Nicotinamide and skin-cancer chemoprevention: evidence update to July 2026

Dr Paul Tervit

Domain	Current evidence	Clinical interpretation
Biological rationale	Nicotinamide replenishes cellular NAD^+, mitigates the UV-induced cellular energy deficit, supports DNA repair and reduces UV-induced immunosuppression. It is **nicotinamide/niacinamide**, not nicotinic acid/niacin; the latter causes flushing and has a different adverse-effect profile.	Mechanistically credible, but biological plausibility does not resolve uncertainty about the magnitude and durability of clinical benefit.
Pivotal RCT: immunocompetent high-risk patients	The 2015 ONTRAC phase III trial randomised 386 adults with ≥2 keratinocyte cancers in the previous five years to nicotinamide **500 mg twice daily** or placebo for 12 months. New BCC and cSCC combined were reduced by **23%**; the estimate was stronger for cSCC than BCC. Actinic keratoses also fell during treatment. Benefit was no longer evident after treatment stopped.	Best evidence supports a **treatment-dependent, modest reduction** in new keratinocyte cancers in selected immunocompetent patients with a substantial prior tumour burden. It does not establish lifelong benefit.
2025 large observational study	A Veterans Health Administration cohort included 33,822 patients with prior skin cancer. Nicotinamide exposure was associated with a **14% lower overall rate** of subsequent skin cancers and a **22% lower cSCC rate**; the apparent effect was greatest when treatment began after the first tumour, with an estimated 54% reduction in subsequent skin cancer.	Important real-world supportive evidence, particularly for **early secondary prevention and cSCC**, but it is non-randomised. The striking 54% subgroup estimate should not be interpreted as causal proof.
Methodological critique of the 2025 cohort	A 2026 appraisal highlighted possible residual confounding, immortal-time bias, exposure misclassification, flexible modelling and limited generalisability because the cohort was predominantly older, White and male.	The cohort strengthens the rationale for another adequately powered RCT; it does not supersede randomised evidence.
Solid-organ transplant recipients	The 2023 ONTRANS phase III trial found that 12 months of nicotinamide did **not** significantly reduce keratinocyte cancers or actinic keratoses in transplant recipients. A separate small kidney-transplant trial similarly did not reduce AK development and reported tolerability limitations.	Nicotinamide should **not be assumed effective in immunosuppressed transplant populations**. Their carcinogenesis and tumour burden differ materially from ONTRAC participants. Retinoids and immunosuppression modification have a stronger evidence base in selected very-high-risk recipients.
Meta-analyses	A 2022 meta-analysis reported an overall reduction in skin cancers, but with substantial heterogeneity and a weak recommendation. After inclusion of the negative transplant evidence, a 2023 meta-analysis found no statistically significant reduction in total NMSC, SCC or BCC.	The pooled conclusion is highly sensitive to population selection and trial inclusion. Combining immunocompetent and transplant cohorts may obscure a genuine effect confined to immunocompetent high-risk patients.
BCC versus cSCC	Across the RCT and subsequent cohort data, the signal is generally more convincing for **cSCC** than BCC. The large veteran study found no clear overall BCC reduction, although its early-initiation subgroup suggested benefit across tumour types.	A patient with recurrent cSCC or marked field cancerisation is a more evidence-concordant candidate than one with isolated, infrequent BCCs.
Melanoma	Existing trials were not designed or powered to establish melanoma prevention. Contemporary reviews continue to regard evidence for melanoma chemoprevention as insufficient.	Nicotinamide should **not be presented as proven melanoma prevention**. Melanoma surveillance and UV protection remain unchanged.

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Primary prevention	There is no robust evidence that pharmacological nicotinamide prevents a first skin cancer in otherwise average-risk individuals. Current studies largely involve patients with prior keratinocyte cancers or extensive actinic damage.	Routine population-wide supplementation is unsupported. Absolute benefit will be small when baseline tumour risk is low.
Safety	At 500 mg twice daily, trial tolerability has generally been favourable; gastrointestinal adverse effects occur more often than with control. Nicotinamide does not typically cause niacin-type flushing. Long-term safety beyond the durations studied remains less certain, particularly in multimorbid populations.	Review renal/hepatic disease, diabetes, polypharmacy and total vitamin-B3 exposure. Avoid accidentally substituting sustained-release **nicotinic acid**. Routine laboratory monitoring is not universally required at 1 g/day, but may be reasonable in significant hepatic or metabolic disease.

