Nicotinamide (niacinamide) is an effective skin chemopreventive.

Steve Minsky

American College of Healthcare Sciences

NUT 510

Eleni Delfakis BS, MS, RD, RDN

July 31, 2021

Abstract

Vitamin B3, also known as niacin, is an essential, water-soluble B-vitamin. The hydrophilic amide oral supplemental source of niacin, called niacinamide or nicotinamide, has become popular for preventive and treatment of nonmelanoma skin cancers by dermatologists, Mohs surgeons, and even internists. Skin cancer is an especially prevalent disease world-wide. As the sun gets stronger due to climate change, there are few recommendations public health experts have in their arsenal for prevention and treatment other than avoiding the sun. What is not clear is the evidence for nicotinamide for chemoprevention. Of the 62 published articles evaluated, 13 were chosen. The articles covered a wide variety of evidence for nicotinamide, elucidating its actions as a chemopreventive and treatment mainly for nonmelanoma carcinomas. There was a dearth of evidence from human clinical trials, which led to questions as to why nicotinamide seemed to be so widely prescribed by skin health professionals. Other evidence in cell culture studies brought to light evidence that suggests further research should be explored for other cancers besides nonmelanoma. In this unusual case, it seems the evidence of nicotinamide as a chemopreventive trails its commonly accepted reputation as safe, economical preventive and treatment. Ultimately, more evidence is needed for its acceptance as a worldwide recommendation as a cancer preventive and treatment, but for now, the number of skin care health professionals recommending it has increased significantly.

Keywords: nicotinamide, niacinamide, niacin, hydrophilic amide, squamous cell carcinoma, basal cell carcinoma, melanoma, skin cancer, nonmelanoma cancer, Mohs surgeon, dermatologist, chemoprevention.

Introduction

The purpose of this review was to assess the data concerning the effectiveness of nicotinamide (niacinamide) as a chemopreventive. Aside from avoiding the sun, public health experts, dermatologists, and internists have few options to recommend for their patients when it comes to skin cancer prevention. This strategy is not ideal because when patients have to avoid the sun, they do not go outdoors, which reduces stress, and may lead to vitamin D deficiency.

Within the last ten years, health professionals with expertise in skin cancer and dermatology especially, have discovered the benefits of a hydrophilic amide form of niacin called nicotinamide (also known as niacinamide, but for this paper we will call it nicotinamide). Dermatologists and Mohs surgeons routinely recommend nicotinamide not only as a preventive, but as a treatment for squamous cell cancer, basal cell cancer, and actinic keratoses.

Nicotinamide has a track record of safety at daily doses between 3-6 grams daily and can be used during any cancer treatment. The impetus for prescribing nicotinamide comes from its supposed ability to contribute to DNA repair, accelerate cancer cell apoptosis, enhance cellular energy function, optimize cellular oxygenation, and perform anti-inflammatory action

The purpose of this study is to corroborate nicotinamide prophylaxis with current research, as well as assess its effectiveness as a chemopreventive as shown in the data. There has been substantive research, mostly in small human trials and cell culture trials. After reviewing the current data, nicotinamide seems to be a safe, effective, and cost-effective option as a chemopreventive for numerous forms of cancer, especially of the skin. Thus, nicotinamide (niacinamide) is an effective skin chemo-preventive.

Results

In a phase 3, double-blind, randomized, controlled trial, Chen et. al (2015) found that oral nicotinamide was safe and effective at reducing nonmelanoma skin cancers and actinic keratoses in high-risk subjects. The study covered a sample size of 386 participants over a 12 month period. Participants were instructed to take 500 mg. nicotinamide twice daily or placebo for the duration of the study. Researchers found a 20% lower rate of new basal-cell carcinomas, 30% lower rate of squamous-cell carcinomas, and 11% lower rate of actinic keratoses in those taking nicotinamide versus placebo. There were no differences in adverse events between the two groups. Moreover, when the nicotinamide was discontinued after the study was complete, there was no evidence of benefit when participants were contacted 6 months after the study finished. Half of the high-risk participants did not use sunscreen and still showed a decrease in nonmelanoma skin cancer risk, thus making the case for oral nicotinamide as a strong chemopreventive. One limitation of the study was the focus only on subjects who had two confirmed cases of nonmelanoma skin cancer in the last five years. The project was funded by a grant from the Australian government. None of the authors had any conflicts of interest or affiliation with companies who manufacture nicotinamide supplements.

