

# Manager Brief: Nutrition and Melanoma Prevention



## **Antioxidants (Vitamins, Minerals) in Diet and through Supplements**

A wide variety of vitamins, minerals and supplements and their role in melanoma have been looked at in numerous studies. One study, called the SUVIMAX study, <sup>1</sup> found that daily oral supplementation of vitamin C, vitamin E, beta-carotene, selenium and zinc increased the incidence of melanoma in women. However in a response to the study, Hughes et al<sup>2</sup> dispute the conclusion that antioxidant supplementation increases the risk for melanoma, stating flaws in the methods and interpretation of results including focusing only on the first occurrence of skin cancer within the study population and argue that the melanomas reported in the study were likely to have been present prior to the antioxidant supplement intervention due to the long latent period of the disease. Below, vitamins, minerals and antioxidants are detailed further:

- **Vitamin A**
  - **Beta-carotene:** A systematic review found few articles showed protective roles of beta-carotene against melanoma.<sup>3</sup> However, another study found no association between beta-carotene and melanoma risk.<sup>4</sup>
  - **Retinol:** Several reports of studies, including one meta-analysis, found that retinol intake from foods and supplementation appeared to be protective against melanoma.<sup>5-7</sup> One study found the protective effect for women only<sup>6</sup> and another study found that the protective effect was found only with intake of retinol rather than overall vitamin A or beta-carotene.<sup>7</sup>
  - **Overall Vitamin A:** A population-based case-controlled study conducted in Hawaii with 556 adults 18-79 years of age found a direct association between melanoma and plasma levels of vitamin A components (alpha-carotene, and beta-cryptoxanthin) in men.<sup>8</sup>
- **Vitamin C**
  - Two studies found that plasma vitamin C levels were directly associated with melanoma in women.<sup>6,8</sup>
- **Vitamin D**
  - One narrative review found that two separate studies showed higher plasma levels of the active form of vitamin D were associated with lower Breslow thickness at the time of melanoma diagnosis but that there was no relationship between vitamin D intake and melanoma incidence<sup>9</sup> while another review found that animal, in vitro and small human studies showed vitamin D had a promising protective effect against melanoma but large-scale human studies would be hard to replicate.<sup>10</sup> Yet another review found that inefficient evidence exists to recommend supplementation with vitamin D to prevent melanoma for the general population; however, vitamin D supplementation appeared to lower melanoma risk in high-risk patients.<sup>11</sup> Additionally, two cohorts were prospectively evaluated to determine if dietary and supplemental vitamin D were associated with skin cancer risk and found that vitamin D intake was positively associated with basal cell carcinoma but no association was found with squamous cell carcinoma and melanoma.<sup>12</sup>
- **Vitamin E**
  - A narrative review found that studies suggest that vitamin E supplementation may not offer a clinically significant photoprotective effect.<sup>9</sup> Another study found that plasma levels of a component of vitamin E (alpha-tocopherol) were directly associated with melanoma in men.<sup>8</sup> On the other hand, in vitro tests on human melanoma cells found that a component of vitamin E had a significant antiproliferative/proapoptotic effect, suggesting the vitamin E could be considered in a combinational chemopreventive strategy for melanoma; however, authors state that clinical trials are needed before results can be conclusive.<sup>13</sup>
- **Selenium**
  - Although the results of the SUVIMAX study<sup>1</sup> found that daily oral supplementation with selenium and other antioxidants increased risk for melanoma in women, other studies have not been able to replicate these

results.<sup>4,9</sup> A narrative review found that some studies showed that oral and topical selenium both provided protection against UV- induced sunburn, tanning, and skin cancer but other studies had mixed results.<sup>9</sup>

- **Miscellaneous Antioxidants**

- Other antioxidants that have the potential to protect against melanoma include proanthocyanidins from grape seed extract,<sup>9,10</sup> green tea polyphenols,<sup>9,10,14</sup> lycopene,<sup>10,15</sup> resveratrol from foods like grape and blueberry skins,<sup>10</sup> and rosmarinic acid from rosemary.<sup>10</sup> However, the majority of studies involving these antioxidants were done on animals or in vitro and clinical trials are needed for conclusive results.<sup>9,10</sup>

Furthermore, one meta-analysis found that despite numerous studies on the topic, there were no preventive effects on skin cancer from supplementation of vitamins, minerals and other antioxidants,<sup>16</sup> including vitamins D and E, selenium, resveratrol and lycopene.<sup>11</sup> However, others argue there are promising potential protective effects in animal, in vitro and small human studies but more research is needed.<sup>10,17</sup> Overall, results on the effect of antioxidants on melanoma risk are inconclusive but seem to suggest that a well-balanced diet that includes a variety of antioxidants could provide some protection against melanoma as it does with other cancers.

