Nutrition: The future of melanoma prevention?

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Background: Melanoma is one of the deadliest forms of skin cancer, having a high metastatic potential and afflicting all age groups. The need for successful preventative measures is particularly urgent as metastatic melanoma is largely incurable. The beneficial role of nutrition and other natural compounds in the prevention and treatment of melanoma has been clearly demonstrated in the past, and is an exciting source for potential therapies in the future.

Objective: We sought to review updates in the current literature regarding new developments in the relationship between nutrition and melanoma risk and treatment.

Methods: Articles in the public domain regarding the impact of diet, grape seed proanthocyanidins, selenium, vitamin D, vitamin E, epigallocatechin-3-gallate, resveratrol, rosmarinic acid, lycopene, and fig latex on melanoma were included.

Results: Grape seed proanthocyanidins, epigallocatechin-3-gallate, resveratrol, rosmarinic acid, lycopene, and fig latex have demonstrated clear anticancer effects toward melanoma. The roles of selenium, vitamin D, and vitamin E, however, have been more controversial.

Limitations: None.

Conclusions: The role of natural compounds in the future of melanoma prevention and treatment is promising and one that is worthy of further exploration. (J Am Acad Dermatol 2014;71:151-60.)

Key words: melanoma; nutrition; prevention; resveratrol; skin cancer; vitamins.

Skin cancer is the most common of all cancers.[1] Melanoma is one of the deadliest forms of skin cancer, causing up to 9480 deaths a year because of its high metastatic potential.[1,2] Melanoma occurs in all age groups, and incidence has been rising despite efforts to improve sun protection, highlighting the need for additional preventative measures and treatment.[3]

Although early melanoma can usually be cured by surgical resection, metastatic melanoma is largely incurable. Consequently, recent interest in preventive methods, such as dietary factors, has grown significantly. Epidemiologic and basic science studies have shown promising results supporting the role of natural compounds in the chemoprevention of melanoma. The discovery of effective natural compounds against melanoma may have important public health ramifications. Furthermore, dietary interventions may have systemic benefits in comparison with topical methods of sun protection, and do not require regular reapplication.

Oxidative damage plays a key role in the development of melanoma; free radicals and reactive oxygen species are generated by ultraviolet (UV)

Abbreviations used:

EGCG:	epigallocatechin-3-gallate
GSP:	grape seed proanthocyanidin
RCT:	randomized controlled trial
UV:	ultraviolet

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light, causing oxidative stress, inflammation, photoaging, and DNA damage, which can lead to skin cancer.[4,5] Exposure to UV light is one of the most important factors in the development of both melanoma and nonmelanoma skin cancers, and is largely unavoidable, further underscoring the need to discover novel agents that can help reverse the consequences of this damage.[6,7] In this review, we discuss the relationship between nutrients and melanoma risk, specifically epigallocatechin-3-gallate (EGCG), selenium, grape seed proanthocyanidins (GSPs), vitamin D, vitamin E, diet composition, fatty acids, resveratrol, rosmarinic acid, lycopene, and fig latex.

CAPSULE SUMMARY

- Treatment of metastatic melanoma has been very difficult and expensive. Prevention is key in reducing the incidence of melanoma.
- A clear beneficial relationship has been demonstrated between nutrition and melanoma prevention.
- The role of nutrition in melanoma risk and treatment is one that deserves further exploration.

METHODS

From September to October 2013 we searched PubMed for published studies examining the effects of diet and nutrition on melanoma risk and treatment. PubMed database was searched using search terms "nutrition," "melanoma," "treatment," "risk," "skin cancer," and "prevention." These terms included the subcategories "skin neoplasms," "food," "nutritional status," "nutritional sciences," "therapy," "therapeutics," and "prevention and control." The searches were filtered to include only those written in English. Bibliographies were searched for additional studies that met inclusion criteria. A total of 87 articles were found and examined in this review.

Grades of evidence used to evaluate the existing data for each nutrient (Table I) were based on those set by the Institute for Clinical Systems Improvement.[8] Level Ia refers to evidence from meta-analysis of randomized controlled trials (RCTs); Ib refers to evidence from at least 1 RCT; IIa refers to evidence from at least 1 non-RCT; IIb refers to at least 1 experimental study; III refers to evidence from case, correlation, or comparative studies; and IV refers to evidence from expert opinions.

