The Role of Dietary Antioxidants in Melanoma and Nonmelanoma Skin Cancer

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PRACTICE **POINTS**

- Melanoma and nonmelanoma skin cancer (NMSC) are 2 of the most frequently diagnosed cancers in the United States. UV radiation plays a key role in the pathogenesis of both.
- Dietary antioxidants may mechanistically decrease DNA damage caused by UV radiation and could play a potential role in the prevention or development of melanoma and NMSC.

Dietary supplements, including vitamins and their derivatives, have been utilized within the field of dermatology to treat a variety of skin conditions. Antioxidants inhibit oxidation and decrease cellular damage caused by free radicals, potentially preventing DNA damage due to UV radiation. Laboratory studies have demonstrated promising results supporting the possible role of antioxidants for prevention of skin cancer related to UV exposure. We review the effects of frequently encountered antioxidants and vitamins suggested for the chemoprevention of melanoma and nonmelanoma skin cancer (NMSC) in humans.

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Nonmelanoma skin cancer (NMSC) is the most common cancer in the United States, and cutaneous melanoma is projected to be the fifth most common form of cancer in 2022, with increasing incidence and high potential for mortality.[1-3] Estimates indicate that 35% to 45% of all cancers in White patients are cutaneous, with 4% to 5% occurring in Hispanic patients, 2% to 4% in Asian patients, and 1% to 2% in Black patients.[4] Of the keratinocyte carcinomas, basal cell carcinoma (BCC) is the most prevalent, projected to affect approximately 33% to 39% of White males and 23% to 28% of White females in the United States during their lifetimes. Squamous cell carcinoma (SCC) is the second most common skin malignancy, with a lifetime risk of 9% to 14% for White males and 4% to 9% for White females in the United States.[5] The incidence of melanoma continues to increase, with approximately 99,780 new cases expected in the United States in 2022.[1]

UV-induced DNA damage plays a key role in the pathogenesis and development of various skin malignancies.[6] UV radiation from sunlight or tanning devices causes photocarcinogenesis due to molecular and cellular effects, including the generation of reactive oxygen species, DNA damage due to the formation of cyclobutane pyrimidine dimers and pyrimidine-pyrimidone, melanogenesis, apoptosis, and the increased expression of harmful genes and proteins.[6] The summation of this damage can result in skin malignancies, including NMSC and melanoma.[6,7] Dietary antioxidants theoretically help prevent oxidative reactions from occurring within the body, and it has been suggested that intake of dietary antioxidants may decrease DNA damage and prevent tumorigenesis secondary to UV radiation.[8] Antioxidants exist naturally in the body but can be acquired exogenously. Investigators have studied dietary antioxidants in preventing skin cancer formation with promising results in the laboratory setting.[8-11] Recently, more robust human studies have been initiated to further delineate this relationship. We present clinical evidence of several frequently utilized antioxidant vitamins and their effects on melanoma and NMSC.

Antioxidants

Vitamin A—Vitamin A is a fat-soluble vitamin found in animal sources, including fish, liver, and eggs. Carotenoids, such as beta carotene, are provitamin A plant derivatives

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found in fruits and vegetables that are converted into biologically active retinol and retinoic acid.[12] Retinols play a key role in cellular growth and differentiation and are thought to be protective against skin cancer via the inactivation of free radicals and immunologic enhancement due to their antiproliferative, antioxidative, and antiapoptotic effects.[13-16] Animal studies have demonstrated this protective effect and the ability of retinoids to suppress carcinogenesis; however, human studies reveal conflicting results.[17,18]

Greenberg et al[19] investigated the use of beta carotene in preventing the formation of NMSC. Patients (N=1805) were randomized to receive 50 mg of beta carotene daily or placebo. Over a 5-year period, there was no significant reduction in the occurrence of NMSC (relative risk [RR], 1.05; 95% CI, 0.91-1.22).[19] Frieling et al[20] conducted a similar randomized, double-blind, placebo-controlled trial investigating beta carotene for primary prevention of NMSC in 22,071 healthy male physicians. The study group received 50 mg of beta carotene every other day for 12 years' duration, and there was no significant effect on the incidence of first NMSC development (RR, 0.98; 95% CI, 0.92-1.05).[20]

