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Nicotinamide for Skin Cancer Chemoprevention

Kimberly F. Breglio, MD, DPhil; Katlyn M. Knox, BA; Jonathan Hwang, BS; Rachel Weiss, BS; Kyle Maas, BS; Siwei Zhang, PhD; Lydia Yao, MS; Chris Madden, MD; Yaomin Xu, PhD; Rebecca I. Hartman, MD, MPH; Lee Wheless, MD, PhD

IMPORTANCE Nicotinamide supplementation has been studied as a chemopreventive medication for reducing skin cancer risk, but large-scale data are limited.

OBJECTIVE To determine the clinical efficacy of nicotinamide supplementation for skin cancer prevention in the general population and among solid organ transplant recipients.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study was conducted using electronic health record data (October 1, 1999, to December 31, 2024) from the Veterans Affairs Corporate Data Warehouse (CDW) of 33 822 patients. Analyses were conducted from January 17, 2025, to May 9, 2025. Patients who were exposed to nicotinamide were propensity score matched based on the number and year of skin cancers after which treatment with nicotinamide was initiated, age, sex, self-reported race, exposure to acitretin, exposure to field therapy, history of chronic lymphocytic leukemia, and history of solid organ transplant. The index date was the first prescription of nicotinamide filled within the VA system. Stratified Cox models were used to investigate the association of nicotinamide with skin cancer development.

EXPOSURES Nicotinamide, 500 mg, twice daily for longer than 30 days as documented in the electronic health record.

MAIN OUTCOMES AND MEASURES Time to the next skin cancer after baseline.

RESULTS There were 12 287 patients (mean [SD] age, 77.2 [8.9] years; 241 women [2.0%]; 31 [0.3%] American Indian or Alaska Native, 3 [<0.1%] Asian, 13 [0.1%] Black or African American, 59 [0.5%] Native Hawaiian or other Pacific Islander, and 11 662 [94.9%] White individuals) exposed to oral nicotinamide, 500 mg, twice daily for longer than 30 days who were matched to 21 479 unexposed patients (mean [SD] age, 76.9 [8.7] years; 374 women [2.0%]; 49 [0.2%] American Indian or Alaska Native, 3 [<0.1%] Asian, 16 [0.1%] Black or African American, 88 [0.4%] Native Hawaiian or other Pacific Islander, and 20 517 [95.3%] White individuals). Within the matched dataset, there were 10 994 instances of basal cell carcinoma after nicotinamide exposure and 12 551 cutaneous squamous cell carcinoma (cSCC). A total of 1334 (3.9%) in the matched cohort were solid organ transplant recipients. Overall, there was a significant 14% reduction in skin cancer risk. When nicotinamide was initiated after a first skin cancer, the risk reduction rose to 54%, although this benefit declined with initiation following subsequent skin cancers. This risk reduction was seen for skin cancers overall, basal cell carcinoma, and cSCC, with the greatest risk reduction seen for cSCC. Among solid organ transplant recipients, no overall significant risk reduction was observed, although early nicotinamide use was associated with reduced cSCC incidence.

CONCLUSIONS AND RELEVANCE The results of this cohort study suggest that there is a decreased risk of skin cancer among patients treated with nicotinamide, with the greatest effect seen when initiated after the first skin cancer.

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Multimedia

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Lee Wheless, MD, PhD, 719 Thompson Ln, Ste 26300, Nashville, TN 37215 (lee.e.wheless@vumc.org).

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Nicotinamide is a vitamin B_3 derivative that is sold as an over-the-counter (OTC) medication and has shown promise in skin cancer chemoprevention, with up to 75% of dermatologic surgeons reporting using nicotinamide for this indication.[1] In 2015, a phase 3, double-blind randomized clinical trial with 386 participants demonstrated that nicotinamide, 500 mg, twice daily was associated with a reduced number of new skin cancers in a population with a history of skin cancer.[2] Following this study, dermatologists began using OTC nicotinamide for skin cancer chemoprevention, particularly in patients at high risk of skin cancer development. A follow-up phase 3 trial with 158 solid organ transplant recipients (SOTRs) failed to demonstrate a reduced risk of skin cancer development in patients using nicotinamide, 500 mg, twice daily,[3] although this study has been criticized for being underpowered,[4,5] and a subsequent small study showed decreased numbers of keratinocyte carcinomas at 1 and 2 years after initiating nicotinamide.[6]