Practical synthesis for clinician discussion

Question	Evidence-based position
Who is the most defensible candidate?	An immunocompetent adult with recurrent keratinocyte cancers—particularly cSCC—or extensive field cancerisation, after discussion of modest and uncertain benefit.
Regimen with the strongest evidence	Oral nicotinamide **500 mg twice daily**, generally continued while benefit is desired; evidence suggests protection attenuates after cessation.
Who should not routinely receive it for this indication?	Average-risk individuals with no previous skin cancer; patients seeking melanoma prevention alone; transplant recipients where it is being used as a substitute for proven risk-reduction strategies.
What must accompany it?	Rigorous UV protection, sunscreen, field-directed AK treatment where indicated, regular skin examination and lesion-directed biopsy. Nicotinamide is an adjunct, not an alternative. Cancer Council Australia's current keratinocyte-cancer pathway likewise describes it as a potentially useful adjunct to sun protection.
How should benefit be framed?	"There is one positive phase III RCT and supportive observational evidence, with the clearest signal for cSCC in high-risk immunocompetent patients; confirmatory contemporary RCT evidence remains lacking."

Key research gaps

- A large, multicentre, placebo-controlled RCT stratified by baseline tumour number, cSCC versus BCC phenotype, sex, age and immunosuppression.
- Longer follow-up to assess durability, cumulative toxicity and whether earlier initiation is genuinely more effective.
- Absolute-risk and number-needed-to-treat estimates across clinically recognisable risk strata.
- Dedicated melanoma endpoints rather than incidental event reporting.
- Better evidence in women, younger adults, diverse skin phototypes and non-US/non-Australian populations.
- Trials comparing nicotinamide with, or adding it to, field therapy such as topical 5-fluorouracil.
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Bottom line:

Nicotinamide remains a reasonable, low-toxicity option for shared decision-making in **high-risk immunocompetent patients with previous keratinocyte cancers**, particularly recurrent cSCC. The latest observational evidence is encouraging, but the totality of evidence remains mixed, transplant data are negative, melanoma prevention is unproven, and broad routine use is premature.