A case-control study by Naldi et al[21] found an inverse association between vitamin A intake and development of melanoma. Study participants were stratified into quartiles based on level of dietary intake and found an odds ratio (OR) of 0.71 for beta carotene (95% CI, 0.50-1.02), 0.57 for retinol (95% CI, 0.39-0.83), and 0.51 for total vitamin A (95% CI, 0.35-0.75) when comparing the upper quartile of vitamin A intake to the lower quartile. Upper-quartile cutoff values of vitamin A intake were 214 µg/d for beta carotene, 149 µg/d for retinol, and 359 µg/d for total vitamin A.[21] More recently, a meta-analysis by Zhang et al[22] pooled data from 8 case-control studies and 2 prospective studies. Intake of retinol but not total vitamin A or beta carotene was associated with a reduced risk for development of melanoma (retinol: OR, 0.80; 95% CI, 0.69-0.92; total vitamin A: OR, 0.86; 95% CI, 0.59-1.25; beta carotene: OR, 0.87; 95% CI, 0.62-1.20).[22] Feskanich et al[23] demonstrated similar findings with use of food-frequency questionnaires in White women, suggesting that retinol intake from food combined with supplements may be protective for women who were otherwise at a low risk for melanoma based on nondietary factors. These factors included painful or blistering sunburns during childhood, history of more than 6 sunburns, more than 3 moles on the left arm, having red or blonde hair, and having a parent or sibling with melanoma (P=.01). However, this relationship did not hold true when looking at women at an intermediate or high risk for melanoma (P=.16 and P=.46).[23]

When looking at high-risk patients, such as transplant patients, oral retinoids have been beneficial in preventing NMSC.[24-27] Bavinck et al[24] investigated 44 renal transplant patients with a history of more than 10 NMSCs treated with 30 mg of acitretin daily vs placebo. Patients receiving oral retinoid supplementation developed fewer NMSCs over a 6-month treatment period (P=.01).[24] Similarly, George et al[25] investigated acitretin in renal transplant patients and found a statistically significant decrease in number of SCCs in patients on supplementation (P=.002). Solomon-Cohen et al[26] performed a retrospective case-crossover study in solid organ transplant recipients and found that those treated with 10 mg of acitretin daily for 2 years had a significant reduction in the number of new keratinocyte carcinomas (P=.002). Other investigators have demonstrated similar results, and in 2006, Otley et al[27] proposed standardized dosing of acitretin for chemoprevention in high-risk patients, including patients developing 5 to 10 NMSCs per year, solid organ transplant recipients, and those with syndromes associated with the development of NMSC.[28,29] Overall, in the general population, vitamin A and related compounds have not demonstrated a significant association with decreased development of NMSC; however, oral retinoids have proven useful for high-risk patients. Furthermore, several studies have suggested a negative association between vitamin A levels and the incidence of melanoma, specifically in the retinol formulation.

Vitamin B_3—Nicotinamide (also known as niacinamide) is a water-soluble form of vitamin B_3 and is obtained from animal-based and plant-based foods, such as meat, fish, and legumes.[30] Nicotinamide plays a key role in cellular metabolism, cellular signaling, and DNA repair, including protection from UV damage within keratinocytes.[31,32] Early mouse models demonstrated decreased formation of skin tumors in mice treated with topical or oral nicotinamide.[32,33] A number of human studies have revealed similar results.[34-36]

Chen et al[34] conducted the ONTRAC study, a phase 3, double-blind, randomized controlled trial (RCT) looking at 386 participants with a history of at least 2 NMSCs in the preceding 5 years. At 12 months, those treated with 500 mg of nicotinamide twice daily demonstrated a statistically significant decreased rate of SCC formation (P=.05). A decreased incidence of BCC development was noted; however, this trend did not reach statistical significance (P=.12). Precancerous skin lesions also were found to be decreased in the treatment group, with 20% lower incidence of actinic keratoses (AKs) after 9 months of treatment (P<.001).[34] Drago et al[35] specifically studied the incidence of AKs in 38 transplant recipients—8 liver and 30 kidney—and found that previously noted AKs had decreased in size for 18 of 19 patients taking 500 mg of nicotinamide daily when originally photographed AKs were remeasured at 6-month follow-up, with 7 of these 18 patients demonstrating complete clinical regression. Of those on nicotinamide supplementation, no new AKs developed compared to the control group, which demonstrated increased size of AKs or development of new AKs in 91% of patients, with 7 AKs progressing into SCC.[35]

Nicotinamide has been demonstrated to be useful in preventing skin cancer in high-risk populations, such as transplant patients or those with a high incidence of

NMSC.[34,36] Despite promising results within the laboratory setting, nicotinamide's effects on melanoma in humans remains less clear.[31,37] Studies suggest that nicotinamide enhances tumor-infiltrating lymphocytes and DNA repair mechanisms in melanocytes, which may translate into nicotinamide, providing chemoprevention for melanoma, but research in human patients is limited.[31,37]