## **Dietary Habits**

A few studies have looked at the overall dietary habits of participants with melanoma when compared to case-controlled participants and found that even with control for individual characteristics and sun exposure, there was a protective effect from melanoma for weekly consumption of fish, shellfish, and fish rich in n-3 fatty acids (like EPA and DHA), daily tea drinking, high consumption of vegetables (particularly carrots, cruciferous and leafy vegetables) and fruits (particularly citrus fruits).<sup>18</sup> These are all components of the Mediterranean diet and other studies have come to similar conclusions.<sup>3,19</sup> A different population-based case-control study looked at components of 4 different diets: the Healthy Eating Index 2010 (HEI-2010), Dietary Approaches to Stop Hypertension (DASH) index, Greek Mediterranean index (GMI) and Italian Mediterranean index (IMI).<sup>20</sup> In this study of almost 2,000 participants, results showed an inverse association between disease risk and the HEI-2010 and DASH index but not the Mediterranean indexes with a stronger association for women.<sup>20</sup> In the same study, authors examined the possible association between glycemic index (GI) and glycemic load (GL), which are indicators of dietary carbohydrate quantity and quality.<sup>21</sup> A direct association between melanoma risk and GL emerged in females, even after adjusting for several potential confounders, while there was no evidence of association between GI and melanoma risk.<sup>21</sup> Overall, a diet high in fruits, vegetables and with weekly consumption of fish seems to have a potential protective factor against melanoma.

Other studies examined specific dietary factors independently and are listed out below:

- **Fats**

- Diets that consist mostly of plant-based fats (i.e. omega-3 and omega-9 polyunsaturated fats) seem to be associated with lower risk of melanoma,<sup>10,22-26</sup> especially when compared to the fat commonly found in the Western diet (animal-based fats like omega-6 fatty acids).<sup>22</sup> However, a study in Australia using a population-based case-control method found that a diet with high fat intake, including animal fats, seemed to reduce the risk of melanoma.<sup>27</sup> Most studies found that diets high in omega-3 fatty acids<sup>26</sup> and long-chain omega-3 fatty acids docosahexaenoic acid (DHA)<sup>23</sup> and eicosapentaenoic acid (EPA).<sup>23,25</sup> However, other studies found polyunsaturated fats (PUFAs) little or no effect on the risk of melanoma<sup>28</sup> and one small study (51 newly diagnosed cases of melanoma and matching controls) found that there was a direct association between melanoma and DHA in males.<sup>29</sup> Generally speaking, there is no solid evidence yet that suggests amount of type of fat intake has any effect on melanoma.

- **Protein**

- One study showed through tests on melanoma cells and mice with melanoma tumors that cysteine inhibited melanoma viability and development.<sup>30</sup> However, human trials are still needed.

- **Alcohol**

- While several studies have shown a link between regular alcohol consumption and sunburn and cutaneous melanoma,<sup>31</sup> one small study showed that it took less UV light to damage participants' skin after consuming alcohol.<sup>32</sup> Authors also discovered a decrease in antioxidant concentration in the skin, specifically carotenoids which plays a role in protecting skin against UV damage.<sup>32</sup>

## Caffeine

There are quite a few studies that have looked at the association between caffeine and melanoma risk. Most studies showed some association between caffeinated coffee only or total coffee consumption (both caffeinated and decaffeinated)<sup>33-35</sup> and lower risk of melanoma<sup>36-41</sup> but not for decaffeinated coffee consumption alone. Furthermore, one prospective cohort study with over 475,000 participants found there was no significant association between caffeinated tea intake and the risk of melanoma.<sup>36</sup> Another study only found a decreased risk of melanoma associated with coffee consumption in women.<sup>35</sup> Conversely, a study that utilized food-frequency questionnaires to determine use of foods and beverages for the previous two years found that there was no inverse association between melanoma risk and caffeine intake.<sup>42</sup>

Some studies showed that higher coffee consumption was related to reduced melanoma risk.<sup>33,34,37-39</sup> One study showed that the risk for melanoma decreased if more than one cup of coffee per day was consumed.<sup>33</sup> A study showed a 3% reduction<sup>37</sup> of risk of melanoma and another study showed a 4% reduction<sup>34</sup> for risk of melanoma with each one cup per day increase of caffeinated coffee.