Studying nicotinamide's clinical effects is challenging. As an OTC medication, prescriptions are not captured in national claims databases. Unlike many other cancers, most US cancer registries do not capture information about keratinocyte carcinomas. Additionally, no guidelines specify after how many skin cancers nicotinamide should be initiated. The Veterans Health Administration (VA) is uniquely positioned to overcome these barriers. Nicotinamide is on the VA formulary, so prescriptions are documented among veterans. The VA also maintains comprehensive records of treatments, which allows for highly granular data on skin cancers.[7] Lastly, the large size of the VA population allows for detailed matching on the timing of multiple variables to control for differences in when nicotinamide was initiated.[8] In this study, we sought to determine the clinical efficacy of nicotinamide supplementation for skin cancer prevention.

Key Points

Question Does nicotinamide supplementation prevent skin cancer development?

Findings In this retrospective study of 33 822 veterans, there was a decreased risk of 3 types of skin cancer associated with use of nicotinamide. The magnitude of reduction was associated with the number of skin cancers before nicotinamide use.

Meaning The results of this study suggest that use of nicotinamide is associated with a reduced risk of skin cancer development.

Methods

We conducted a retrospective cohort study using the VA Corporate Data Warehouse (CDW). Following approval from the Tennessee Valley Healthcare System VA Medical Center institutional review board, we used the CDW, with data through December 31, 2024. Analyses were conducted from January 17, 2025, to May 9, 2025. Informed consent was waived due to the use of deidentified data. Because we wanted to capture indications for skin cancer prevention, we identified all patients with at least 1 skin cancer based on our previously validated phenotyping algorithm of the cooccurrence of an *International Classification of Diseases, Ninth Revision (ICD-9)* or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* and *Current Procedural Terminology* (*CPT*) code for skin cancer and its procedural treatment on the same day (eTables 1-3 in Supplement 1).[9] Patients missing date of birth were excluded (45 402 [3.2%]). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

The primary outcome was the time to skin cancer after baseline, which was defined as the co-occurrence of a skin cancer *CPT* and *ICD* code on the same day (eTables 1-3 in Supplement 1). The primary exposure was nicotinamide, 500 mg, twice daily for at least 30 days. The baseline time was defined as the first prescription of nicotinamide filled within the VA system. Unexposed patients were propensity score matched primarily based on the number and year of skin cancers after which nicotinamide was begun in the matched exposed patient. For example, patients who initiated treatment with nicotinamide after 3 skin cancers and whose third skin cancer occurred at age 60 years, second at age 59 years, and first at age 57 years were matched to an unexposed control who developed their third skin cancer at age 60 years and their second skin cancer at age 59 years. Among the unexposed matched patients, baseline was considered the first nicotinamide prescription for the exposed patient in each matched stratum.

Patients often had 1 or more skin cancer specimens biopsied during the appointment leading to initiation of nicotinamide. Because these were diagnosed before nicotinamide was initiated but not yet treated, they were not counted as events. We considered the event date to be the date of the first *CPT* code beyond 90 days after baseline. Because patients could also have new skin cancer specimens biopsied within this 90-day window, we considered the event date to be the first treatment *CPT-ICD* code pair occurring after a biopsy *CPT* code (11102-7) with a skin cancer *ICD* code if patients had a biopsy code within 90 days after baseline. A 90-day window was determined as follows: (1) the most frequently that patients would generally be seen would be every 90 days,[10] and (2) although some low-risk skin cancers can safely be treated beyond 90 days, we elected to count a skin cancer treated later than 90 days as a new skin cancer, biasing the risk estimate toward the null, rather than risk omitting new skin cancers, which could falsely inflate the risk estimate.[11] Thus, it would be unlikely that a patient would receive a diagnosis of a new skin cancer within the first 90 days, and it would likely be that all previously diagnosed skin cancers would be treated within this window.

