Dietary Factors in the Prevention and Treatment of Nonmelanoma Skin Cancer and Melanoma

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BACKGROUND. **The endogenous antioxidant system of the skin scavenges reactive oxygen species and combats ultraviolet induced oxidative skin damage. Supporting this cutaneous defense system with topical or oral antioxidants may provide a successful strategy for the treatment and prevention of skin cancer.**

OBJECTIVE. **Review evidence regarding treatment and prevention of melanoma and nonmelanoma skin cancers through dietary and topical antioxidants, vitamins, and herbal supplements.**

METHODS. **Literature review.**

RESULTS. **Review of the literature demonstrates that the administration of synthetic retinoids has not proved beneficial for otherwise healthy patients with nonmelanoma skin cancer. Selenium supplementation has reduced the incidence of several internal malignancies but not of nonmelanoma skin cancer. Synergistic use of β-carotene with vitamins C and E has demonstrated prophylaxis against reactive oxygen radicals involved in nonmelanoma skin cancer and reduced sunburn reactions significantly. 1,25-dihydroxyvitamin D3 analog CB1093 has demonstrated promise as a therapeutic agent in the regression of the early stages of melanoma in specific cell lines.**

CONCLUSION. **Delivery of exogenous antioxidants in combination appears to be a more successful strategy for enhancing the cutaneous antioxidant system than the administration of isolated antioxidants alone. Vitamin D analogs may have a role in the medical therapy of melanoma. However, avoiding exposure to ultraviolet light appears to be the only true panacea against the development of melanoma and NMSC.**

T. L. BIALY, MD, MPH, M. J. ROTHE, MD, J. M. GRANT-KELS, MD HAVE INDICATED NO SIGNIFICANT INTEREST WITH COMMERCIAL SUPPORTERS.

IN THE last decade, patients have shown an increased interest in the use of dietary supplements such as vitamins and herbal preparations. In a recent mail survey of 1035 people, 40% of respondents reported the use of some form of alternative health care during the prior year.[1] Of the four alternative treatments most commonly used, dietary changes or changes in "lifestyle diet" were the second most frequently reported.[1] Knowledge regarding the efficacy of complementary therapies and dietary modifications on the prevention and treatment of skin cancer is becoming increasingly essential for both patients and dermatologists. Dermatologists need evidence-based information about the effects of dietary intake and topical antioxidants, vitamins, and herbal remedies in order to develop appropriate treatment plans for their patients.

The antioxidant system of the skin battles reactive oxygen species and helps to prevent ultraviolet (UV)-induced oxidative skin damage. Cutaneous damage, premature aging of the skin, and skin cancer ensue when UV exposure exceeds the protective capacity of the antioxidant system.[2] The utilization of topical or oral antioxidants may enhance the endogenous cutaneous defense system, thereby contributing to the prevention of skin cancer. This literature review explores the synergetic effect of antioxidants such as retinoids, selenium, β-carotene, vitamins C, D and E, as well as alternative treatment modifiers including fat intake, phytochemicals, and herbal supplements in the prevention and treatment of both malignant melanoma (MM) and nonmelanoma skin cancer (NMSC).

Nonmelanoma Skin Cancer

The Antioxidants

Retinoids. The term retinoid encompasses both naturally occuring molecules that are present in low levels in the peripheral blood and also synthetic compounds with biological activities of vitamin A or retinol. Natural sources of vitamin A include liver, egg yolk, butter, fish, yellow and orange fruits and vegetables including carrots, tomatoes, apricots, and cantaloupes and green leafy vegetables. Vitamin A and its metabolic derivatives, retinaldehyde and retinoic acid, are fat-soluble molecules essential for growth, differentiation, and maintenance of epithelial tissues.[3] Extensive

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ISSN: 1076-0512/02/$15.00/0 • Dermatol Surg 2002;28:1143–1152

laboratory investigation has demonstrated that retinoids inhibit growth and induce normal differentiation of malignant cell lines.[4]