Because nicotinamide has shown to reduce the risk of keratinocyte carcinoma, Desai, S., Olbricht, S., Ruiz, E. S., & Hartman (2021) performed a survey of Mohs surgeons from The American College of Mohs Surgeons to ascertain the prescribing habits of nicotinamide for skin cancer prevention. The survey was robust, with 1,500 subjects, and extensive with numerous questions about efficacy, longevity, and safety of nicotinamide. 76% of surgeons surveyed

recommend nicotinamide for keratinocyte carcinoma prevention. Moreover, the surgeons were confident in its safety record. Authors reported no conflicts of interest.

In this study, Malesu et. al (2020) are some of the first researchers to postulate that nicotinamide may be chemoprotective for melanoma. All previous studies have shown chemoprevention against squamous cell cancer. The study was performed ex-vivo and in-vivo on human melanoma cell lines against a placebo, so clinical trials are indicated. Researchers noted a significant lymphocyte response in the nicotinamide samples versus no response in placebo. There were no author conflicts of interest.

This letter to the editor by Minocha et. al (2019) was an in-depth explanation about the chemopreventive properties of nicotinamide for prevention of keratinocyte cancers. The authors cited numerous studies indicating the inhibition of inflammatory cytokines from macrophages and monocytes may be the reason behind nicotinamide's chemopreventive capabilities. Nicotinamide may assist with DNA repair, thus reducing DNA photolesions which can launch ultraviolet-induced immune dysfunction. Another discovery of Minocha's own research was a reduced number of macrophages in subjects taking nicotinamide with keratinocyte carcinomas, thus reducing tumor cell expression. The authors report no conflicts of interest.

In this epidemiological statistical analysis, Park et. al (2017) were the first to examine the effect of niacin/nicotinamide intake in a cohort of male and female Americans. It is the largest study of its kind on the chemopreventive effects of niacin to date. The authors discovered that the quartile with the largest nicotinamide intake was inversely associated with squamous cell cancer compared with the lowest quartile. The authors were meticulous in eliminating confounding factors but took detailed lifestyle and dietary data from questionnaires. The researchers followed

the subjects for 24-26 years. One drawback was that the bulk of the population studied were Caucasian. Authors had no competing financial interests and the funding came from the National Institutes of Health of the United States and National Research Foundation of Korea.

In a cell culture study, Zhen et. al (2019) examined the protective effect of nicotinamide on keratinocyte cells from oxidative stress due to air pollution particulate matter. It is well known that particulate matter in the air from pollution creates excess reactive oxygen species in many organ systems. Until this study, little research had been done of the effect of pollution on skin cells. The researchers discovered that particulate matter less than less than 2.5 μm can attach to skin cells and induce oxidative stress. The results of the study found that nicotinamide protected keratinocyte cells by exhibiting an anti-oxidative effect, thus limiting lipid peroxidation, DNA damage, mitochondrial dysfunction, stress on proteins, and limited excessive apoptosis. The limitations of this study is that nicotinamide's effects were only tested in cell cultures. The authors listed no conflicts of interest and funding came from educational and government grants.