Key references: nicotinamide and skin-cancer chemoprevention

Year	Reference	Study type / population	Main relevance	PubMed
2015	Chen AC, Martin AJ, Choy B, et al. **A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention.** *N Engl J Med.* 2015;373:1618–1626.	Phase III RCT; 386 immunocompetent adults with ≥2 non-melanoma skin cancers in the preceding 5 years	ONTRAC pivotal trial: nicotinamide 500 mg twice daily reduced new keratinocyte cancers by 23% during 12 months of treatment	PMID 26488693
2016	Chen AC, Martin AJ, Dalziell RA, et al. **A phase II randomized controlled trial of nicotinamide for skin cancer chemoprevention in renal transplant recipients.** *Br J Dermatol.* 2016;175:1073–1075.	Small phase II RCT; renal-transplant recipients	Early transplant evidence; underpowered for definitive cancer outcomes	PMID 27061568
2017	Damian DL. **Nicotinamide for skin cancer chemoprevention.** *Australas J Dermatol.* 2017.	Clinical review	Reviews photoprotection, DNA repair, immune effects and early clinical-trial evidence	PMID 28321860
2019	Snaidr VA, Damian DL, Halliday GM. **Nicotinamide for photoprotection and skin cancer chemoprevention: A review of efficacy and safety.** *Exp Dermatol.* 2019;28 Suppl 1:15–22.	Mechanistic and clinical review	Useful summary of NAD^+ replenishment, DNA repair, photoimmunosuppression and safety	PMID 30698874
2019	Chung EYM, Palmer SC, Strippoli GFM. **Interventions to prevent nonmelanoma skin cancers in recipients of a solid organ transplant: systematic review of randomized controlled trials.**	Systematic review; solid-organ transplant recipients	Found limited and uncertain evidence for nicotinamide and several other interventions in transplant recipients	PMID 31246934
2022	Mainville L, Smilga AS, Fortin PR. **Effect of Nicotinamide in Skin Cancer and Actinic Keratoses Chemoprophylaxis, and Adverse Effects Related to Nicotinamide: A Systematic Review and Meta-Analysis.** *J Cutan Med Surg.* 2022.	Systematic review and meta-analysis; 29 trials overall	Reported reduced skin-cancer rates, but with substantial heterogeneity; recommendation graded as weak	PMID 35134311
2023	Allen NC, Martin AJ, Snaidr VA, et al. **Nicotinamide for Skin-Cancer Chemoprevention in Transplant Recipients.** *N Engl J Med.* 2023;388:804–812.	Phase III placebo-controlled RCT; 158 solid-organ transplant recipients	ONTRANS trial: no reduction in keratinocyte cancers, BCC, cSCC or actinic keratoses	PMID 36856616
2023	Zhang H, George-Washburn EA, Hashemi KB, et al. **Oral Nicotinamide for Actinic Keratosis Prevention in Kidney Transplant Recipients: A Pilot Double-Blind, Randomized, Placebo-Controlled Trial.** *Transplant Proc.* 2023;55:2079–2084.	Pilot RCT; kidney-transplant recipients	No significant reduction in actinic keratoses; gastrointestinal intolerance and high attrition in the nicotinamide arm	PMID 37838527
2024	Tosti G, et al. **The Role of Nicotinamide as Chemo-Preventive Agent in NMSCs: A Systematic Review and Meta-Analysis.** *Nutrients.* 2024;16:100.	Systematic review and meta-analysis; immunocompetent and immunosuppressed populations	Found insufficient pooled evidence for a significant reduction in keratinocyte cancers	PMID 38201930
2024	**Nicotinamide for high-risk skin cancer patients: An update.**	Contemporary clinical review	Reviews patient selection, dosing and uncertainty following the negative transplant trial	PMID 39297848

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2025	Breglio KF, et al. **Nicotinamide for Skin Cancer Chemoprevention.** *JAMA Dermatol.* 2025.	Retrospective Veterans Health Administration cohort; 33,822 patients with previous skin cancer	Nicotinamide was associated with a 14% lower overall skin-cancer rate and a 22% lower cSCC rate; strongest association when started early	PMID 40960808
2025	Camillo L, et al. **Nicotinamide: A Multifaceted Molecule in Skin Health and Beyond.**	Narrative review	Updated overview of NAD^+ biology, oxidative stress, DNA repair, ageing and dermatological applications	PMID 40005371
2026	Tan E, Williams HC. **Nicotinamide for Skin Cancer Chemoprevention: The Jury Was Out and Still Is.** *Am J Clin Dermatol.* 2026;27:209–215.	Critical appraisal	Highlights residual confounding, immortal-time bias, exposure misclassification and limited generalisability in the 2025 veteran study	PMID 41505062
2026	Gilaberte Y, Ederra-Galé A, García-Alfonso JJ, Gracia-Cazaña T. **Photoprotection for Skin Cancer: What's New.** *Cancers (Basel).* 2026;18:634.	Narrative review of photoprotection literature through 2025	Places nicotinamide within broader photoprotection; supports potential benefit mainly in immunocompetent high-risk patients	PMID 41749887
2026	**Skin Cancer Prevention and Antiaging: Role of Nicotinamide.**	Updated review	Recent review specifically addressing nicotinamide in skin-cancer prevention and cutaneous ageing	PMID 42278444

Most important papers to prioritise

For a concise evidence review, the five most informative references are:

1. **ONTRAC phase III RCT — Chen et al., 2015**
2. **2022 systematic review and meta-analysis — Mainville et al.**
3. **ONTRANS transplant RCT — Allen et al., 2023**
4. **2024 updated meta-analysis — Tosti et al.**
5. **2025 VHA observational cohort plus the 2026 critical appraisal**