Early clinical studies (well reviewed by Lippman et al.[5]) demonstrated the efficacy of retinoids in the chemoprevention and treatment of NMSC. However, the number of patients studied was small and the therapeutic benefits were generally observed with high doses of retinoids that were associated with significant deleterious side-effects.[6] In contrast, a randomized, double blind, placebo-controlled study of 981 patients with a prior history of 2 or more basal cell carcinomas (BCC's) showed that low dose isotretinoin (10 mg daily) was ineffective in the prevention of new BCC's.[7] Similarly, when isotretinoin (5–10 mg daily), retinol (25,0000 U), or placebo were administered to 525 patients at high risk for development of skin cancer (previous history of 4 or more NMSCs) no significant difference was observed between the three treatment groups with respect to time to first occurence or total number of tumors diagnosed.[8] A randomized, double-blind, placebo-controlled 5-year clinical trial confirmed the efficacy of vitamin A (25,000 IU) in the chemoprevention of SCC but not BCC in 2297 moderate-risk patients (previous history of more than 10 actinic keratoses but fewer than 3 squamous cell carcinomas (SCC's) or BCC's).[9] During an 8-year period of follow-up, dietary retinols showed no effect on the development of BCC as measured by an assessment of the dietary habits of more than 43,000 40–75-year-old male health professionals residing in the United States who were cancer free at baseline.[10] A prospective study of the diet of more than 73,000 34–59-year-old female nurses absent a prior history of skin cancer, failed to show an association between dietary intake of either retinol or vitamin A and the risk of BCC over a four year follow-up period.[11]

Although only small numbers of patients have been studied, synthetic retinoids have shown the most promise as a chemopreventive agent for NMSC in special populations at unusually high risk for malignancy. For example, treatment of 5 patients with xeroderma pigmentosum with high dose isotretinoin (2 mg/kg/day) for 2 years resulted in an average reduction of 63% in the number of skin cancers over a 2-year period as compared to the 2 years prior to treatment.[12] However, upon discontinuation of isotretinoin therapy, skin neoplasms developed within 2–3 months. These findings suggest that the chemopreventive effect of isotretinoin is limited to the active treatment period.

Transplant recipients, particularly in areas of the world with high levels of ultraviolet exposure, are another extremely high-risk group for skin cancer. The incidence of NMSC in Australian renal transplant recipients increases exponentially over time: 3% within the first year, 25% at 5 years and 44% at 9 or more years post-transplant.[13,14] The use of retinoids as chemoprevention has been explored in studies of transplant patients. A double-blind placebo controlled study in which acitretin 30 mg daily or placebo was administered to 38 Dutch renal transplant recipients for 6 months showed that the patients who received acitretin developed significantly fewer SCC's (1 new SCC each in 2 patients) than the placebo group (18 new SCC's in 9 patients) ($p = 0.01$).[15]

It has been proposed that combination therapy of retinoids with PUVA may reduce the risk of SCC's associated with PUVA treatment.[16] A patient treated for over 14 years with PUVA therapy and topical steroids developed 34 SCC in total, 21 of which developed during subsequent treatment with cyclosporine. An inhibition of tumor formation occurred with the initiation of acitretin therapy (60 mg daily) and the patient remained tumor free for a prospective four-year period of continuous treatment with acitretin.[17]

Selenium. Selenium is found in fish, shellfish, red meat, egg yolks, chicken, garlic, tuna, bread, cereal, mushrooms, asparagus and grain products. This trace element is necessary for the function of the detoxifying enzyme glutathione peroxidase, which helps to reduce the presence of highly reactive hydroxyl free radicals. It is thought that these hydroxyl radicals attack DNA and cause mutations.[18] Studies in mice have shown that increased levels of dietary selenium provide protection against ultraviolet induced skin tumors.[19] In humans, a case control study by Clark et al. illustrated that otherwise healthy skin cancer patients had significantly lower mean serum selenium values than did controls.[20] The most extensive study evaluating the effects of selenium supplementation for cancer prevention in patients with known carcinoma of the skin was conducted by Clark and colleagues as a large, multicenter, double-blind, randomized, placebo-controlled trial.[21] 1312 patients, with a previous history of BCC or SCC, from selenium deficient areas of the eastern United States, were randomized to either an oral selenium supplementation group (200 μg/day) or placebo group for a mean of 4.5 years and were followed for 6.4 years. The selenium treated group did not have a significantly different incidence of either BCC or SCC. Thus the investigators concluded that selenium supplementation does not protect against the development of BCC's or SCC's in the skin. However, there was a significant reduction in noncutaneous cancers in the group receiving selenium. Although the numbers of cases were small, treatment with selenium was shown to reduce the incidence of cancers involving the lung, colon/rectum and prostate as well as the mortality of lung cancer.