RESULTS

Diet

Dietary composition has been demonstrated to impact skin cancer risk. Polyunsaturated fatty acids in particular are thought to play a role in melanoma prevention by protecting against UV skin damage, promoting tumor latency, inhibiting tumor multiplicity, and reducing cutaneous p53 expression.[9] In a major study investigating the link between dietary fatty acids and melanoma involving 50,757 Norwegian men and women, higher intake of cod liver oil (odds ratio 2.9, 95% confidence interval 1.7-5.1) and polyunsaturated fats (odds ratio 4.1, 95% confidence interval 1.4-11.8) was found to increase the risk of melanoma in women.[10]

In a case-control study performed by Fortes et al,[11] shellfish, daily tea consumption, vegetables, and fish were found to have protective benefits. This may be a result in part of the high isoprenoid content found in fruits and vegetables, as isoprenoids are known to inhibit melanoma B16 cell proliferation.[12] Consequently, the Mediterranean diet, which has long been touted for its high concentration of fish and vegetables, was also shown to have chemopreventive effects against melanoma.[11] Other studies supporting the Mediterranean diet have demonstrated a higher percentage of subcutaneous tissue polyunsaturated fatty acids and linoleic acid in patients with melanoma versus control subjects.[13] Thus, diets supporting the use of vegetable oil and fish consumption have been recommended.[13]

Grape seed proanthocyanidins

GSPs are effective antioxidants and anti-inflammatory agents and are found in particularly high concentrations in grapes.[14-16] GSPs have been found to reduce UV skin damage, such as photoaging, and to decrease melanin synthesis.[17] In human beings, GSPs have been shown to reduce mutant p53-positive epidermal cells and prevents depletion of Langerhans cells after sunburn.[18]

Mouse studies have also shown strong evidence supporting the inhibition of UV-induced tumor incidence, growth, and size, as well as metastatic pulmonary nodules, after the administration of grape seed extract.[15,19] GSPs were also shown to inhibit cell migration in highly metastasis-specific human A375 and Hs294t melanoma cell lines: 22% to 65%, $P <$ .01 to .001 and 29% to 69%, $P <$ .01 to .001, respectively.[20] In addition, GSPs decreased tissue plasminogen activator–induced activation of extracellular-signal-regulated kinase 1/2 protein and nuclear factor-κB/p65. These proteins have been shown to enhance and mediate migration of

Table I. Nutrients and their mechanisms of antimelanoma effects

Nutrient	Antimelanoma effect	Studies	Human RCTs? Yes/no, level of evidence*
Fatty acids	• Protect against UV damage • Promote tumor latency • Inhibit tumor multiplicity • Reduce cutaneous p53 expression	Noel et al,[9] 2013 Veierød et al,[10] 1997	No, level III (supportive)
Vegetable oil and fish consumption (Mediterranean diet)	• High isoprenoid content, which is known to inhibit melanoma B16 cell proliferation	Tatman and Mo,[12] 2002 Fortes et al,[11] 2008 Mackie et al,[13] 1987	No, level III (supportive)
Grape seed proacanthocyanidins	• Inhibit cell migration • Decreased TPA-induced activation of ERK1/2 protein and NF-κB/p65 • Reversed epithelial-to-mesenchymal transition • Reduced endogenous cytochrome c oxidase 2 expression, TPA activity, and prostaglandin-E_2 synthesis	Cos et al,[14] 2004 Li et al,[15] 2001 Bors and Saran,[16] 1987 Cho et al,[17] 2009 Yuan et al,[18] 2012 Mittal et al,[19] 2003 Vaid et al,[20] 2011 Lucas et al,[21] 2006 Meeran et al,[22] 2009	No, limited human studies
Selenium	• Controversial; thought to regulate skin redox homeostasis • Possible increased risk at moderate dosages with therapeutic potential at high dosages	Chen et al,[23] 2008 Chen and Wong,[24] 2008 Vinceti et al,[25] 2012 Cassidy et al,[26] 2013 Clark,[27] 1985 Combs and Clark,[28] 1985 Overvad et al,[29] 1985 Burke et al,[30] 1992 Helzlsouer et al,[31] 2000 Shamberger,[32] 1970 Li et al,[33] 2004 Yan et al,[34] 1999 Burke,[35] 1992 Walshe et al,[36] 2007 Wenk et al,[37] 2004 Ip et al,[38] 2000	No, level III (supportive), level III (nonsupportive)
Epigallocatechin-3-gallate	• Modulation of Bcl-2 proteins and the cki-cyclin-cdk network, inducing apoptosis and cell cycle arrest • Inhibition of UV-induced matrix metalloproteinase-2, -3, -7, and -9 expression in mice • Decreased UV-induced skin tumor incidence, burden, and size • Inhibition of skin papilloma growth in mice	Hsu,[39] 2005 Katiyar and Elmets,[40] 2001 Wang et al,[41] 1992 Vayalil et al,[42] 2004 Katiyar,[43] 2003	No, limited human studies