In summary, consumption of caffeinated coffee seems to provide a protective effect against melanoma through risk reduction.

## Conclusion

There are emerging ideas for diets and supplements that may provide protection against melanoma. However, most study results are either inconclusive or conflicting with the exception of caffeinated coffee consumption. The overarching theme seems to suggest that eating a diet rich in healthy fats, high in fruits and vegetables, and that regularly includes fish could provide some reduced risk for melanoma. Regular caffeinated coffee consumption of more than one cup a day also seems to reduce risk for melanoma. Additionally, evidence suggests avoiding alcohol consumption while spending time in the sun. However, nutrition is not a primary means for preventing melanoma.

## References

1. Hercberg S, Ezzedine K, Guinot C, et al. Antioxidant supplementation increases the risk of skin cancers in women but not in men [published online ahead of print 2007/08/22]. *J Nutr*. 2007;137(9):2098-2105. doi: 10.1093/jn/137.9.2098
2. Hughes MC, Ibiebele TI, Green ALC, Williams GM, van der Pols JC, Ortonne J-P. Antioxidant Supplementation and Risk of Skin Cancers. *The Journal of Nutrition*. 2008;138(5):978-978. doi: 10.1093/jn/138.5.978
3. de Waure C, Quaranta G, Gualano MR, et al. Systematic review of studies investigating the association between dietary habits and cutaneous malignant melanoma [published online ahead of print 2015/07/28]. *Public Health*. 2015;129(8):1099-1113. doi: 10.1016/j.puhe.2015.06.015
4. Asgari MM, Maruti SS, Kushi LH, White E. Antioxidant supplementation and risk of incident melanomas: results of a large prospective cohort study [published online ahead of print 2009/08/19]. *Arch Dermatol*. 2009;145(8):879-882. doi: 10.1001/archdermatol.2009.176.PMC2729504
5. Asgari MM, Brasky TM, White E. Association of vitamin A and carotenoid intake with melanoma risk in a large prospective cohort [published online ahead of print 2012/03/02]. *J Invest Dermatol*. 2012;132(6):1573-1582. doi: 10.1038/jid.2012.21.PMC3352977
6. Feskanich D, Willett WC, Hunter DJ, Colditz GA. Dietary intakes of vitamins A, C, and E and risk of melanoma in two cohorts of women [published online ahead of print 2003/06/05]. *Br J Cancer*. 2003;88(9):1381-1387. doi: 10.1038/sj.bjc.6600882.PMC2741035
7. Zhang YP, Chu RX, Liu H. Vitamin A intake and risk of melanoma: a meta-analysis [published online ahead of print 2014/07/23]. *PLoS One*. 2014;9(7):e102527. doi: 10.1371/journal.pone.0102527.PMC4105469
8. Le Marchand L, Saltzman BS, Hankin JH, et al. Sun exposure, diet, and melanoma in Hawaii Caucasians [published online ahead of print 2006/03/10]. *Am J Epidemiol*. 2006;164(3):232-245. doi: 10.1093/aje/kwj115
9. Jensen JD, Wing GJ, Dellavalle RP. Nutrition and melanoma prevention [published online ahead of print 2010/11/03]. *Clin Dermatol*. 2010;28(6):644-649. doi: 10.1016/j.clindermatol.2010.03.026
10. Tong LX, Young LC. Nutrition: the future of melanoma prevention? [published online ahead of print 2014/03/25]. *J Am Acad Dermatol*. 2014;71(1):151-160. doi: 10.1016/j.jaad.2014.01.910
11. Murzaku EC, Bronsnick T, Rao BK. Diet in dermatology: Part II. Melanoma, chronic urticaria, and psoriasis [published online ahead of print 2014/12/03]. *J Am Acad Dermatol*. 2014;71(6):1053.e1051-1053.e1016. doi: 10.1016/j.jaad.2014.06.016