Vitamin B_9—Folate, the natural form of vitamin B_9, is a water-soluble compound that is found in many foods, especially green leafy vegetables, and often is supplemented because of its health benefits.[38,39] In the skin, folic acid plays a key role in cellular replication and proliferation.[38] Controversy exists regarding folate's effects on cellular growth and turnover with respect to cancer incidence.[38,40] Donnenfeld et al[41] conducted a prospective study assessing dietary folic acid intake and development of NMSC. A total of 5880 participants completed dietary records throughout the first 2 years of the study. After an average follow-up period of 12.6 years, there was an overall increased incidence of skin cancer in those with increased dietary folate (P=.03). Furthermore, when striating by skin cancer type, there was an increased incidence of NMSC overall as well as BCC when analyzing by type of NMSC (P=.03 for NMSC; P=.05 for BCC). However, when stratifying by gender, these findings only held true for women.[41] Similar effects were observed by Fung et al,[42] who prospectively studied the intake of various vitamins in relationship to the development of BCC in women. During 12 years of follow-up, a positive association was observed between folate intake and BCC development (OR, 1.2; 95% CI, 1.10-1.31).[42] Fung et al[43] also investigated the role of several vitamins in the development of SCC and found that folate showed a negative association, which did not reach statistical significance (RR, 0.79; 95% CI, 0.56-1.11). Furthermore, Vollset et al[40] conducted a meta-analysis comparing folic acid to placebo in the incidence of various types of cancer. The study excluded NMSC but reported no significant association between the development of melanoma and folic acid supplementation.[40] In summary, the effects of folate have diverse consequences, potentially promoting the formation of NMSC, but studies suggest that an individual's gender and other genetic and environmental factors also may play a role.

Vitamin C—Vitamin C (also known as ascorbic acid) is a water-soluble vitamin with antioxidant immune-mediating effects. It is found in various fruits and vegetables and serves as a cofactor for enzymes within the body playing a key role in immune function and collagen formation.[44,45] It has been postulated that ascorbic acid can provide protection from UV radiation damage via its intracellular activity but conversely can contribute to oxidative damage.[44] Multiple in vitro laboratory studies and animal models have demonstrated photoprotective effects of ascorbic acid.[46-48] Despite these findings, minimal photoprotective effects have been found in the human population.

Kune et al[49] performed a case-control study of 88 males with previously diagnosed NMSC undergoing surgical removal and investigated patients' prior dietary habits. Patients with NMSC had a statistically significantly lower level of vitamin C–containing food in their diet than those without NMSC (P=.004).[49] In addition, Vural et al[50] analyzed plasma samples and blood cells of patients with AK and BCC and found a significant decrease in ascorbic acid levels in both the AK (P<.001) and BCC (P<.001) groups compared with controls. However, studies have found that consumption of certain dietary compounds can rapidly increase plasma concentration levels, which may serve as a major confounding variable in this study. Plasma concentrations of ascorbic acid and beta carotene were found to be significantly increased following consumption of a high-antioxidant diet for as short a duration as 2 weeks (P<.05).[51] More recently, Heinen et al[52] performed a prospective study on 1001 adults. In patients without a history of skin cancer, they found that vitamin C from food sources plus dietary supplements was positively associated with the development of BCC (P=.03).[52] Similarly, Fung et al[42] performed a study in women and found a positive association between vitamin C intake and the development of BCC (OR, 1.13; 95% CI, 1.03-1.23).

The relationship between vitamin C intake—either in dietary or supplemental form—and melanoma remains controversial. Mice-based studies found that high concentrations of orally administered vitamin C induce cytotoxicity in melanoma cell lines, but at low concentrations they promote tumor growth of malignant melanoma.[53] Feskanich et al[23] examined the relationship between vitamin C intake and melanoma development via food frequency questionnaires in White women and found that vitamin C was associated with a higher risk for melanoma (P=.05), and furthermore, a positive dose response with frequency of orange juice intake was observed (P=.008). Overall, despite promising laboratory studies, there is a lack of RCTs investigating the use of vitamin C supplementation for prevention of NMSC and melanoma in humans, and the oral benefits of vitamin C for chemoprevention remain unclear.

Vitamin D—Vitamin D is a fat-soluble vitamin that is found in fish, liver, egg, and cheese, and is endogenously produced when UV radiation from sun exposure interacts with the skin, triggering the synthesis of vitamin D.[54] Vitamin D is biologically inactive and must be converted to its active form 1,25-dihydroxyvitamin D after entering the body. Vitamin D modulates many genes involved in cellular proliferation and differentiation.[54] Vitamin D receptors are expressed on keratinocytes and melanocytes.[55] Animal studies have demonstrated a potentially protective effect of vitamin D in the development of NMSC.[56] In a mouse model, Ellison et al[56] found that mice without vitamin D receptors developed skin tumors more rapidly than those with vitamin D receptors.