Propensity score–matching models included acitretin exposure, field therapy, history of solid organ transplant, and history of chronic lymphocytic leukemia (CLL). Field therapy was defined as having a *CPT* code for photodynamic therapy (PDT: 96567, 96573, and 96574) or a medication entry for fluorouracil within 1 year before baseline and before the end date. We assumed all exposures to be used with the intent of field therapy and that all exposures led to a complete treatment course. We did not include imiquimod in the field therapy, as this is commonly used to treat warts and superficial basal cell

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carcinomas (BCCs), both of which have high prevalence in our cohort. As such, it would have been difficult to determine if this medication was being used for a spot treatment or field therapy. SOTRs were defined as patients with 4 or more *ICD* codes for transplant or 1 or more transplant *CPT* codes.[12] CLL was defined as 2 or more *ICD* codes (*ICD-9* 204.1 or *ICD-10* C91.1) due to lack of a validated phenotype at the time of matching. While stem cell transplant (SCT) recipients face elevated skin cancer risk, we excluded them from matching due to the difficulty in distinguishing autologous from allogeneic SCT and their differing risk profiles. A post hoc analysis showed only 121 patients with SCT *ICD* codes, suggesting a limited association with findings.

The median number of skin cancers before nicotinamide treatment was 3, with a maximum of 73. To determine how many skin cancers to match on, we conducted an elbow test on a histogram of prior cancers that approximated a scree plot (eFigure 1 in Supplement 1). The elbow was at 9, so patients who initiated nicotinamide after their tenth skin cancer or more were all considered as a single group, which represented 15% of all patients with nicotinamide exposure. To evaluate the clinical association of nicotinamide with skin cancer risk and align with prior clinical trials, we elected to include these patients for the overall analyses only. Propensity score matching without replacement was performed in backward stepwise fashion based on the number of skin cancers, starting at 10 or more and decreasing to 1. For example, patients initiating nicotinamide after the fourth skin cancer would be matched based on the previously mentioned variables, as well as the years of the first 4 skin cancers only to avoid matching on an outcome. Absolute standardized mean differences (ASMDs) of less than 0.1 were considered well balanced factors (eFigures 2-11 in Supplement 1). Preliminary analyses showed failure of matching for patients starting after 9 (ASMD = 0.11) or after 10 or more skin cancers (ASMD = 0.20), so stratified analyses of these are not presented due to the inability to draw valid conclusions from them.

Statistical Analysis

Differences between groups were tested using χ^2 tests and *t* tests for categorical and continuous variables, respectively. We used log-rank tests to compare differences in skin cancer–free survival and conditional Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs, adjusting for residual confounding on acitretin or field therapy exposure, history of CLL, and history of organ transplant. This model was selected over Fine-Grey as the intent was to determine the etiologic association between skin cancer and nicotinamide. All analyses were conducted using R, version 4.0.3 (R Foundation). Two-sided $P < .05$ was considered statistically significant.

Ancillary analyses were performed to investigate the association of nicotinamide supplementation with skin cancer types of invasive cSCC and BCC. Skin cancer type was determined by the *ICD* code entered on the date of treatment (eTable 1 in Supplement 1). We additionally conducted models that were restricted to only those patients with a history of a solid organ transplant, or only those without exposure to the effects of field therapy during the risk window. Stratified analysis by number of skin cancers before initiation among SOTRs was limited by small numbers. Dose response was measured with models stratified by patients' cumulative exposure to nicotinamide, defined as low (30-90 days), medium (91-364 days), and high (365 or more).

Results

There were 12 287 patients exposed to oral nicotinamide, 500 mg, twice daily for 30 days or longer (**Table**). Most patients were self-reported White and male, with a similar mean (SD) age (76.9 [8.7] years vs 77.2 [8.9] unexposed and exposed, respectively) and mean (SD) age at first skin cancer (67.1 [9.7] years for both). There were 10 994 same-day *ICD* and *CPT* codes for

Table. Demographic Characteristic of Patients in the Veterans Affairs Corporate Data Warehouse Cohort at the Index Date

Characteristic	No. (%)		*P* value
	Unexposed (n = 21 535)	Nicotinamide exposed (n = 12 287)	
Age, mean (SD), y	76.9 (8.7)	77.2 (8.9)	.01
Age at first skin cancer, mean (SD), y	67.1 (9.7)	67.1 (9.7)	.82
Sex			
Female	374 (2.0)	241 (2.0)	.85
Male	21 105 (98.0)	12 046 (98.0)	
Race			
American Indian or Alaska Native	49 (0.2)	31 (0.3)	.73
Asian	3 (<0.01)	3 (<0.1)	
Black or African American	16 (0.1)	13 (0.1)	
Native Hawaiian or other Pacific Islander	88 (0.4)	59 (0.5)	
Unknown	851 (4.0)	513 (4.2)	
White	20 517 (95.3)	11 662 (94.9)	
Solid organ transplant recipient	762 (3.5)	572 (4.7)	<.001
History of CLL	421 (2.0)	314 (2.6)	<.001
Exposure to acitretin	728 (3.4)	758 (6.2)	<.001
Exposure to field therapy	18 099 (84.0)	10 404 (84.7)	.13

Abbreviation: CLL, chronic lymphocytic leukemia.