Continued

Table I. Cont'd

Nutrient	Antimelanoma effect	Studies	Human RCTs? Yes/no, level of evidence*
Resveratrol	• Suppression of the α-MSH signal transduction pathway • Down-regulation of MHC and CD40, CD80, and CD86 costimulatory molecules, resulting in modulation of chronic inflammation • Reduced proliferation of melanoma A431 cells • Induction of apoptosis in A475 and SK-mel28 cells	Zheng et al,[44] 2012 Larrosa et al,[45] 2004 Polonini et al,[46] 2013 Wu et al,[47] 2013 Chen et al,[48] 2013 Wu et al,[49] 2013 Svajger et al,[50] 2010 Feng et al,[51] 2004 Aggarwal et al,[52] 2004 Niles et al,[53] 2003 Ahmad et al,[54] 2001 Adhami et al,[55] 2001 Larrosa et al,[56] 2003 Guan et al,[57] 2012	No, Limited human studies
Rosmarinic acid	• Induction of apoptosis • Inhibition of melanoma cell growth in animal cell lines and in human M14 and A375 cell lines	Ngo et al,[58] 2011 Russo et al,[59] 2009	No, limited human studies
Vitamin E	• Human studies have failed to find a conclusive relationship between vitamin E and melanoma risk	Anstey,[60] 2002 Kogure et al,[61] 2003 Keller and Fenske,[62] 1998 Malafa et al,[63] 2002 Lonn et al,[64] 2005 McArdle et al,[65] 2004 Stryker et al,[66] 1990	Yes, level Ib (nonsupportive)
Vitamin D	• Although some studies have shown increased vitamin D intake may reduce melanoma incidence and improve prognosis, it has been difficult to replicate these results in large-scale human studies, leaving the relationship still unclear	Nürnberg et al,[67] 2009 Gilchrest et al,[68] 1999 Newton-Bishop et al,[69] 2009 Weinstock et al,[71] 1992 Asgari et al,[72] 2009	Yes, level Ib (supportive), level III (nonsupportive)
Lycopene	• Reduction of oxidative stress • Inhibition of platelet-derived growth factor-BB, reducing melanoma-induced fibroblast migration and signaling transduction	Di Franco et al,[73] 2012 Stahl and Sies,[75] 2012 Costa et al,[76] 2012 Rizwan et al,[77] 2011 Di Mascio et al,[78] 1989 Mein et al,[79] 2008 Wu et al,[80] 2007	No, level IIa (supportive)

melanoma cells.[20] The inhibitory effects of GSP on NF-κB also helped to reverse the epithelial-to-mesenchymal transition occurring in both melanoma cell lines. In addition, tumor invasion was reduced in both cell lines, possibly secondary to GSP-induced reduction in endogenous cytochrome c oxidase 2 expression, tissue plasminogen activator activity, and prostaglandin-E_2 synthesis.

These results underline the GSPs' potential as an antimelanoma agent, particularly in preventing rapid metastasis, which has been shown to cause significant mortality.[21] Furthermore, no toxicity has been shown in vivo, supporting GSPs as a promising candidate for treatment of metastatic melanoma.[22]

Selenium

Selenium, a nonmetal element found in sunflower seeds, fish, shellfish, and red meat, has recently been implicated in dose-dependent apoptosis secondary to the induction of mitochondrial oxidative stress in human A375 melanoma cells.[23,24] Selenoproteins glutathione peroxidase 2 and 3 are thought to regulate skin redox homeostasis.

There have been conflicting data surrounding the effects of selenium consumption and the risk of melanoma with some human studies suggesting a decreased risk with increased selenium intake, whereas others suggest an opposite association.[25] However, a recent study demonstrated a dose-dependent difference in the impact of selenium on melanoma risk, with a moderate dosage thought to increase the risk of tumor growth acceleration, whereas a high dosage was shown to be effective at treating and preventing recurrence of fully malignant tumors.[26] This may complicate use of selenium as a nutritional supplement in patients with melanoma, but may suggest that selenium is a better candidate as an oral adjuvant agent where higher doses can be administrated. Many studies have shown an inverse relationship between overall mortality from various forms of cancer (including skin cancers)[27-32] and both selenium dietary intake and topical application. Mouse studies have shown a decrease in melanoma lung metastases with increased dietary amounts of selenium,[33,34] although the relationship between selenium exposure and human melanoma incidence remains unclear.[34,35] Adverse effects of brittle hair and nails and garlic breath have been reported at higher doses, and, of concern, the metabolite selenomethionine has been shown to be toxic in nonskin cancer mouse models.[36-38] However, no significant toxicities have been shown in human beings.[26]

