

A Review of Common Tanning Methods

^aMICHAEL GARONE, JR., DO; ^bJOHN HOWARD, DO; ^cJORDAN FABRIKANT, DO

^aLargo Medical Center, Largo, Florida; ^bBroward Health Medical Center, Ft. Lauderdale, Florida; ^cLarkin Hospital, Miami, Florida

ABSTRACT

Tanning in the United States has become an increasingly popular activity in our culture. Tanning methods have evolved through the years to become more readily accessible and easier to use for all consumers, regardless of geographic location. With the rising incidence of skin cancer, the demand for safe and efficient tanning methods remains high. There are currently many different tanning methods being utilized, and still more are being researched. This article serves to summarize some of the most common tanning methods used in the United States today as well as some potential methods currently under study. (*J Clin Aesthet Dermatol.* 2015;8(2):43–47.)

Tanning remains an incredibly popular activity in our society despite the well-known risks. Many people view tan skin as more aesthetically pleasing. In fact, 90 percent of women perceive tan skin as being more attractive than non-tan skin.¹ As such, approximately 10 percent of the US population uses indoor tanning salons, the majority of which are female.² Studies have shown that the high prevalence of tanning is because the perceived aesthetic benefits outweigh the risks and is not due to lack of knowledge about the dangers of tanning with ultraviolet radiation (UVR).³ Aside from UVR tanning, which includes both sunbathing and the use of indoor tanning salons, there are forms of sunless tanning that are popular as well. While these have traditionally been viewed as safer than UVR tanning, some concerns have been raised about the safety profile of these methods. This article serves to summarize the various methods of tanning that are used today, as well as some new potential tanning options that are being researched and explored.

SKIN CANCER OVERVIEW

Skin cancer is one of the most significant risks of UV exposure. It is the most common form of cancer in the United States. Each year, it is estimated that there are more new cases of skin cancer than the combined incidences of all other cancers.⁴ There are three major forms of skin cancer—basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. BCC is the most common type and there are an estimated 2.8 million cases diagnosed in the United States every year.⁵ SCC is the second most common

form of skin cancer. An estimated 700,000 cases of SCC are diagnosed each year in the United States.^{5,6} The treatment of nonmelanoma skin cancers increased by nearly 77 percent between 1992 and 2006.⁷ Melanoma, while less common than BCCs and SCCs, is the most dangerous skin cancer. It contributes to 75 percent of deaths associated with skin cancer.⁸ The incidence of melanoma has been increasing faster than any other cancer at 2.8 percent per year from 1981 to 2008.⁹

ULTRAVIOLET RADIATION

UVR is light spectrum from the sun. This spectrum is made up of three different wavelengths—ultraviolet A (UVA), ultraviolet B (UVB), and ultraviolet C (UVC). UVA rays make up the majority of the light spectrum and are the longest of the three UV wavelengths at 320 to 400nm. UVB rays make up an estimated five percent of the light spectrum and extend 290 to 320nm. UVC rays are the shortest of the three wavelengths and most do not reach earth as the ozone absorbs them.

UVA is primarily responsible for skin aging, wrinkling, and the formation of free radical species.^{10,11} UVB is less prevalent, but much more intense than UVA. UVB is the chief cause of skin reddening and sunburn.^{12,13} UVB light is responsible for direct damage to deoxyribonucleic acid (DNA) in the form of pyrimidine dimers.^{12,13} It plays a main role in the development of skin cancer.^{12,13}

Excessive UVA and UVB exposure damages the skin's cellular DNA and leads to mutations that can trigger skin cancer. The World Health Organization classified all wavelengths of UVR as a Group 1 carcinogen. This label is

DISCLOSURE: The authors report no relevant conflicts of interest.

ADDRESS CORRESPONDENCE TO: John Howard, DO; E-mail: Jch812@gmail.com

given to compounds that have proven carcinogenicity in humans.