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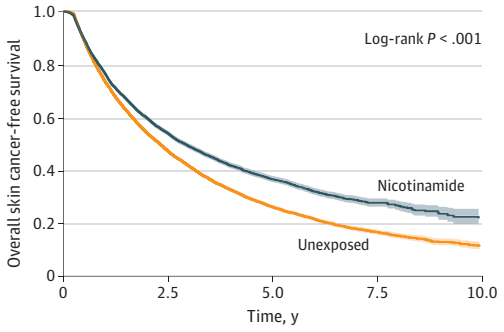
BCC after nicotinamide exposure and 12 551 for invasive cSCC. There were 1334 SOTRs in the cohort, with more receiving nicotinamide (4.7% vs 3.5%; $P < .001$). Patients with nicotinamide exposure were more likely to have a history of CLL (2.6% vs 2.0%; $P < .001$) and to have been exposed to acitretin (6.2% vs 3.4%; $P < .001$). Most patients in the exposed and unexposed groups received field therapy during the study window (84.7% vs 84.0%; $P = .13$).

Overall, there was a significant improvement in skin cancer-free survival in the nicotinamide group compared with the unexposed group (log-rank 198.9; $P < .001$; **Figure 1**A). Stratifying by the number of skin cancers before treatment revealed that patients who initiated nicotinamide before their seventh skin cancer experienced an improvement in skin cancer-free survival, with the benefit diminishing with each subsequent skin cancer until there was no difference (**Figure 2** and **Figure 3**). After further adjusting for residual confounding in stratified Cox models, we observed similar patterns overall, as well as for BCC and cSCC, with much larger reductions in cSCC (**Figure 4**). Overall, there was a 14% reduction in the rate of new skin cancers after initiating nicotinamide compared with unexposed patients (HR, 0.86; 95% CI, 0.82-0.89), no reduction overall for BCC (HR, 1.00; 95% CI, 0.96-1.05), and a 22% reduction in cSCC (HR, 0.78; 95% CI, 0.75-0.82). For all 3, there was roughly a 50% decreased rate of skin cancer when nicotinamide was initiated at the time of the first skin cancer (Figure 4).

There was no significant association of nicotinamide and skin cancer reduction among SOTRs overall (HR, 1.02; 95% CI, 0.84-1.25). When examining those SOTRs with only 1 or 2 prior skin cancers, there was a significant reduction in the risk of cSCC among those taking nicotinamide (n = 412; HR, 0.47;

Figure 1. Overall Skin Cancer–Free Survival Among Patients With or Without Exposure to Nicotinamide

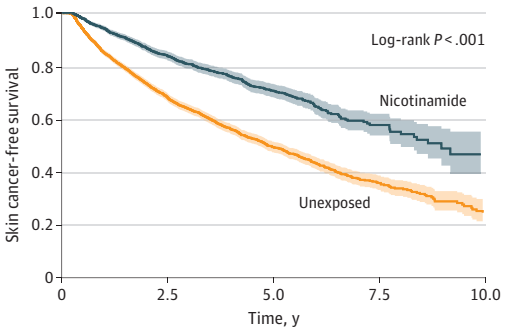


No. at risk (events)

Unexposed	21 535 (0)	6797 (9880)	1898 (12 200)	272 (12 612)	68 (12 664)
Nicotinamide	12 287 (0)	4120 (4849)	1265 (5813)	177 (5989)	33 (6007)

Figure 2. Skin Cancer–Free Survival Among Patients With or Without Exposure to Nicotinamide When Initiated After 1 to 4 Skin Cancers