Fig latex

• Inhibition of peroxidation • Scavenging of free radicals and reduction of tumor growth in human C32 melanoma cell lines	Ghazanfar,[81] 1994 Ullman et al,[82] 1945 Ullman,[83] 1952 Wang et al,[84] 2008 Conforti et al,[85] 2012 Menichini et al,[86] 2012 Oliveira et al,[87] 2009	No, limited human studies

ERK, Extracellular-signal-regulated kinase; *MSH*, melanocyte-stimulating hormone; *RCT*, randomized controlled trial; *TPA*, tissue plasminogen activator; *UV*, ultraviolet.
*Grades of evidence used to evaluate the existing data for each nutrient were based on those set by the Institute for Clinical Systems Improvement.[8] Level Ia refers to evidence from meta-analysis of RCTs; Ib refers to evidence from at least 1 RCT; IIa refers to evidence from at least 1 non-RCT; IIb refers to at least 1 experimental study; III refers to evidence from case, correlation, or comparative studies; and IV refers to evidence from expert opinions.

Epigallocatechin-3-gallate

Green tea has long been known for its antioxidant properties; the flavanoid EGCG is of particular interest as it helps to reverse damage caused by UV light.[39] Drinking green tea has demonstrated a decrease in UV-induced skin tumor incidence, burden, and size compared with controls, whereas topical application showed partial inhibition of skin papilloma growth in mice.[40,41] EGCG may induce melanoma cell apoptosis and cell cycle arrest by modulating B-cell lymphoma 2 (Bcl-2) and the cki-cyclin-cdk pathway. Animal studies have clearly shown the anticarcinogenic effects of EGCG. Green tea polyphenols have also demonstrated inhibition of UV-induced matrix metalloproteinase-2, -3, -7, and -9 expression in mice, all of which are involved in degradation of the basement membrane, a prelude to metastasis.[42]

Green tea may be a particularly useful chemopreventive tool as it is easy to administer, inexpensive, and has low toxicity. Preliminary human studies have demonstrated reduced oxidative stress, pyrimidine dimer formation, and inflammatory leukocytes with topical administration of EGCG.[43] However, there is currently a dearth of human studies specifically regarding the effects of green tea consumption and melanoma.

Resveratrol

Resveratrol is a natural polyphenol commonly found in peanuts, fruits, grape skins, mulberries, and red wine.[44,45] It has been previously shown to protect human skin from the effects of sun damage by decreasing sunburn cell formation.[46,47]

Melanoma cells often rely on alpha-melanocyte-stimulating hormone signal transduction, a process crucial to the development and spread of melanoma cells that is suppressed by resveratrol.[48] The alpha-melanocyte-stimulating hormone has also demonstrated immunosuppressive properties and beneficial effects in modulating chronic inflammation by down-regulating major histocompatibility complex (MHC) molecules in addition to CD40, CD80, and CD86 costimulatory molecules.[49-51] Resveratrol has been shown to have many anticancer properties; it in particular has been shown to be antiproliferative against melanoma A431 cells, and induces apoptosis in A475 and SK-mel28 cells.[52-56]

Although human studies are still limited, data so far have shown that resveratrol is pharmacologically safe, making it a prime candidate for potential future cancer therapeutic agents. Resveratrol may also be an effective adjuvant treatment, as it prevents endothelial cell injury in high-dose interleukin 2 therapy for melanoma.[57]

Rosmarinic acid

Found in rosemary, rosmarinic acid has been shown to have a potent antioxidant effect, and has been traditionally been used for a variety of medicinal purposes, from dysmenorrhea to ischemic heart disease.[58] Studies show that it induces apoptosis and inhibits melanoma cell growth in animal cell lines and in human M14 and A375 cell lines.[58,59] However, there have not yet been significant clinical data from human RCTs.

Vitamins D and E

Vitamin E and its various forms (alpha-tocopherol, alpha-tocopherol acetate) have demonstrated photoprotective and antioxidative properties against melanoma in animal studies.[60-63] However, the results of human studies have been less convincing. Studies have failed to show a clear relationship between dietary intake of vitamin E and melanoma incidence, suggesting that oral supplementation may not have a clinically significant effect.[64-66]

Results regarding vitamin D have also been variable as well. Recent studies have suggested higher levels of 25-hydroxyvitamin D_3 are associated with lower melanoma incidence, decreased relapse incidence, and lower Breslow thickness at time of diagnosis, suggesting improved prognosis.[67-70] However, other large-scale studies have failed to demonstrate similar relationships.[70,71] Although earlier studies explored the potential effects of vitamin D and E, subsequent studies have shown that vitamin D and E do not have a clear role in reducing the risk for melanoma in human beings.