A review by Fania et. al (2019) elucidates the positive effect of nicotinamide for ultraviolet-mediated immunosuppression, preventing skin aging, maintaining genomic stability, preventing nonmelanoma skin cancers, and suppressing tumor development. While most studies focus on oral supplementation of nicotinamide, the researchers list foods that are rich in nicotinamide, such as meat, fish, eggs, legumes, mushrooms, nuts, and grains. The researchers explained how nicotinamide is widely absorbed in the gastrointestinal tract, but can also be synthesized through tryptophan metabolism. The study connected skin aging with greater risk of tumor development and explained that a diet rich in nicotinamide can attenuate skin aging. The researchers have a detailed explanation about the positive chemopreventive effect of oral

supplementation of nicotinamide, including the fact that it is non-flushing, unlike regular niacin. Finally, the authors emphasized numerous times the importance of cellular energy for DNA repair, and that nicotinamide was effective for maintaining this function.

The cell line culture study by Kim et. al (2017) was the first to exhibit a positive effect of nicotinamide on triple negative breast cancer cell growth. The researchers were spurred on from the positive results of nicotinamide on squamous and basal cancer cells. The researchers treated the breast cancer cells with different dosages of nicotinamide, including a dose similar to those used in skin cancer cell studies, as well as the maximum dose that is believed to be tolerable. Researchers saw a significantly reduced number of colony numbers through the apoptosis action of nicotinamide, even in the most aggressive breast cancer cells. This study was the first to test nicotinamide's ability to reduce SIRT1 protein expression, which is associated with cancer cell proliferation. The researchers discerned that nicotinamide significantly enhanced p53 activity, which reduced SIRT1 expression. Researchers were also able to explain how nicotinamide promotes DNA damage in cancer cells but leaves healthy cells untouched. The authors have no conflict of interest and funding came from university grants.

Two *Skin Therapy Letters* reviews from Nazarali & Kuzel (2017) and Huber & Wong (2020) lauded the chemopreventive benefits of nicotinamide. Both evaluated existing evidence and explained nicotinaminde's actions. The reviews were important because they emphasized the great difference between nicotinamide and niacin. The authors elucidated that nicotinamide does not create HDL-cholesterol-modifying or detrimental vasodilatory effects that niacin does because nicotinamide is the result of niacin conversion, or the activated form of niacin.

Discussion

There cannot be a discussion about nicotinamide without starting with the study performed by Chen et. al (2015). This study was really the impetus for health professionals, dermatologists, and surgeons to pay attention to nicotinamide as a chemopreventive for nonmelanoma skin cancers and actinic keratoses. While the number of participants was fairly small for a human clinical trial (386), the fact that it is a phase 3, double-blind, randomized, controlled trial, is enough to draw a tremendous amount of credibility in the allopathic medical field. The 12 month study with a follow up 6 months later is long enough to satisfy early adopters. Additionally, there are so few options for skin cancers that can act not only as a preventive, but treatment. This is why there was such excitement around the study. There was no industry influence, and the authors had no conflicts of interest, so the study rises above controversy. There is very little to fault in the structure of the study except that the treated individuals had previously been diagnosed with skin cancer. It would be interesting to see the results of a study done on subjects without a history of skin cancer followed for a long period of time. In addition, there should be a study performed on the effectiveness of nicotinamide in subjects after being diagnosed with their first case of skin cancer. Nevertheless, the fact that high-risk subjects could glean skin cancer prevention from 500 mg. nicotinamide twice daily from something with virtually no side effects and is economical was noticeable. Specifically, the researchers found a 20% lower rate of new basal-cell carcinomas, 30% lower rate of squamous-cell carcinomas, and 11% lower rate of actinic keratoses in those taking nicotinamide versus placebo. There were no differences in adverse events between the two groups.

Nicotinamide seems to have a protective effect in high-risk subjects that do not use sunscreen when in the sun. This is important for those wanting to be outdoors and get sun exposure. Unfortunately, it seems that nicotinamide may need to be taken long-term as the researchers found no benefit six months after the subjects stopped taking it. But the fact that nicotinamide is inexpensive makes it ideal for long-term prophylaxis.