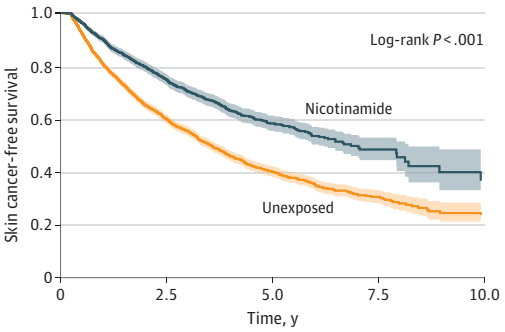
A After 1 skin cancer



No. at risk (events)

Unexposed	4352 (0)	1855 (1182)	665 (1555)	131 (1669)	40 (1695)
Nicotinamide	2392 (0)	1224 (312)	469 (455)	82 (504)	20 (513)

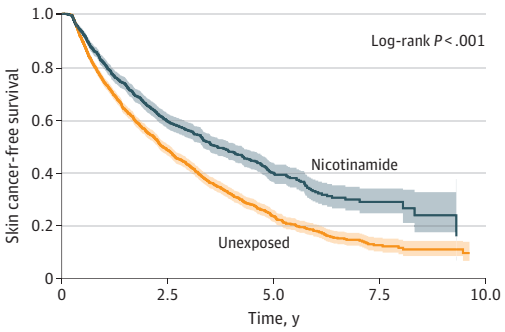
B After 2 skin cancers



No. at risk (events)

Unexposed	3413 (0)	1265 (1267)	407 (1637)	61 (1708)	21 (1721)
Nicotinamide	1865 (0)	836 (417)	291 (569)	38 (598)	9 (604)

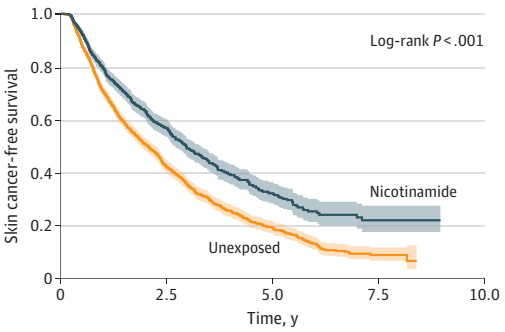
C After 3 skin cancers



No. at risk (events)

Unexposed	2682 (0)	851 (1192)	213 (1523)	30 (1585)	6 (1589)
Nicotinamide	1481 (0)	520 (499)	151 (616)	24 (642)	2 (645)

D After 4 skin cancers



No. at risk (events)

Unexposed	1967 (0)	574 (980)	130 (1225)	13 (1272)	0 (1273)
Nicotinamide	1091 (0)	389 (399)	97 (522)	14 (542)	1 (542)

