM, Barnetson RS, Halliday GM. Cyclobutane pyrimidine dimer formation is a molecular trigger for solar-simulated ultraviolet radiation-induced suppression of memory immunity in humans. *Photochem Photobiol Sci* 2005;4:577-82.
- Damian DL, Patterson CRS, Stapelberg M, Park J, Barnetson RS, Halliday GM. UV radiation-induced immunosuppression is greater in men and prevented by topical nicotinamide. *J Invest Dermatol* 2008;128:447-54.
- Yiasemides E, Sivapirabu G, Halliday GM, Park J, Damian DL. Oral nicotinamide protects against ultraviolet radiation-induced immunosuppression in humans. *Carcinogenesis* 2009;30:101-5.
- Surjana D, Halliday GM, Martin AJ, Moloney FJ, Damian DL. Oral nicotinamide reduces actinic keratoses in phase II double-blinded randomized controlled trials. *J Invest Dermatol* 2012;132:1497-500.
- LeBoit PE, Burg G, Weedon D, Sarasain A, eds. World Health Organization classification of tumours: pathology and genetics of tumours of the skin. Lyon, France: International Agency for Research on Cancer, 2006.
- Liu D, Pitta M, Jiang H, et al. Nicotinamide forestalls pathology and cognitive decline in Alzheimer mice: evidence for improved neuronal bioenergetics and autophagy procession. *Neurobiol Aging* 2013;34:1564-80.
- Tanno O, Ota Y, Kitamura N, Katsube T, Inoue S. Nicotinamide increases biosynthesis of ceramides as well as other stratum corneum lipids to improve the epidermal permeability barrier. *Br J Dermatol* 2000;143:524-31.
- Elmets CA, Viner JL, Pentland AP, et al. Chemoprevention of nonmelanoma skin cancer with celecoxib: a randomized, double-blind, placebo-controlled trial. *J Natl Cancer Inst* 2010;102:1835-44.
- Li X, Wu XB, Chen Q. Statin use is not associated with reduced risk of skin cancer: a meta-analysis. *Br J Cancer* 2014;110:802-7.
- Moon TE, Levine N, Cartmel B, et al. Effect of retinol in preventing squamous cell skin cancer in moderate-risk subjects: a randomized, double-blind, controlled trial. *Cancer Epidemiol Biomarkers Prev* 1997;6:949-56.
- Kraemer KH, DiGiovanna JJ, Moshell AN, Tarone RE, Peck GL. Prevention of skin cancer in xeroderma pigmentosum with the use of oral isotretinoin. *N Engl J Med* 1988;318:1633-7.
- Bavinck JN, Tieben LM, Van der Woude FJ, et al. Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. *J Clin Oncol* 1995;13:1933-8.
- McKenna DB, Murphy GM. Skin cancer chemoprophylaxis in renal transplant recipients: 5 years of experience using low-dose acitretin. *Br J Dermatol* 1999;140:656-60.
- George R, Weightman W, Russ GR, Bannister KM, Mathew TH. Acitretin for chemoprevention of non-melanoma skin cancers in renal transplant recipients. *Australas J Dermatol* 2002;43:269-73.
- Marquez C, Bair SM, Smithberger E, Cherpelis BS, Glass LF. Systemic retinoids for chemoprevention of non-melanoma skin cancer in high-risk patients. *J Drugs Dermatol* 2010;9:753-8.
- Yarosh D, Klein J, O'Connor A, Hawk J, Rafal E, Wolf P. Effect of topically applied T4 endonuclease V in liposomes on skin cancer in xeroderma pigmentosum: a randomised study. *Lancet* 2001;357:926-9.
- Shuttleworth D, Marks R, Griffin PJ, Salaman JR. Treatment of cutaneous neoplasia with etretinate in renal transplant recipients. *Q J Med* 1988;68:717-25.
- Pietkiewicz P, Gornowicz-Porowska J, Bowszyc-Dmochowska M, et al. Discordant expression of desmoglein 2 and 3 at the mRNA and protein levels in nodular and superficial basal cell carcinoma revealed by immunohistochemistry and fluorescent in situ hybridization. *Clin Exp Dermatol* 2014;39:628-35.
- Bastiaens MT, Hoefnagel JJ, Bruijn JA, Westendorp RG, Vermeer BJ, Bouwes Bavinck JN. Differences in age, site distribution, and sex between nodular and superficial basal cell carcinoma indicate different types of tumors. *J Invest Dermatol* 1998;110:880-4.
- Knip M, Douek IF, Moore WP, et al. Safety of high-dose nicotinamide: a review. *Diabetologia* 2000;43:1337-45.
- Chen AC, Damian DL. Nicotinamide and the skin. *Australas J Dermatol* 2014;55:169-75.
- Ranchoff RE, Tomecki KJ. Niacin or niacinamide? Nicotinic acid or nicotinamide? What is the difference? *J Am Acad Dermatol* 1986;15:116-7.

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