The importance of corroborating real-world use of any treatment that has few human clinical trials cannot be understated. A survey performed by Desai, S., Olbricht, S., Ruiz, E. S., & Hartman (2021) with a group of Mohs surgeons from The American College of Mohs Surgeons to ascertain the prescribing habits of nicotinamide for skin cancer prevention was critical to further legitimize nicotinamide. If there were any health professionals on the fence about nicotinamide, the survey of 1,500 skin professionals, with numerous questions about efficacy, longevity, and safety of nicotinamide, laid any doubts to rest. 76% of surgeons surveyed recommend nicotinamide for keratinocyte carcinoma prevention. Moreover, the surgeons are confident in its safety record and economic value. *Skin Therapy Letter* is a valued journal for dermatologists and all types of skin surgeons. Minocha et. al (2017, 2019) wrote two detailed synopses of nicotinamide that explained the current research, as well as provides a nicotinamide roadmap for its use, further legitimizing its use from 500 mg to 3 grams depending upon the situation. A review by Fania et. al (2019) elucidates the myriad chemopreventive methods of nicotinamide though ultraviolet-mediated immunosuppression, preventing skin aging, maintaining genomic stability, preventing nonmelanoma skin cancers, and suppressing tumor development. Instead of focusing on just oral supplementation of nicotinamide, researchers list foods rich in nicotinamide, such as meat, fish, eggs, legumes, mushrooms, nuts, and grains.

The focus of discussion about nicotinamide's effectiveness targeted only nonmelanoma cancers, until recently. An ex-vivo and in-vivo study performed by Malesu et. al (2020) is the first to explore nicotinamide as a chemoprotective for melanoma. A cell line culture study by Kim et. al (2017) is the first to explore the effect of nicotinamide on triple negative breast cancer cell growth. Because both were not performed on human subjects, the success of both trials against human cancer cells must be tempered. The melanoma study is significant because it was the first to discover a significant lymphocyte response in the nicotinamide samples versus no response in placebo. The breast cancer study is the first to test nicotinamide's ability to reduce SIRT1 protein expression, which is associated with cancer cell proliferation. The discovery that nicotinamide significantly enhances p53 activity, which reduced SIRT1 expression, is a novel finding.

In the one major epidemiological study performed on niacin/nicotinamide use, Park et. al (2017) discovers that the quartile with the largest nicotinamide intake is inversely associated with squamous cell cancer compared with the lowest quartile. The study is impressive because intake was taken from the 72,308 women in the Nurses' Health Study (1984–2010) and 41,808 men in the Health Professionals Follow-up Study (1986–2010). Moreover, niacin/nicotinamide intake was assessed every 2 to 4 years during follow-up over a 24-26 year span.

A significant cell culture study performed by Zhen et. al (2019) sheds light on the protective effect of nicotinamide on keratinocyte cells from oxidative stress due to air pollution particulate matter, which can be especially important for low income countries seeking inexpensive preventive treatments for pollution exposure.

Conclusion

The evidence points to a chemoprotective effect from nicotinamide against several forms of cancer. The one major human trial elucidates beneficial effects of oral supplementation of nicotinamide for squamous cell and basal cell skin cancers, and actinic keratoses. Cell culture testing indicates nicotinamide as successful in reducing breast cancer and melanoma cancer cells.

It is surprising that oral nicotinamide supplements have become such an integral part of prevention and treatment by dermatologists and Mohs surgeons without many large, human trials. Perhaps the track record of nicotinamide's safety and patient success allays any concern. The future for nicotinamide as a chemopreventive seems encouraging and looks to become a long-term stalwart for prevention and treatment of multiple types of cancer.