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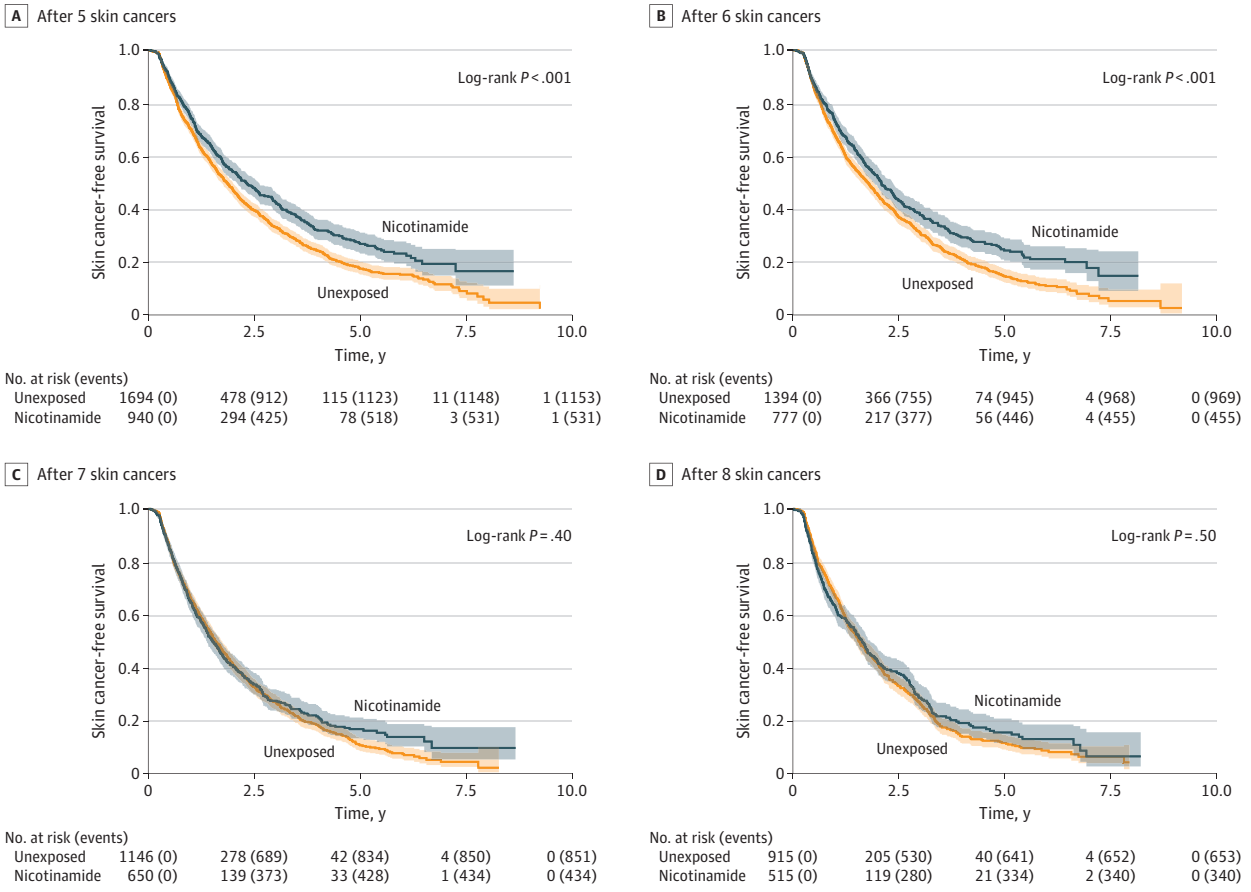
Figure 3. Skin Cancer–Free Survival Among Patients With or Without Exposure to Nicotinamide When Initiated After 5 to 8 Skin Cancers



95% CI, 0.23-0.97). Among those in the overall cohort without field therapy or acitretin exposure, there was also a significantly reduced risk of skin cancer (n = 5115; HR, 0.63; 95% CI, 0.58-0.69). Overall, patients with 30 to 90 days of nicotinamide use (HR, 0.81; 95% CI, 0.74-0.88) or 91 to 364 days of nicotinamide use (HR, 0.84; 95% CI, 0.80-0.89) had a lower risk of skin cancer compared with those with at least 365 days of exposure. The risk difference was already significant at 30 days, which was the minimum exposure duration (log-rank = 28.49; $P < .001$). More patients with longer exposure to nicotinamide initiated treatment after their tenth skin cancer or later (20.6% high vs 15.9% low; 16.0% medium; $\chi^2 = 77.52$; $P < .001$).

Discussion

In this retrospective cohort study, nicotinamide use was associated with reduced skin cancer risk in those with at least 1 prior skin cancer. This risk reduction was greatest when nicotinamide was initiated after the first skin cancer, with gradual attenuation of the protective effect when initiated after each subsequent skin cancer. The benefit was greatest for cSCC, but also was seen for BCC when initiated after the first or second skin cancer.

Our results aligned with the risk estimates previously reported that showed a 30% to 50% reduction in risk of skin cancer.[2,3,13] While these reports have been criticized for being underpowered,[3] our study included more than 4 times the number of cases included in a recent systematic review and meta-analysis.[13] However, most of these other studies were randomized clinical trials, whereas ours was observational. We attempted to address this limitation by matching not just on history of prior skin cancer, but rather on the number and timing of these cancers. We have previously shown that this approach does an excellent job at capturing disease duration and trajectory.[7] The matching did not perform well for patients with 9 or more skin cancers, so the validity of conclusions drawn from these individual strata is weak.

Timing of treatment was a crucial variable in our study, with patients experiencing benefit only when initiated after the first few skin cancers and then a gradual attenuation of the protective effect. While there is some evidence suggesting that nicotinamide could potentiate cancer growth and metastasis,[14] our data did not support this concern. Rather, our results argued that earlier initiation of chemoprevention with nicotinamide might yield better results.

