Does vit B3 prevent skin cancer?

Trial suggests modest benefit of nicotinamide but only for select patients

**CLINICAL SCENARIO**
Greg, a 75-year-old Anglo-Australian retiree, presented with a nodular basal cell carcinoma on his shoulder, which I excised. Greg had been an avid surfer in his youth—a lot of sun exposure with no sunscreen. Afterwards, I read in an online GP discussion forum that oral vitamin B3 (nicotinamide) might prevent further skin cancers in people like Greg. What is the evidence?

**CLINICAL QUESTION**
What is the effect of nicotinamide, used as preventive therapy, on the incidence of skin cancers?

What does the research evidence say?

**Step 1: The Cochrane Library**
No Cochrane systematic review exists for this question, although the search engine identified several papers.

**Step 2: TripDatabase**
I conducted a search using the TripDatabase PICO search tool (Participant: “adults”, Intervention: “nicotinamide”, Comparator: “placebo”, Outcomes: “skin cancer”). The TRIP search engine also identified no systematic reviews. The primary study, a randomised trial by Chen and colleagues published in the New England Journal of Medicine in 2015, was the first result.

**CRITICAL APPRAISAL**
I will use the randomised controlled trial appraisal sheet from the Centre for Evidence-Based Medicine.

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**PICO**
Participants: Who was studied?
Chen and colleagues studied 386 adults from Sydney, recruited through two teaching hospitals, who had at least two histologically confirmed non-melanoma skin cancers in the previous five years.

Important exclusions: immunosuppression, pregnancy or breastfeeding, cancer (metastatic cancer, invasive melanoma, or internal malignancy) in the previous five years, a genetic skin-cancer syndrome, large areas of confluent skin cancer (where individual lesions could not be counted), and had used several therapies (nicotinamide-containing supplements, oral retinoids, field therapies for actinic keratosis) in the previous four weeks.

Intervention: what was the exposure?
Nicotinamide 500mg twice daily × 12 months.

Comparator: what was the control/alternative?
Placebo, identical-looking coated tablets.

Outcomes: what was measured?
Primary outcome: number of new, histologically confirmed non-melanoma skin cancers (basal and squamous cell carcinomas).
Other outcomes: number of new BCCs, SCCs, and actinic keratoses.

The mean age of participants was 66, 63% were male, and about half had never smoked.
The mean number of non-melanoma skin cancers in the previous five years was eight.

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EXAMINING THE EVIDENCE

What were the results?
Primary outcomes:
• Mean number of non-melanoma skin lesions per participant at 12 months (nicotinamide vs placebo):
  • 1.8 vs 2.4, which is a relative difference of 23% (95% CI 4 to 38), \( p = 0.02 \).
  • The result favours the nicotinamide group.
Other outcomes:
• Actinic keratosis: 13% fewer at 12 months (nicotinamide vs placebo).
• Adverse events: no clinically significant differences.

DISCUSSION AND CONCLUSION
This was a well-conducted study. That nicotinamide may have a beneficial effect on non-melanoma skin cancers is well established in prior bench and phase two trials (see Stat Facts), and thus, a plausible hypothesis. However, there is imprecision in the estimate in the primary outcome. The confidence interval of the relative difference between groups ranged over an order of magnitude from 4% to 38%.

We need to consider questions about external validity:
• Is my patient so different from those in the study that the results cannot apply?
• Is the treatment feasible in my setting?
• Will the potential benefits of treatment outweigh the potential harms?

Thinking back to Greg, the participants in this study had many more prior skin cancers. This could be expected as a difference between patients in primary care compared with an academic dermatology clinic. Moreover, one of the analyses in the appendix to this paper (available from NEJM online) seems to suggest participants who had less than six skin cancers in the preceding five years had little effect from nicotinamide.

Oral nicotinamide therapy is simple, appears safe, and is relatively inexpensive — 60 tablets of nicotinamide 500mg (one month’s supply) was less than $15 when I did a price check at a local pharmacy.

My conclusion is that this treatment has a small-modest effect as prophylaxis against future non-melanoma skin cancers and may benefit patients with a history of many skin cancers the most (roughly one or more a year). UV protection remains a must. The benefit to patients with a lesser history of skin cancers is unclear.

A shared-decision making process that balances the potential benefit with the financial cost and pill burden might be appropriate.

References at medobs.com.au

Internal Validity
Are the results valid?

Randomised patient assignment?
Yes. The randomisation method is described in the supplemental protocol document available from the NEJM website. Randomisation was performed centrally by the NHMRC Clinical Trials Centre, and participants were allocated to groups, stratified by baseline skin cancer count, gender and study site.

Groups similar at the start?
Yes. The groups were very similar (see Table 1 from the paper).

Groups treated equally apart from assigned treatment?
Yes.

All patients accounted for?
Yes. Relatively few participants dropped out and the analysis was conducted on an intention-to-treat basis.

Measures objective? Or patients and clinicians kept blinded?
Yes/Probably. This primary outcome measure (histologically confirmed skin cancers) is arguably objective. Both clinicians and participants were blinded, though the effectiveness of this blinding was not reported.