References

Chen, A. C., Martin, A. J., Choy, B., Fernández-Peñas, P., Dalziell, R. A., McKenzie, C. A., Scolyer, R. A., Dhillon, H. M., Vardy, J. L., Kricker, A., St George, G., Chinniah, N., Halliday, G. M., & Damian, D. L. (2015). A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention. The New England journal of medicine, 373(17), 1618–1626. https://doi.org/10.1056/NEJMoa1506197

Chhabra, G., Garvey, D. R., Singh, C. K., Mintie, C. A., & Ahmad, N. (2019). Effects and Mechanism of Nicotinamide Against UVA- and/or UVB-mediated DNA Damages in Normal Melanocytes. Photochemistry and photobiology, 95(1), 331–337. https://doi.org/10.1111/php.12994

Desai, S., Olbricht, S., Ruiz, E. S., & Hartman, R. I. (2021). Nicotinamide for Keratinocyte Carcinoma Chemoprevention: A Nationwide Survey of Mohs Surgeons. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.], 47(4), 452–453. https://doi.org/10.1097/DSS.0000000000002788

Fania, L., Mazzanti, C., Campione, E., Candi, E., Abeni, D., & Dellambra, E. (2019). Role of Nicotinamide in Genomic Stability and Skin Cancer Chemoprevention. International journal of molecular sciences, 20(23), 5946. https://doi.org/10.3390/ijms20235946

Huber, R., & Wong, A. (2020). Nicotinamide: An Update and Review of Safety & Differences from Niacin. Skin therapy letter, 25(5), 7–11.

Kim, J. Y., Lee, H., Woo, J., Yue, W., Kim, K., Choi, S., Jang, J. J., Kim, Y., Park, I. A., Han, D., & Ryu, H. S. (2017). Reconstruction of pathway modification induced by nicotinamide using multi-omic network analyses in triple negative breast cancer. Scientific reports, 7(1), 3466. https://doi.org/10.1038/s41598-017-03322-7

Malesu, R., , Martin, A. J., , Lyons, J. G., , Scolyer, R. A., , Chen, A. C., , McKenzie, C. A., , Madore, J., , Halliday, G. M., , & Damian, D. L., (2020). Nicotinamide for skin cancer chemoprevention: effects of nicotinamide on melanoma in vitro and in vivo. Photochemical & photobiological sciences : Official journal of the European Photochemistry Association and the European Society for Photobiology, 19(2), 171–179. https://doi.org/10.1039/c9pp00388f

Minocha, R., Martin, A. J., Chen, A. C., Scolyer, R. A., Lyons, J. G., McKenzie, C. A., Madore, J., Halliday, G. M., & Damian, D. L. (2019). A Reduction in Inflammatory Macrophages May Contribute to Skin Cancer Chemoprevention by Nicotinamide. The Journal of investigative dermatology, 139(2), 467–469. https://doi.org/10.1016/j.jid.2018.08.018

Nazarali, S., & Kuzel, P. (2017). Vitamin B Derivative (Nicotinamide) Appears to Reduce Skin Cancer Risk. Skin therapy letter, 22(5), 1–4.

New skin cancer prevention method discovered. Aesthetics Journal. Retrieved from: https://aestheticsjournal.com/news/new-skin-cancer-prevention-method-discovered

Nikas, I. P., Paschou, S. A., & Ryu, H. S. (2020). The Role of Nicotinamide in Cancer Chemoprevention and Therapy. Biomolecules, 10(3), 477. https://doi.org/10.3390/biom10030477

Park, S. M., Li, T., Wu, S., Li, W. Q., Weinstock, M., Qureshi, A. A., & Cho, E. (2017). Niacin intake and risk of skin cancer in US women and men. International journal of cancer, 140(9), 2023–2031. https://doi.org/10.1002/ijc.30630

Zhen, A. X., Piao, M. J., Kang, K. A., Fernando, P., Kang, H. K., Koh, Y. S., Yi, J. M., & Hyun, J. W. (2019). Niacinamide Protects Skin Cells from Oxidative Stress Induced by Particulate Matter. Biomolecules & therapeutics, 27(6), 562–569. Advance online publication. https://doi.org/10.4062/biomolther.2019.061