β-carotene. β-carotene is available in food sources such as green leafy vegetables, cantaloupes, sweet potatoes, meat, butter, cheese, carrots, tomatoes, beets, and berries. There are more than 600 carotenoids in the food supply but some of the most common are β-carotene, alpha-carotene, lycopene, crocetin, and fucoxanthin.[6] In the last decade, investigators have attempted to establish a relationship between NMSC risk and the most frequently studied carotene, β-carotene, which has been postulated to reduce free radical damage of DNA after ultraviolet exposure.[10,11,22–25]

Small cohort human studies have shown that oral β-carotene supplementation reduces ultraviolet immunosuppression.[23] However, in a large, randomized, double blind, placebo-controlled trial in which 1805 patients with recent NMSC were given β-carotene 50 mg daily or placebo for up to 5 years, no significant difference was found in the rate of occurence of the first new NMSC despite an increase of plasma β-carotene levels up to 8.5 times baseline.[24] Similar findings were observed in a randomized, placebo-controlled trial of 1383 26–75-year-old Australian patients, followed over a 4.5-year period, to examine the relationship between the use of daily sunscreen application and β-carotene supplementation (30 mg daily) in the prevention of NMSC. There was no significant difference in the incidence of NMSC between the β-carotene/sunscreen and the placebo pills/sunscreen groups.[25] However, daily sunscreen application did significantly reduce the incidence of SCC.

In the aforementioned dietary studies of health care professionals, no relationship was identified between dietary β-carotene intake and the risk for the development of BCC.[10,11] Investigators for the Nurse's Health Study Cohort speculate that large supplemental doses of nutrients may be required to reduce the risk of BCC and that diet during youth, rather than that during adulthood, is critical in the prevention of BCC.[11]

Vitamin C. Vitamin C, or ascorbic acid, is present in citrus fruits, strawberries, tomatoes, cantaloupes, potatoes, and dark green leafy vegetables. Inasmuch as vitamin C is a known antioxidant, it has been studied in both animal and human cell lines as a therapeutic means to protect the skin against free radical damage.

Studies with murine epidermis and dermis have shown that UV exposure leads to the depletion of vitamin C.[26,27] Porcine studies examining the use of vitamin C as a topical photoprotectant have shown it to concentrate in the skin while decreasing erythema, UVB and PUVA-induced photodamage.[28] Studies in mice have also shown vitamin C to offer a photoprotective effect against chronic skin damage induced by UVB but not by UVA.[29]

Miyai et al. examined the ability of ascorbic acid 2-O-alpha-glucoside (AA-2G), a derivative of ascorbic acid which is highly stable under oxidative conditions, to induce resistance against cell injury due to UVB in a human keratinocyte cell line established from squamous cell carcinoma.[30] Cells were preincubated in the AA-2G solution for 9 h, exposed to UVB radiation, and then reincubated in the same solution for 24 h. AA-2G showed a significant preventive effect against UVB-induced cellular damage and this photoprotective effect had greater statistical significance for increasing concentrations of AA-2G when compared with ascorbic acid or controls.

Murray and colleagues performed a small study examining the effect of UVB radiation on the forearms of 10 human volunteers (skin type II or III) who were pretreated with 10% topical vitamin C solution or placebo for 5 days. A photoprotective effect of vitamin C was observed. The erythematous response to UVB was less intense at sites pretreated with vitamin C than control sites pretreated with vehicle alone.[31]

Vitamin E. Vitamin E is found in foods such as nuts, vegetable oils, shortening, margarine, whole grains, olives, asparagus, spinach, and egg yolk. Vitamin E protects cell membrane lipids from peroxidation and scavenges free radicals.[32] In mice, topical vitamin E has been shown to confer photoprotection by the inhibition of UV-induced thymine dimer formation,[33,34] absorption of UVB radiation,[34] and prevention of UV-induced immunosuppression.[35] Alpha-tocopherol is the most active form of vitamin E but has limited stability at room temperature in comparison with the thermostable esters, alpha-tocopherol acetate and alpha-tocopherol succinate.[35] Alpha-tocopherol acetate is the most common commercial form of vitamin E and is a popular ingredient added to skin lotions, sunscreens, and cosmetic preparations. Different forms of topical vitamin E have demonstrated variable potencies and activities in animal models. For example, in a murine study, alpha-tocopherol acetate and alpha-tocopherol succinate failed to prevent, and at some concentrations appeared to enhance, UV-induced skin cancer formation.[35] A study by McVean and Liebler found that UVB-induced thymine dimer formation in mice topically treated with 1% alpha-tocopherol was 43% less than in controls while other forms of vitamin E (including alpha-tocopherol acetate, alpha-tocopherol methyl ether, gamma-tocopherol, and delta-tocopherol) also inhibited DNA thymine dimer formation but were 5–10 fold less potent than alpha-tocopherol.[33]

