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, photo-
aging, and DNA damage, which can lead to skin
cancer.\textsuperscript{4,5} Exposure to UV light is one of the most
important factors in the development of both mel-
noma and nonmelanoma skin cancers, and is largely
unavoidable, further underscoring the need to
discover novel agents that can help reverse the
consequences of this dam-
age.\textsuperscript{6,7} In this review, we
discuss the relationship be-
tween nutrients and mela-
noma 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.

METHODS
From September to
October 2013 we searched
PubMed for published studies examining the effects
of diet and nutrition on melanoma risk and treat-
ment. 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 con-
trol.” 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.\textsuperscript{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 ref-
ers to evidence from case, correlation, or compara-
tive 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 expres-
sion.\textsuperscript{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.\textsuperscript{10}

In a case-control study
performed by Fortes et al,\textsuperscript{11}
shellfish, daily tea consump-
tion, vegetables, and fish
were found to have protec-
tive benefits. This may be a
result in part of the high iso-
prenoid content found in
fruits and vegetables, as iso-
prenoids are known to inhibit
melanoma B16 cell prolifera-
tion.\textsuperscript{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.\textsuperscript{11} Other studies supporting the
Mediterranean diet have demonstrated a higher per-
centage of subcutaneous tissue polyunsaturated fatty
acids and linoleic acid in patients with melanoma
versus control subjects.\textsuperscript{13} Thus, diets supporting
the use of vegetable oil and fish consumption have been
recommended.\textsuperscript{13}

Grape seed proanthocyanidins
GSPs are effective antioxidants and anti-
inflammatory agents and are found in particularly
high concentrations in grapes.\textsuperscript{14-16} GSPs have been
found to reduce UV skin damage, such as photoag-
ing, and to decrease melanin synthesis.\textsuperscript{17} In human
beings, GSPs have been shown to reduce mutant
p53-positive epidermal cells and prevents depletion
of Langerhans cells after sunburn.\textsuperscript{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.\textsuperscript{15,19} GSPs were also shown to inhibit cell
migration in highly metastasis-specific human A375
and Hs294t melanoma cell lines: 22% to 65%, \(P \leq .01\) to .001
and 29% to 69%, \(P \leq .01\) to .001, respectively.\textsuperscript{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

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.

In a case-control study performed by Fortes et al,\textsuperscript{11}
shellfish, daily tea consump-
tion, vegetables, and fish
were found to have protec-
tive benefits. This may be a
result in part of the high iso-
prenoid content found in
fruits and vegetables, as iso-
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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