12. Park SM, Li T, Wu S, Li WQ, Qureshi AA, Cho E. Vitamin D Intake and Risk of Skin Cancer in US Women and Men [published online ahead of print 2016/08/25]. *PLoS One*. 2016;11(8):e0160308. doi: 10.1371/journal.pone.0160308.PMC4996491
13. Montagnani Marelli M, Marzagalli M, Moretti RM, et al. Vitamin E delta-tocotrienol triggers endoplasmic reticulum stress-mediated apoptosis in human melanoma cells [published online ahead of print 2016/07/28]. *Sci Rep*. 2016;6:30502. doi: 10.1038/srep30502.PMC4996065
14. Katiyar S, Elmets CA, Katiyar SK. Green tea and skin cancer: photoimmunology, angiogenesis and DNA repair [published online ahead of print 2006/10/20]. *J Nutr Biochem*. 2007;18(5):287-296. doi: 10.1016/j.jnutbio.2006.08.004
15. Tuong W, Kuo S, Sivamani RK. Photoprotective effect of botanicals and vitamins: A systematic review of clinical trials [published online ahead of print 2015/04/14]. *J Dermatolog Treat*. 2015;26(6):558-570. doi: 10.3109/09546634.2015.1027647
16. Chang YJ, Myung SK, Chung ST, et al. Effects of vitamin treatment or supplements with purported antioxidant properties on skin cancer prevention: a meta-analysis of randomized controlled trials [published online ahead of print 2011/08/19]. *Dermatology*. 2011;223(1):36-44. doi: 10.1159/000329439
17. Russo I, Caroppo F, Alaibac M. Vitamins and Melanoma. *Cancers*. 2015;7(3):1371-1387. doi: 10.3390/cancers7030841
18. Fortes C, Mastroeni S, Melchi F, et al. A protective effect of the Mediterranean diet for cutaneous melanoma [published online ahead of print 2008/07/16]. *Int J Epidemiol*. 2008;37(5):1018-1029. doi: 10.1093/ije/dyn132
19. Shapira N. Nutritional approach to sun protection: a suggested complement to external strategies [published online ahead of print 2010/02/09]. *Nutr Rev*. 2010;68(2):75-86. doi: 10.1111/j.1753-4887.2009.00264.x
20. Malagoli C, Malavolti M, Agnoli C, et al. Diet Quality and Risk of Melanoma in an Italian Population [published online ahead of print 2015/06/26]. *J Nutr*. 2015;145(8):1800-1807. doi: 10.3945/jn.114.209320.PMC4516764
21. Malavolti M, Malagoli C, Crespi CM, et al. Glycaemic index, glycaemic load and risk of cutaneous melanoma in a population-based, case-control study [published online ahead of print 2017/02/16]. *Br J Nutr*. 2017;117(3):432-438. doi: 10.1017/s000711451700006x
22. Cario-Andre M, Briganti S, Picardo M, Nikaido O, de Verneuil H, Taieb A. Polyunsaturated fatty acids partially reproduce the role of melanocytes in the epidermal melanin unit [published online ahead of print 2005/03/03]. *Exp Dermatol*. 2005;14(3):194-201. doi: 10.1111/j.0906-6705.2005.00273.x
23. Donat-Vargas C, Berglund M, Glynn A, Wolk A, Akesson A. Dietary polychlorinated biphenyls, long-chain n-3 polyunsaturated fatty acids and incidence of malignant melanoma [published online ahead of print 2016/12/30]. *Eur J Cancer*. 2017;72:137-143. doi: 10.1016/j.ejca.2016.11.016
24. Gamba CS, Stefanick ML, Shikany JM, et al. Low-fat diet and skin cancer risk: the women's health initiative randomized controlled dietary modification trial [published online ahead of print 2013/05/24]. *Cancer Epidemiol Biomarkers Prev*. 2013;22(9):1509-1519. doi: 10.1158/1055-9965.epi-13-0341.PMC3880824
25. Rhodes LE, Shahbakhti H, Azurdia RM, et al. Effect of eicosapentaenoic acid, an omega-3 polyunsaturated fatty acid, on UVR-related cancer risk in humans. An assessment of early genotoxic markers [published online ahead of print 2003/05/29]. *Carcinogenesis*. 2003;24(5):919-925.
26. Yin X, Yu XW, Zhu P, et al. Endogenously synthesized n-3 fatty acids in fat-1 transgenic mice prevent melanoma progression by increasing E-cadherin expression and inhibiting beta-catenin signaling [published online ahead of print 2016/08/31]. *Mol Med Rep*. 2016;14(4):3476-3484. doi: 10.3892/mmr.2016.5639
27. Granger RH, Blizzard L, Fryer JL, Dwyer T. Association between dietary fat and skin cancer in an Australian population using case-control and cohort study designs [published online ahead of print 2006/06/01]. *BMC Cancer*. 2006;6:141. doi: 10.1186/1471-2407-6-141.PMC1481578
28. Liyanage UE, Law MH, Ong JS, et al. Polyunsaturated fatty acids and risk of melanoma: A Mendelian randomisation analysis [published online ahead of print 2018/02/24]. *Int J Cancer*. 2018;143(3):508-514. doi: 10.1002/ijc.31334
29. Vinceti M, Malagoli C, Iacuzio L, et al. Serum Fatty acids and risk of cutaneous melanoma: a population-based case-control study [published online ahead of print 2013/02/23]. *Dermatol Res Pract*. 2013;2013:659394. doi: 10.1155/2013/659394.PMC3569884
30. Chu P-Y, Liu M-Y. Amino acid cysteine induces senescence and decelerates cell growth in melanoma. *Journal of Functional Foods*. 2015;18:455-462. doi: https://doi.org/10.1016/j.jff.2015.08.010
31. Rota M, Pasquali E, Bellocco R, et al. Alcohol drinking and cutaneous melanoma risk: a systematic review and dose-risk meta-analysis. *Br J Dermatol*. 2014;170(5):1021-1028. doi: 10.1111/bjd.12856
32. Darvin ME, Sterry W, Lademann J, Patzelt A. Alcohol consumption decreases the protection efficiency of the antioxidant network and increases the risk of sunburn in human skin. *Skin Pharmacol Physiol*. 2013;26(1):45-51. doi: 10.1159/000343908
33. Fortes C, Mastroeni S, Boffetta P, et al. The protective effect of coffee consumption on cutaneous melanoma risk and the role of GSTM1 and GSTT1 polymorphisms [published online ahead of print 2013/07/19]. *Cancer Causes Control*. 2013;24(10):1779-1787. doi: 10.1007/s10552-013-0255-4