Additionally, there has been further research into whether Vitamin E in the form of alpha-tocopherol acetate is converted in human skin to alpha-tocopherol. In a double-blind study, 19 patients greater than 30 years of age, who had at least three actinic keratoses on their forearms, were randomly assigned to the treatment group

(alpha-tocopherol acetate) or vehicle control group. Both groups applied the creams to their arms twice daily for three months. Blood samples, photographs, and punch biopsies were taken before the start of the study and after the study was completed. Plasma and skin concentrations of free alpha-tocopherol and alpha-tocopherol acetate were calculated. The investigators found that while alpha-tocopherol acetate was substantially absorbed in the skin, there was no evidence of cutaneous or systemic conversion to the active alpha-tocopherol form of vitamin E.[36]

In humans, a 12 patient double-blind study comparing oral vitamin E 400 IU/day for 6 months vs. placebo failed to show a significant difference between treatment groups in clinical or histologic response to UVB as measured by MED and sunburn cells.[37] In this study, the specific form of oral vitamin E was not specified. The various forms of oral vitamin E also show varying potencies and the dosage of a particular oral preparation is expressed in terms of international units (IU), based on activity. For example, 1 mg of d-alpha tocopherol = 1.49 IU.

A study of 13 patients with actinic keratoses (AK's), 12 patients with BCC's, and 16 healthy controls showed significantly lower plasma levels of the antioxidants alpha-tocopherol, ascorbic acid, and RBC glutathione in AK and BCC patients compared with the controls.[38] The investigators suggested that reduced plasma levels of these antioxidants were due to prolonged UV irradiation.

Synergy of the Antioxidants

The administration of nutrients and antioxidants in combination appears to be a more effective treatment strategy in the prevention of UV-induced damage and skin cancer than the administration of the agents alone. This synergy is exemplified by the efficacy of vitamin C administered in combination with vitamin E. On a molecular level, this may be due to the capacity of vitamin C to regenerate vitamin E from its free radical form.[32,39] This hypothesis has been supported by other investigations who examined the effects of antioxidant interactions on membrane lipid oxidation.[40,41] By combining vitamins C and E, the free radical scavenging capabilities of each agent may be enhanced, thereby increasing the total antioxidant capacity of the skin.

A double-blind, placebo-controlled study assessed the photoprotective effect of systemic vitamins C and E in 20 patients with skin types II and III.[42] Ten subjects were randomly assigned to the vitamin group and given daily doses of vitamin C (ascorbic acid 2 g) and Vitamin E (d-alpha-tocopherol 1000 IU) for 8 days, while the other randomly assigned 10 subjects, matched to the first group by skin type, were given the placebo. The sunburn reaction was assessed by determining the MED and by measuring cutaneous blood flow of irradiated and nonirradiated skin before and after administration of the oral vitamins or the placebo. Patients given the oral vitamin combination demonstrated a significant increase in their MED ($p < 0.01$) in comparison with patients in the placebo group. Cutaneous blood flow was significantly decreased in the treatment group and increased in the placebo group ($p < 0.05$). The authors concluded that the combined use of oral vitamins C and E created a synergistic effect to significantly reduce sunburn reactions. However, the study did not assess the effect on the sunburn reaction of either vitamin employed alone.

In another randomized and placebo controlled human trial, oral supplementation with vitamin E (d-alpha-tocopherol 2 g daily) and vitamin C (l-ascorbic acid 3 g daily) were studied alone and in combination to examine their effects on UV-induced skin inflammation in 40 individuals with skin type II.[43] A dose–response curve of UV-induced erythema was generated and the MED was determined by visual grading before and after supplementation for 50 days. Combination therapy led to a significant flattening of the dose–response curve and a significant increase in MED. In the groups treated with a single vitamin, there was no significant change in the response to UV radiation.