Unfortunately, these findings have not been demonstrated in humans, and studies have even reported

an increased risk for development of NMSC in patients with normal or increased vitamin D levels compared with those with low levels of vitamin D.[57-60] Eide et al[57] studied 3223 patients seeking advice for low bone density by recording their vitamin D levels at the time of presentation and monitoring development of NMSC. Vitamin D levels greater than 15 ng/mL were positively associated with the development of NMSC (OR, 1.7; 95% CI, 1.04-2.7). This association held true for both SCC and BCC, with a higher risk estimated for SCC (OR, 3.2; 95% CI, 0.4-24.0 for SCC; OR, 1.7; 95% CI, 0.5-5.8 for BCC).[57] An increased vitamin D serum level also was found to be significantly associated with a higher risk for BCC and melanoma by van der Pols et al.[58] This prospective study looked at the incidence of skin cancer over 11 years. Study participants with vitamin D levels over 75 nmol/L more frequently developed BCC (P=.01) and melanoma (P=.05). In contrast, SCC was less frequently observed in participants with these high levels of vitamin D (P=.07).[58] Furthermore, Park et al[60] looked at vitamin D and skin cancer risk for men and women in the United States and found no association with risk for SCC or melanoma but a positive association with BCC (P=.05 for total vitamin D; P<.01 for dietary vitamin D). Additional studies have been performed with inconsistent results, and multiple authors suggest the possible confounding relationship between vitamin D levels and UV radiation exposure.[59-62] Furthermore, some studies have even demonstrated a negative association between vitamin D and NMSC. Tang et al[63] performed a retrospective case-control study in elderly males, investigating serum levels of vitamin D and patients' self-reported history of NMSC, which demonstrated that higher levels of vitamin D were associated with a decreased risk for NMSC. Overall, the relationship between vitamin D and skin cancer development remains unclear for both melanoma and NMSC.

Vitamin E—Vitamin E is a fat-soluble vitamin that is found in plant-based oils, nuts, seeds, fruits, and vegetables.[64] It works as an antioxidant to protect against free radicals and heighten immune function, and it also serves as a pro-oxidant.[65,66] Vitamin E naturally exists in 8 chemical forms, of which gamma-tocopherol is the most frequently obtained form in the diet, and alpha-tocopherol is the most abundant form found in the body.[64,65]

Early animal studies demonstrated the inhibition of UV-induced damage in mice receiving vitamin E supplementation.[67,68] Human studies have not consistently shown these effects. Vural et al[50] investigated plasma samples and blood cells of patients with AKs and BCCs and reported a significant decrease in alpha-tocopherol levels in both the AK (P<.05) and BCC (P<.001) groups compared with controls. However, studies also have demonstrated a positive association between vitamin E intake and the development of BCC, including one by Fung et al,[42] which found a significant association in women (OR, 1.15; 95% CI, 1.06-1.26).

Vitamin E has been found to inhibit melanin synthesis in the laboratory, suggesting a potentially protective effect in melanoma.[69,70] However, in the study performed by Feskanich et al[23] examining vitamin intake and melanoma incidence via food-frequency questionnaires, vitamin E was not associated with a lower risk for melanoma. Despite promising laboratory studies, the data surrounding the use of a vitamin E supplement for prevention of melanoma and NMSC in humans remains unclear.

Selenium—Selenium is a trace mineral found in plants, meat, and fish. It plays a key role in reproduction, hormone metabolism, DNA synthesis, and protection from oxidative damage.[71] In mice studies, lack of selenium-containing proteins resulted in skin abnormalities, including the development of a hyperplastic epidermis and aberrant hair follicle morphogenesis with alopecia after birth, and numerous experimental studies have demonstrated a negative association between selenium intake and cancer.[72,73] However, human studies have yielded alternative results.