Lycopene

Lycopene is a carotene usually found in red fruits and vegetables, of which the most well known is the tomato, but also includes red carrots, papayas, and watermelons.[71,72] It is known for its photoprotective properties; oral supplementation has been shown to increase human basal dermal defense against UV damage and counteract photoaging, and is used to reduce skin toxicity secondary to chemoradiation in patients with breast cancer.[72-74] Lycopene is thought to be the most effective carotene at reducing oxidative stress, and may be an excellent addition to the diets of patients at risk for melanoma.[75,76] In vitro studies have shown that lycopene also inhibits platelet-derived growth factor-BB, which reduces melanoma-induced fibroblast migration and signaling transduction and is suggestive of antitumor properties.[77]

Fig latex

Recent interest has developed in fig latex (*Ficus carica*) because of the antiproliferative properties of

its leaves. Fig products are most commonly used in both food and medicine in the Middle East, and have a history of being used to treat warts and skin tumors.[78] The first study investigating the medicinal properties of fig latex in the 1940s demonstrated inhibition of tumor growth.[79,80] Fig latex has previously been shown to be highly effective in exhibiting toxicity against various human cancer cells, specifically hepatocellular carcinoma and glioblastoma cell lines.[81]

In comparison with the bark and wood of *F carica*, fruits have the most antioxidant activity, as a result of significant polyphenolic compound content. *F carica* leaves have the highest inhibition of peroxidation, most likely because of a higher concentration of flavonoids, furanocoumarins, and linolenic acid methyl ester.[82-84] Recent studies have further supported the ability of fig latex to scavenge free radicals and reduce tumor growth in human C32 melanoma cell lines.[82] This may be particularly useful in developing therapies in the treatment of skin cancer.

Multiple studies have clearly demonstrated the importance of diet and nutrition on the risk and progression of melanoma (Table I). Many natural substances have strong anticancer effects such as reducing oxidative stress, down-regulating chronic inflammation, and inducing melanoma cell apoptosis. This in turn plays a role in the prevention and treatment of melanomas by reversing oxidative damage caused by UV light and decreasing tumor growth and invasiveness.

Conclusion

The relationship between dietary and nutritional intake and melanoma has a deep potential that should be further explored. Although animal evidence is abundant, there is still a need for more human RCTs to further evaluate the role of nutrition in the treatment and/or prevention of melanoma. This may also lead to more effective preventative measures and potential development of new pharmaceutical agents, which is crucial, as the incidence of melanoma is on the rise, and metastatic melanoma responds poorly to current chemotherapy.

Presently, the Mediterranean diet, polyunsaturated fatty acids, and lycopene have strong supportive evidence of reduced melanoma risk from case-control, cohort, and experimental studies, emphasizing the need for human RCTs to determine appropriate guidelines or possible pharmacologic roles. There is less clinical evidence for most specific nutrients, such as EGCG, resveratrol, GSPs, and rosmarinic acid, but it is worth further exploring these nutrients to uncover potential improvements in melanoma treatment and prevention. Vitamin D and vitamin E have been more controversial. RCTs have failed to prove an association between vitamin E and reduction in melanoma risk, and there has been fairly strong evidence both for and against the antimelanoma effects of vitamin D. The evidence for and against selenium has also been uncertain. It may be beneficial to conduct additional large-scale human studies to determine more conclusive evidence regarding the effects of vitamin D and selenium on melanoma. As there are so few human data, it is difficult to currently evaluate the precise ramifications nutrients may have on treatment and prevention. Although nutrients might never be as effective as chemotherapy or other pharmaceutical agents, their potential is clear, and may also be effective as adjuvants to pharmaceutical drugs. The role nutrients may play in preventative care is very exciting, especially as they may be incorporated into daily diet and lifestyle regimens. As treatment for metastatic melanoma is largely ineffective, preventing melanoma before it begins is the most cost-effective method. Although no solid current patient recommendations can be suggested, it is clear that nutrients may play a role in melanoma treatment and prevention. When the role of individual nutrients is further clarified, it seems likely that diet can serve as an effective adjuvant therapy for the treatment of melanoma and nonmelanoma skin cancers.

Melanoma can be a deadly disease, and novel preventative primary and adjuvant therapies are essential to improving its prognosis and mortality. Natural remedies are exciting potential candidates, given their low cost and potentially low side-effect profile. Further human studies comparing topical and oral nutrient combinations with markers of UV damage such as erythema, matrix metalloproteinase expression, DNA damage, lipid peroxidation, and apoptosis are thus greatly needed.

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