The combined photoprotective effect of topical vitamin C, vitamin E, and melatonin was investigated in a small randomized, double blind human study.[39] Twelve patients of Fitzpatrick skin type II or III were selected and all patients served as their own respective controls. All patients received combinations of the antioxidant mixtures and vehicle controls, which were applied to the lower backs of the patients in a randomized, double blind manner. Thirty minutes after treatment, all patients were subjected to UV radiation and their response was measured in terms of erythema. Application of melatonin alone resulted in a dose-dependent inhibition of erythema, while application of vitamin C or E alone had only a slight effect on the amount of erythema observed. The combination of vitamins C and E showed a more prominent inhibition of erythema. The combination of vitamins C, E, and melatonin showed the greatest photoprotective effect.

The protective effect of oral supplementation with β-carotene and vitamin E, alone and in combination, against the development of ultraviolet induced erythema in humans was recently examined in 20 adults with skin type I or II.[44] Serum concentrations of the nutrients increased after oral supplementation. After 8 weeks of treatment with a carotenoid supplement (25 mg) or carotenoid plus vitamin E (500 IU), the erythema reaction after UV irradiation was significantly

diminished ($p < 0.01$). The combination of supplements showed a greater, but not statistically significant, suppression of erythema than the carotenoid supplement alone. The study lacked a placebo group and the investigators were not blinded to the identity of the experimental groups.

Human lymphoid cells have been examined before and after treatment in a study in which patients consumed a combination of oral β-carotene (150 mg/day), vitamin C (1000 mg/day), and vitamin E (α-tocopherol 800 mg/day).[45] All cells were then exposed to the free radicals NO_2 and OONO-, in sequential experiments. Cell staining with eosin highlighted cells with membrane destruction leading to cell death. In response to NO_2 exposure, eosin staining was 61.4% before and 6% after antioxidant treatment. Protection by any antioxidant singly was less than that conferred by the combination.

Fat Intake

Black and colleagues studied the relationship between fat intake and the development of actinic keratoses (AK's) and NMSC.[46,47] One-hundred fifteen patients were randomly assigned to either the control or dietary intervention group for a 2-year clinical trial. Patients within the control group maintained their regular diets in which fat intake was 40% of their total calories. Patients within the dietary intervention group lowered their fat intake to 20% of their total calories. The cumulative numbers of new AK's per patient over the 2 years was significantly ($p < 0.001$) fewer in the experimental group than in the control group. There were no significant changes in the numbers of new NMSC skin cancers per patient in the control group over the 2-year period. However, in the experimental group the numbers of new NMSC decreased significantly over the last 8 months of the study ($p < 0.02$) and were significantly fewer than in the control group. Black notes that unsaturated fatty acids are a major object of free radical attack and that decreased dietary fats could potentially reduce free radical attack and carcinogenesis.[47]

Herbal and Alternative Therapies

Chemoprevention by means of phytochemicals has been the focus of many studies within the last decade. Components of tea are among the most extensively evaluated phytochemicals. Comprehensive reviews have detailed the findings supporting the role of green tea polyphenolic (GTPs) antioxidants as chemopreventive agents.[48–51] The most active chemopreventive ingredient of green tea is (–)-epigallocatechin-3-gallate (EGCG).[50] The potential therapeutic effects of tea appear to be due to a variety of mechanisms including: inhibition of lipid peroxidation, inhibition of reactive oxygen species-induced DNA damage, inhibition of UVB-induced cutaneous inflammation and immunosuppression, inhibition of oncogene expression, induction of apoptosis of tumor cells, inhibition of chemical- and UV-initiated tumor growth, inhibition of tumor promoter-induced activities, and inhibition of malignant transformation.[51]

Studies in humans have demonstrated the photoprotective effects of topically applied components of green tea. Different concentrations of GTP preparations, as well as a placebo dose, were applied to the backs of volunteers who were then subjected to UV radiation at twice the MED 30 min after application.[52] Sites that were pretreated with the GTP solutions exhibited significantly less erythema than the controls. The duration of the photoprotective effect of GTP was at least 72 h.

In another trial, application of topical EGCG prior to UVB exposure significantly blocked the infiltration of leukocytes, led to decreased erythema, and produced fewer inflammatory prostaglandin metabolites in human skin.[53] Additionally, the topical application of GTPs before UVB exposure of human skin led to a decreased formation of cyclobutane pyrimidine dimers in DNA.[54]

A myriad of small cohort studies examining the relationship between herbal and alternative remedies for the treatment and prevention of NMSC have been published in the oncology literature and are summarized in Table 1.[55–66] The vast majorities of these studies have involved small cohorts and were conducted with animal models. Several of the herbal preparations such as Ginkgo biloba and Ginseng illustrated promising results as chemoprotective agents. Future human studies are needed to establish the role these agents have in skin cancer prevention and treatment.