34. Wang J, Li X, Zhang D. Coffee consumption and the risk of cutaneous melanoma: a meta-analysis [published online ahead of print 2015/12/24]. *Eur J Nutr.* 2016;55(4):1317-1329. doi: 10.1007/s00394-015-1139-z
35. Veierod MB, Thelle DS, Laake P. Diet and risk of cutaneous malignant melanoma: a prospective study of 50,757 Norwegian men and women [published online ahead of print 1997/05/16]. *Int J Cancer.* 1997;71(4):600-604.
36. Caini S, Masala G, Saieva C, et al. Coffee, tea and melanoma risk: findings from the European Prospective Investigation into Cancer and Nutrition [published online ahead of print 2017/02/22]. *Int J Cancer.* 2017;140(10):2246-2255. doi: 10.1002/ijc.30659.PMC6198927
37. Micek A, Godos J, Lafranconi A, Marranzano M, Pajak A. Caffeinated and decaffeinated coffee consumption and melanoma risk: a dose-response meta-analysis of prospective cohort studies [published online ahead of print 2017/09/12]. *Int J Food Sci Nutr.* 2018;69(4):417-426. doi: 10.1080/09637486.2017.1373752
38. Liu J, Shen B, Shi M, Cai J. Higher Caffeinated Coffee Intake Is Associated with Reduced Malignant Melanoma Risk: A Meta-Analysis Study [published online ahead of print 2016/01/28]. *PLoS One.* 2016;11(1):e0147056. doi: 10.1371/journal.pone.0147056.PMC4729676
39. Loftfield E, Freedman ND, Graubard BI, et al. Coffee drinking and cutaneous melanoma risk in the NIH-AARP diet and health study [published online ahead of print 2015/01/22]. *J Natl Cancer Inst.* 2015;107(2) doi: 10.1093/jnci/dju421.PMC4311176
40. Yew YW, Lai YC, Schwartz RA. Coffee consumption and melanoma: A systematic review and meta-analysis of observational studies. *Am J Clin Dermatol.* 2016;17(2):113-123. doi: 10.1007/s40257-015-0165-1
41. Wrzesniok D, Rzepka Z, Respondek M, et al. Caffeine modulates growth and vitality of human melanotic COLO829 and amelanotic C32 melanoma cells: Preliminary findings [published online ahead of print 2018/07/30]. *Food Chem Toxicol.* 2018;120:566-570. doi: 10.1016/j.fct.2018.07.049
42. Song F, Qureshi AA, Han J. Increased caffeine intake is associated with reduced risk of basal cell carcinoma of the skin [published online ahead of print 2012/07/04]. *Cancer Res.* 2012;72(13):3282-3289. doi: 10.1158/0008-5472.can-11-3511