The Nutritional Prevention of Cancer Study Group analyzed 1312 dermatology patients with a history of NMSC.[74] The study population was obtained from 7 dermatology clinics with randomization to control for confounding variables. Study participants received either 200 µg of selenium daily or placebo.[74] Baseline characteristics of each study group were overall balanced. Selenium intake was found to have no effect on the development of BCC (hazard ratio [HR], 1.09; 95% CI, 0.94-1.26) but an increased risk for developing SCC (HR, 1.25; 95% CI, 1.03-1.51) and total NMSC (HR, 1.17; 95% CI, 1.02-1.34).[74,75] Similarly, Reid et al[76] performed an RCT comparing patients treated with 400 µg/d of selenium to those treated with 200 µg/d of selenium. When compared with placebo, those treated with 200 µg/d of selenium had a statistically significantly increased incidence of NMSC (P=.006); however, those treated with 400 µg/d of selenium had no significant change in total incidence of NMSC (P=.51).[76] Furthermore, Vinceti et al[77] performed a review of 83 studies from the literature investigating the effect of dietary selenium, and from the RCTs, there was no beneficial effect of selenium in reducing cancer risk in general; however, some studies demonstrated an increased incidence of other types of cancer, including melanoma. Of the RCTs included in the study investigating NMSC incidence specifically, it was found that the incidence was not affected by selenium administration (RR, 1.16; 95% CI, 0.30-4.42; 2 studies, 2027 participants).[77] Despite data from several studies demonstrating an increased risk for NMSC, the effects of selenium on the risk for NMSC and melanoma remain unclear.

Combination Antioxidant Studies

In addition to investigating the use of single antioxidants in skin cancer prevention, studies utilizing the combination of various antioxidants or other dietary minerals have been conducted. Hercberg et al[78] performed a

randomized, double-blinded, placebo-controlled trial of 13,017 adults (7876 women and 5141 men) receiving a combination of 120 mg vitamin C, 30 mg vitamin E, 100 µg selenium, 6 mg beta carotene, and 20 mg zinc. Study participants were followed for an average of 7.5 years, and the development of skin cancers were recorded. Overall, the incidence rate of skin cancer did not differ between the 2 treatment groups; however, when segregated by gender, the study found that there was an increased risk for developing skin cancer in women taking the antioxidant supplement combination compared with placebo (P=.03). This difference was not observed in the 2 treatment groups of male patients (P=.11). When looking specifically at NMSC, there was no difference between treatment groups for male or female patients (P=.39 for males; P=.15 for females). In contrast, there was a higher incidence of melanoma identified in female patients taking the combination antioxidant supplement (P=.01), but this was not seen within the male study population (P=.51).[78] In addition, Chang et al[79] performed a meta-analysis of 10 previously published RCTs. Analysis revealed that treatment with a variety of supplements, including vitamins A, C, E, and beta carotene, were found to have no preventative effects on the incidence of skin cancer development (RR, 0.98; CI, 0.98-1.03). Notable limitations to this study included the variability in protocols of the studies included in this meta-analysis, the limited number of RCTs investigating vitamin supplementation and the risk for skin cancer development, and the influence of dietary intake on study outcomes.[79]

Other Dietary Agents

Furocoumarins—Furocoumarins are botanical substances found in various fruits and plants, including many citrus products. Furocoumarins are activated by UV light radiation and can lead to development of a phototoxic eruption. Several studies have suggested a pharmacogenetic effect of furocoumarins.[80] Sun et al[80] collected dietary data from 47,453 men and 75,291 women on furocoumarin intake and correlation with the development of NMSC. Overall, the study suggested that the intake of furocoumarins may lead to an increase in the development of BCC (HR, 1.16; 95% CI, 1.11-1.21; P=.002); however, there was no significant association identified between total intake of furocoumarins in the risk for SCC or melanoma.[80] Furthermore, Sakaki et al[81] conducted a survey study looking at the consumption of citrus products and the development of NMSC. The group found that there was an increased risk for NMSC in those consuming an increased amount of citrus products (P=.007).[81]

Conclusion

Dietary antioxidants have been investigated for their potential role in the prevention of tumorigenesis. Specific antioxidant vitamins, such as vitamin A derivatives and niacinamide, have demonstrated clinical utility in the prevention of NMSC in high-risk populations. Retinol also has been associated with a reduced incidence of melanoma. Numerous antioxidants have demonstrated promising data within the laboratory setting; however, inconsistent results have been appreciated in humans. Furthermore, several research studies suggest that folate, vitamin D, and furocoumarins may be associated with an increased risk for skin cancer development; however, these studies are inconclusive, and dietary studies are challenging to conduct. Overall, RCTs investigating the role of antioxidants for chemoprevention are limited. Moreover, the study of dietary antioxidants and vitamins may be affected by various confounding variables that can be difficult to account for because of patients' potentially poor recall of dietary intake and the effect of dietary intake in supplemental studies. Given the increasing prevalence of skin cancer worldwide, further research into the clinical utility of antioxidants in skin cancer prevention is warranted.

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CONTINUED ON PAGE 48

CONTINUED FROM PAGE 38

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