Melanoma

Phytochemicals

Studies in mice have examined a variety of dietary supplements that may prove to be helpful in the prevention of cutaneous melanoma and the metastasis of melanoma. Evaluation of the effect of dietary supplementation with a flaxseed derivative known as secoisolariciresinol diglycoside (SDG) on the metastasis of melanoma in mice demonstrated a reduction in the volume and number of pulmonary melanoma metastases as compared to the control group ($p < 0.01$).[67] Flaxseed is the richest source of lignan precursors which are also found in whole grains and legumes. Lignans are a group of phytestrogens, or plant estrogens, which are converted by bowel microflora to enterodiol and enterolactone.

Table 1. Herbal and Alternative Remedies for the Treatment and Prevention of NMSC

Study	*Plant, Seed or Herb*	*Active Ingredient*	*Experimental Milieu*	*Route of Dosing*	*Mechanism of Action*	*Findings*
1 Hibatallah et al., 1999[55]	*Ginkgo biloba*	33% extract of Ginkgo flavone glycosides	*In vitro* and *in vivo* (human models)	Topical	Ginkgo biloba is 24% flavonoids, similar to superoxide dismutase. (free radical scavenger)	Ginkgo extract inhibited the cutaneous blood flow by 37%, decreases inflammation
2 Lin & Chang, 1997[56]	*Ginkgo biloba*	Ginkgo biloba Extract in 50% alcohol	*In vivo* (rat models)	Topical	Induces superoxide dismutase and catalase enzyme activity in epidermis of rats	Ginkgo biloba pre-treated skin showed significant protection against UVB damage
3 Guevara et al. 1999[57]	Seeds of *Moringa oleifera* Lam Horse radish	Niazimicin	*In vitro* and *in vivo* (mouse models)	Topical	Antitumor promoter in chemical carcinogenesis	Antitumor promoting activity against the two stage mouse tumor carcinogenesis model
4 Keum et al., 2000[58]	Ginseng	Methanol extract of processed ginseng	*In vitro* and *in vivo* (mouse models)	Topical	Abolished epidermal ornithine decarboxyase activity and mRNA expression	Significantly decreases the formation of skin papillomas
5 Srivastava & Shukla, 1998[59]	Cruciferous vegetables: cauliflower, cabbage	Indole-3-carbinol	*In vivo* (mouse models)	Topical	Inhibits chemical carcinogenesis	Inhibited tumor number, induction time and development in indole-3-carbinol-supplemented
6 Yasukawa et al., 1998[60]	Rice bran	Cycloartenol ferulate	*In vivo* (mouse model)	Topical	Improves peripheral blood flow, possesses anti-inflammatory effect, possesses antitumor promoting effect	Dose dependent inhibition of DMBA/TPA tumor induction and inflammation in mice
7 Ichihashi et al., 2000[61]	Extra virgin olive oil	Extra virgin olive oil	*In vivo* (mouse model)	Topical	Reduced UV-induced DNA photoproducts	Olive oil painted on the skin after UVB exposure delayed onset and reduced the number of skin cancers
8 Zhao et al., 1999[62]	Grape seeds	Procyanidins present in polyphenolic fraction of grape seeds (GSP)	*In vitro* SENCAR mouse skin	Topical	The polyphenols isolated significantly inhibited epidermal lipid peroxidation	The observed anti-tumor-promoting effects of GSP were dose dependent and resulted in a reduction of tumor incidence, multiplicity and volume
9 Gensler et al., 1999[63]	Niacin	Vitamin B3	*In vivo* mouse model	Oral	Elevated skin NAD content modulating the function of DNA strand scission surveillance proteins p53 and ADP ribose polymerase	A dose-dependent preventive effect of oral niacin on photocarcinogenesis and photo-immunosuppression
10 Huang et al., 1994[64]	Rosemary	Carnusol/ursolic acid	*In vivo* mouse model	Topical	Inhibition of binding of promoter to DNA; free radical scavenger; antiinflammatory	Topically applied rosemary inhibits skin tumor initiation by DMBA and tumor promotion by TPA
11 Limtrakul et al., 1997[65]	The plant *Curcuma longa Lina*	Curcumin, the yellow pigment used as a spice and food coloring agent	*In vivo* mouse model	Oral	Possesses antiinflammatory and antioxidant properties that inhibit DMBA initiated TPA-induced epidermal DNA synthesis	Dietary administration of curcumin inhibited tumor number ($P<0.05$) and volume ($P<0.01$)
12 Lahiri-Chatterjee et al., 1999[66]	Milk Thistle	The flavonoid Silymarin	SENCAR mouse model	Topical	Highly significant dose-dependent inhibition of epidermal hyperplasia, DNA synthesis, and lipid peroxidation	Applied prior to DMBA/TPA reduced tumor incidence ($P<0.001$), multiplicity ($P<0.001$) and volume ($P<0.001$)