The same association of timing was observed in a trial of kidney transplant recipients who switched from a calcineurin inhibitor to an mammalian target of rapamycin inhibitor;

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only those with a single prior cSCC had reduced risk, while no benefit was seen in those with multiple prior cancers.[15] As we and others have shown, once a SOTR has developed the first skin cancer, the rates of subsequent skin cancer no longer differ based on organ type,[16] and the rates of subsequent skin cancers only increase with each one.[17,18] When we restricted our analyses to only those SOTRs with 2 or fewer prior skin cancers, we observed a 53% risk reduction in cSCC, which aligned with the 30% risk reduction seen in the ONTRANS trial.[3] While still small numbers, our study provides additional data to suggest earlier use of oral chemoprevention in SOTR than guidelines currently recommend.[19] A recent study suggested no protective effect of nicotinamide among SOTRs, finding an overall HR of 1.0 but a nonsignificant HR for invasive cSCC of 0.76, which was similar to that found in that group's prior trial.[2,3] The latter study of only 158 patients had a mean of more than 7 skin cancers in the 5 years before baseline. Our study with nearly 10 times the sample size suggests that initiating nicotinamide this late might not result in protective benefits. Still, among the SOTRs in this study, we observed an even stronger significant protective effect than the point estimate from the original ONTRAC trial when initiated early.[2,20]

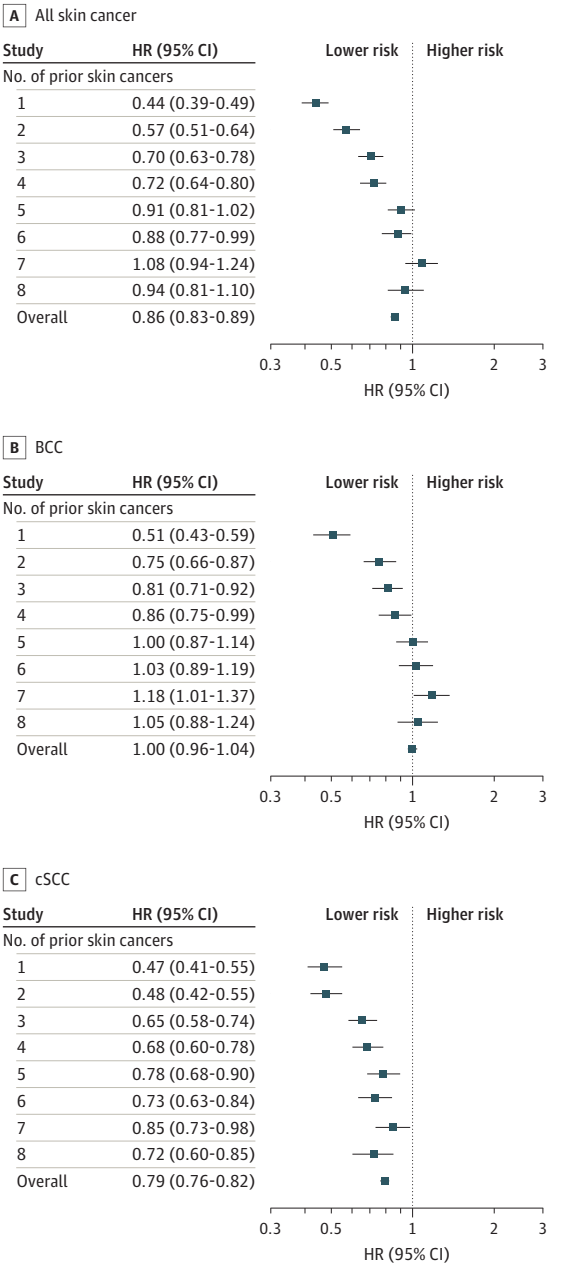
In type-specific models, we observed a reduced risk of BCC and cSCC when defining these cancers using *ICD* codes. We have previously shown that the use of *ICD* codes to determine skin cancers and types is limited, and this misspecification could potentially affect all of the subtype analyses.[9] We included only invasive cSCC codes and not SCC in situ. Studies with histologic confirmation for each skin cancer will be needed to clarify the risks for each type, although our findings were consistent with prior clinical trials.