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Antimelanoma effect</th>
<th>Studies</th>
<th>Human RCTs? Yes/no, level of evidence</th>
</tr>
</thead>
</table>
| 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  
• 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-E2 synthesis | Tatman and Mo, 12 2002  
Fortes et al, 11 2008  
Mackie et al, 13 1987  
Yuan et al, 18 2012  
Mittal et al, 15 2003  
Vaid et al, 20 2011  
Lucas et al, 21 2006  
Meeran et al, 22 2009 | No, level III (supportive) |
| Grape seed proanthocyanidins | • 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-E2 synthesis | Cos et al, 14 2004  
Li et al, 15 2001  
Bors and Saran, 16 1987  
Yuan et al, 18 2012  
Mittal et al, 15 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
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<thead>
<tr>
<th>Nutrient</th>
<th>Antimelanoma effect</th>
<th>Studies</th>
<th>Human RCTs? Yes/no, level of evidence</th>
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<tbody>
<tr>
<td>Resveratrol</td>
<td>• Suppression of the α-MSH signal transduction pathway</td>
<td>Zheng et al, 2012</td>
<td>No, Limited human studies</td>
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<td></td>
<td>• Down-regulation of MHC and CD40, CD80, and CD86 costimulatory molecules, resulting in modulation of chronic inflammation</td>
<td>Larrosa et al, 2004</td>
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<td></td>
<td>• Reduced proliferation of melanoma A431 cells</td>
<td>Polonini et al, 2013</td>
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<td>• Induction of apoptosis in A475 and SK-mel28 cells</td>
<td>Wu et al, 2013</td>
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<td>Chen et al, 2013</td>
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<td>Wu et al, 2013</td>
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<td>Svajger et al, 2010</td>
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<td>Feng et al, 2004</td>
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<td>Aggarwal et al, 2004</td>
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<td>Guan et al, 2012</td>
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<td>Rosmarinic acid</td>
<td>• Induction of apoptosis</td>
<td>Ngo et al, 2011</td>
<td>No, limited human studies</td>
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<td></td>
<td>• Inhibition of melanoma cell growth in animal cell lines and in human M14 and A375 cell lines</td>
<td>Russo et al, 2009</td>
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<tr>
<td>Vitamin E</td>
<td>• Human studies have failed to find a conclusive relationship between vitamin E and melanoma risk</td>
<td>Anstey, 2002</td>
<td>Yes, level Ib (nonsupportive)</td>
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<td></td>
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<td>Kogure et al, 2003</td>
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<td>Keller and Fenske, 1998</td>
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<td>Malafa et al, 2002</td>
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<td>Lonn et al, 2005</td>
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<td>McArdle et al, 2004</td>
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<td>Stryker et al, 1990</td>
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<td>Vitamin D</td>
<td>• 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</td>
<td>Nürnberg et al, 2009</td>
<td>Yes, level Ib (supportive), level III (nonsupportive)</td>
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<td>Gilchrest et al, 1999</td>
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<td>Newton-Bishop et al, 2009</td>
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<td>Weinstock et al, 1992</td>
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<td>Asgari et al, 2009</td>
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<td>Lycopene</td>
<td>• Reduction of oxidative stress</td>
<td>DI Franco et al, 2012</td>
<td>No, level Ila (supportive)</td>
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<td>• Inhibition of platelet-derived growth factor-BB, reducing melanoma-induced fibroblast migration and signaling transduction</td>
<td>Stahl and Sies, 2012</td>
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<td>Costa et al, 2012</td>
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<td>Rizwan et al, 2011</td>
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<td>DI Mascio et al, 1989</td>
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<td>Mein et al, 2008</td>
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<td>Wu et al, 2007</td>
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melanoma cells. 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-E2 synthesis.

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

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. 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. 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. 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 administered. Many studies have shown an inverse relationship between overall mortality from various forms of cancer (including skin cancers) and both selenium dietary intake and topical application. Mouse studies have shown a decrease in melanoma lung metastases with increased dietary amounts of selenium, although the relationship between selenium exposure and human melanoma incidence remains unclear. 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. However, no significant toxicities have been shown in human beings.
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. 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. 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.

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. 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. It has been previously shown to protect human skin from the effects of sun damage by decreasing sunburn cell formation.

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. 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 costimulator molecules. Resveratrol has been shown to have many anticancer properties; it has in particular been shown to be antiproliferative against melanoma A431 cells, and induces apoptosis in A475 and SK-mel28 cells.

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.

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. Studies show that it induces apoptosis and inhibits melanoma cell growth in animal cell lines and in human M14 and A375 cell lines. 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. 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.

Results regarding vitamin D have also been variable as well. Recent studies have suggested higher levels of 25-hydroxyvitamin D3 are associated with lower melanoma incidence, decreased relapse incidence, and lower Breslow thickness at time of diagnosis, suggesting improved prognosis. However, other large-scale studies have failed to demonstrate similar relationships. 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. 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. 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.

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.

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. The first study investigating the medicinal properties of fig latex in the 1940s demonstrated inhibition of tumor growth. 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. 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. Recent studies have further supported the ability of fig latex to scavenge free radicals and reduce tumor growth in human C32 melanoma cell lines. 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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