DMBA = 7,12-dimethyl-benz(a)anthracene
TPA = 12-O-tetradecanoyl-phorbol-13-acetate

Inhibition of growth of the murine melanoma cell line B16 was demonstrated by the addition of β-Ionone (a cyclic analog of β-carotene) and gamma-tocotrienol (a less potent form of vitamin E). A synergistic and additive growth-suppressive action on the melanoma cells was observed when these phytochemicals were combined.[68]

Vitamin D

Vitamin D is hydroxylated in the liver and kidney to its most active form 1,25-dihydroxyvitamin D3 (VD3). This active steroid hormone binds to the vitamin D receptor (VDR) to exert many functions.[69] VDR has been detected in certain cancer cell lines including melanoma.[69,70] A panel of eight human melanoma cell lines was assessed for the level of VDR expression and the growth inhibitory effects of VD3.[69] VDR expression was illustrated in the various melanoma cell lines. Furthermore, VD3 was a significant ($p < 0.05$) melanoma growth inhibitor in cells with a high receptor concentration.

VD3 and its analogs have been shown to induce apoptosis in human and animal breast cancer lines and leukemic cell lines.[71] The analog CB1093 induced apoptosis in the early stage melanoma cell line, WM1341, at a tenfold lower concentration than VD3 and the analog EB108.[72] However, VD3 and its analogs failed to induce apoptosis in the advanced stage melanoma cell line, MeWo. CB1093 was previously found to induce apoptosis of rat mammary tumors in vivo at a lower concentration than other VD3 analogs and with only 27% of the calcemic effects of VD3.[71]

In further studies, the effect of vitamin D and select retinoids on the induction of apoptosis of human melanoma cells has been examined.[73] The combined treatment of Vitamin D3 with the select retinoid receptor ligand CD437 resulted in a synergistic induction of apoptosis for the specific human melanoma cell line WM1341 but not MeWo cell line. The authors conclude that each type of melanoma cell line has an individual response to combined treatment with vitamin D and select retinoids.

Dietary Supplements

The relationship between diet and the risk of developing melanoma has been examined in human case-control studies over the last decade. For example, a study conducted at the Massachusetts General Hospital included 165 melanoma patients and 209 controls. After controlling for age, hair color, and family history of melanoma, there was no significant association between the total amount of vitamin D intake from food, supplements or milk and the risk of developing melanoma.[74]

The intake of vitamin A, dietary antioxidants, and other dietary nutrients and their relationship to the risk of developing melanoma has been assessed in a case-control study.[75] Patients with a history of melanoma were randomly selected from the Seattle-Puget Sound cancer registry and 234 cases were matched to 248 controls for age, sex, and county. All subjects completed a telephone interview and mailed in food questionnaires in which they were asked to estimate their food intake 7 years prior to diagnosis for melanoma patients and a similar time period for controls. The level of vitamin E obtained from food was inversely related to the risk of developing melanoma at an age, education, and energy intake adjusted odds ratio (OR = 0.34, and $p = 0.01$). Additionally, zinc from food supplements was associated with a decreased risk of melanoma (OR = 0.46, and $p = 0.01$). There were no correlations found with the levels of vitamin A, retinoids, or carotenoids and the risk of melanoma. There was also no increase in the risk of developing melanoma with increased alcohol or polyunsaturated fat consumption. In contrast, body mass index was significantly related to melanoma risk, as melanoma patients were more obese than controls after both populations were age, sex and education adjusted (OR = 1.90, and $p = 0.02$). The authors point out the important confounders of this study including a possible recall bias of the cases who may have been excessively vigilant in recalling their diets previous to diagnoses of their respective melanomas. In addition, the validity of a food questionnaire is always a concern in epidemiological studies; however, other researchers have substantiated the validity of dietary questionnaires of this type.[76] A case-control study from Massachusetts General Hospital assessed dietary intake and plasma levels of nutrients in 204 melanoma patients compared with 248 controls.[76] No significant difference was identified between cases and controls with respect to plasma carotene levels or intake of preformed vitamin A and vitamin E. However, this latter study found a significant correlation between the amount of alcohol consumed and the risk of developing melanoma ($p = 0.03$, OR = 1.8).