Beyond nicotinamide, other modalities exist for skin cancer prevention, although these are often not as well tolerated. Acitretin requires laboratory monitoring and is associated with dryness, lipid elevations, and less commonly birth defects, liver failure, and pseudotumor cerebri. Topical field treatments, including PDT and fluorouracil can be effective additions to skin cancer prevention, but can be painful, invasive, and require downtime.[21,22] Most patients in our study had exposure to at least 1 preventative treatment, but nicotinamide showed benefit even after adjusting for these. When we restricted our analyses to those with no acitretin or field therapy exposure, we observed a 37% risk reduction overall.

Limitations

Our study had several limitations. The VA population is not necessarily generalizable, and the cohort was overwhelmingly White and male. However, this is a population that is at greater risk for skin cancer than the general population, so any risk reduction among this group would likely be similar to those with lesser baseline risks.[23,24] Our study design was a retrospective cohort study rather than a randomized clinical trial. We are currently in the process of developing a trial to overcome many of the limitations of observational cohorts. Despite propensity score matching, there were likely unmeasured confounders that would be better accounted for in a prospective trial.

Figure 4. Cox Proportional Hazard Model for the Risk of Developing Skin Cancer After Nicotinamide Exposure



BCC indicates basal cell carcinoma; HR, hazard ratio; SCC, squamous cell carcinoma; SOTR, solid organ transplant recipient.

It is possible that some patients in the control group were exposed to nicotinamide OTC or via a non-VA dermatologist. Therefore, our results may have underestimated the true effect. We introduced immortal time bias by excluding skin cancers treated within 90 days of baseline. However, these cancers were almost certainly biopsied and diagnosed before initiating nicotinamide, so they could not be considered related to its use. Rather, due to our measurement using *CPT* codes and not pathology reports, these exclusions were necessary to reduce bias. Patients with more synchronous or prior cancers

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might have been more likely to be prescribed nicotinamide, as we observed, which aligned with current guidelines for SOTRs.[19] Having multiple skin cancers at baseline would also indicate a greater baseline risk than we assumed, as patients with multiple skin cancers are known to have increasing risks of subsequent ones.[17,18] Instead, we still observed a protective effect of nicotinamide across most strata. We measured only procedurally treated skin cancers, which could have excluded numerous low-risk skin cancers. This finding was actually a strength of our study, as there have been prior concerns that nicotinamide primarily reduces superficial, low-risk skin cancers.[2] Including these low-risk cancers might have strengthened our measures of association. Lastly, we assumed all PDT and fluorouracil use reflected field therapy, not spot treatment. This approach assumes a lower baseline risk that would make it more difficult to detect the risk reduction that we observed.

Conclusions

This cohort study of 33 822 patients in a clinical setting observed a 16% reduction in the risk of skin cancers among patients taking nicotinamide. This risk reduction was greater for cSCC and was greater when initiated earlier after the first skin cancer.

ARTICLE INFORMATION

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Author Affiliations: Dermatology Division, Durham VA Medical Center, Durham, North Carolina (Breglio); Cutaneous Surgery and Oncology, Department of Dermatology, University of Michigan, Ann Arbor (Breglio); Vanderbilt University School of Medicine, Nashville, Tennessee (Knox, Maas); University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Hwang); Department of Dermatology, Brigham and Women's Hospital, Boston, Massachusetts (Hwang, Hartman); Dermatology Section, VA Boston Healthcare System, Boston, Massachusetts (Hwang, Hartman); Division of Epidemiology, Department of Dermatology, Vanderbilt University Medical Center, Nashville, Tennessee (Weiss, Wheless); Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee (Zhang, Yao, Xu); State University of New York Downstate College of Medicine, Brooklyn (Madden); Tennessee Valley Healthcare System VA Medical Center, Murfreesboro, Tennessee (Wheless); Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee (Wheless).

Author Contributions: Dr Wheless had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Breglio and Ms Knox contributed equally, and Drs Hartman and Wheless contributed equally.
Concept and design: Breglio, Knox, Hwang, Maas, Madden, Hartman, Wheless.
Acquisition, analysis, or interpretation of data: Breglio, Weiss, Zhang, Yao, Madden, Xu, Hartman, Wheless.
Drafting of the manuscript: Breglio, Knox, Wheless.
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Data Sharing Statement: See Supplement 2.

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