A case-control study examined the correlation between prediagnostic serum levels of retinol, β-carotene, vitamin E, and selenium and the subsequent risk of developing NMSC and melanoma among residents of Washington County, MD.[77] There were no significant differences in the serum concentration between the cases or controls.

Diet and the risk of developing melanoma have also been studied in a prospective large human cohort study of 50,757 Norwegian men and women.[78] All patients in the study completed self-administered dietary questionnaires previously tested for their validity and

reproducibility. The questionnaire did not focus on the intake of specific nutrients but instead focused on the consumption of various foods such as milk, potatoes, bread, jam, cheese, meat, fats on bread, fats in cooking, fish, cakes, eggs, oranges, porridge, cod liver oil and vitamin pills. During the study period from 1977 to 1992, 108 cases (47 in men and 61 in women) of cutaneous melanoma were identified. There was an increased risk of melanoma in women who had a higher intake of polyunsaturated fats and cod liver oil supplements. The intake of caffeine was inversely related to the development of melanoma in women. There were no significant correlations for the men in the study. The results were somewhat surprising as cod-liver oil is high in omega-3 fatty acids which have been previously linked to the inhibition of UV-carcinogenesis, a decreased risk of lung cancer, and a protective effect against breast and colon cancer.[79–81]

A Danish case-control study also identified a decreased incidence of melanoma with increased coffee intake.[82] Other studies examining this relationship have not concurred with these results.[83,84] Similar discrepancies exist among studies examining the relationship between melanoma and polyunsaturated fats.[75,76,85]

Conclusion

In terms of NMSC, review of recent clinical trials does not substantiate a beneficial effect for either natural dietary retinoids or synthetic retinoid supplementation for treatment or prevention of BCC or SCC in the general population. Small studies of select populations with defective DNA repair mechanisms, immunosuppression, or patients receiving PUVA have been shown to benefit significantly from systemic retinoid treatments. Additionally, while oral administration of selenium has shown promise for reducing the incidence of several types of cancer, its direct effect in reducing the incidence of BCC or SCC has not been demonstrated. No protective effect for NMSC was achieved with either normal dietary consumption or oral supplementation of β-carotene.

A review of the randomized human clinical trials reveals that the synergistic use of specific antioxidants proves to be more successful than the utilization of the individual components alone. The use of β-carotene with vitamins C and E offered synergistic cell protection against both the NO_2 and OONO- radicals. The combined use of oral vitamin E (d-alpha-tocopherol) and vitamin C (l-ascorbic acid) created a synergistic effect to significantly reduce sunburn reactions. Delivery of exogenous antioxidants in combination may serve as a successful strategy for enhancing the endogenous, natural antioxidant system of the skin.

The most commercially available form of an antioxidant may not necessarily be the best form for the treatment of patients. This fact has been highlighted by studies that emphasize the importance of determining which forms of vitamin E can inhibit photocarcinogenesis and which forms may actually lead to cancer formation.

In terms of herbal remedies for NMSC, the phytochemicals available in tea have been shown to help boost the endogenous antioxidant defense system of the skin for in vitro mouse and human cell lines and in in vivo mouse models. However, randomized, clinical, placebo-controlled trials on human subjects are required. Also, many single studies in mice and humans have identified potential new antioxidants for the treatment and prevention of NMSC including ginkgo biloba, ginseng, horseradish, rosemary, and milk thistle.

Studies have failed to consistently identify any association between dietary intake of diverse agents and the attendant risk of melanoma. In studies with specific melanoma cell lines there appears to be promise for the 1,25-dihydroxyvitamin D3 analog CB1093 as a therapeutic intervention for the treatment of the early stages of melanoma absent the severe calcemic side-effects of its natural vitamin D counterpart.

In sum, there is no topical or systemic panacea against the development of melanoma and NMSC that is better than protective clothing and avoidance of exposure to ultraviolet light. We must continue to educate our patients regarding their behavior and attitude toward the elusive "safe" tan.

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