ULTRAVIOLET TANNING

Despite significant causal evidence linking UVR to skin cancer, people continue to expose themselves to both outdoor and indoor UVR in order to tan. This is not due to lack of knowledge, but rather because the desire to look tan takes precedence over the known risk of UVR.³ Another argument sometimes made in favor of UVR tanning is enhanced mental health. UVR tanning is associated with increased energy, higher self-confidence, and mitigation of seasonal affective disorder symptoms.^{14,15} Beta-endorphins, which are produced endogenously from UVR exposure, contribute to these positive effects.¹⁶ However, in addition to skin cancer, UVR is also responsible for premature aging, photodamage, fine lines, wrinkles, lax skin, and brown spots.^{10,11,17} Sunbathing is a very unsafe method to achieve a golden hue because sunbathers are apt to misjudge the amount of sun they receive, leading to sunburn.

Tanning salons offer an indoor method of UVR with tanning beds and booths. These salons expose people to man-made UV light. Tanning beds were introduced in North America in 1978 and gained considerable popularity in the 1980s. Indoor tanning salons are a common choice among those who tan as they do not require people to spend hours outside in the sunlight. At any given tanning salon, there are typically three to five different types of beds. They are classified as level 1 through 6. In general, increasing levels correspond to increasing concentrations of UVA relative to UVB. Increasing the bed level also increases the pressure and number of lamps, resulting in a deeper tan that appears faster and fades slower than lower level beds.

In tanning salons, the user has the option to stand (e.g., in a booth) or lie supine (e.g., in a bed). The time spent in a bed is limited by the strength of lamps used and ranges from 8 to 20 minutes. One of the most important differences between beds is the percent of UVA versus UVB light. A higher percentage of UVB is believed to cause erythema and sunburn, but it is better for stimulating melanocytes to produce melanin. Beds with a higher percentage of UVA cause oxidation of melanin, triggering color to develop in the skin.¹⁸ At many tanning salons, the employees routinely instruct patrons that the use of tanning beds is safer than outdoor tanning because tanners can limit their dosage of harmful UVB light and limit their time spent in beds to prevent burns, thus minimizing their risk of cancer. In a recent report, only seven percent of tanning salons disclosed the risks of tanning to customers.¹⁹ While indoor tanners can limit the dosage of UVB light and the likelihood of sunburn, indoor tanners tend to tan more often, increasing the total dose of UVA light. One indoor tanning session increases the risk of developing melanoma by 20 percent.²⁰ Among those aged 18 to 29 who were diagnosed with melanoma and had a history of indoor tanning, 76 percent of the melanomas were attributable to their tanning bed use.²¹ This strong correlation between the use of tanning beds and skin cancer legitimizes the danger of their use.

TOPICAL SUNLESS TANNERS

Topical sunless tanners are products that are applied to the skin to give the appearance of a tan. These products come in many forms including lotions, gels, mousses, sprays, wipes, creams, and powders. Temporary bronzers are one type of topical self-tanner. Bronzers come in creams, lotions, and powders. When a bronzer is applied to the skin, it coats the outer layers of the epidermis. Bronzers are considered temporary because they only last until they are washed off by normal soap and water use. The use of a bronzer is similar to putting on make-up every day. Commonly used ingredients for temporary bronzers include caramel, walnut oil extract, and jojoba extract.

Many topical self-tanners contain the compound dihydroxyacetone (DHA). Topical DHA formulations come in lotions, gels, mousses, sprays, and wipes. DHA is a sugar molecule derived from plants that reacts chemically with the amino acids in the stratum corneum to produce pigment when applied to the skin. This reaction is known as the “Maillard reaction,” and it does not require UVR to produce a pigment change. The resulting pigments are called melanoidins, which are similar in pigment to melanin. Once DHA is applied to the skin, it takes approximately two to four hours to begin the tanning process and can continue for 24 to 72 hours. DHA is resistant to normal water, soap, and sweat exposure. The tan will begin to fade gradually three to seven days after application as a result of normal skin exfoliation.²² DHA formulations have become popular among the public due to their relative ease of application and longer lasting tan when compared to temporary color bronzers, which wash off readily with soap and water. The temporary color bronzers also have a higher tendency to cause blotchiness, an uneven tan, and a less natural looking color. However, any activity that causes exfoliation to occur more rapidly, such as scrubbing the skin, prolonged water submersion or heavy sweating will also cause the DHA-induced tan to fade more quickly. Before applying products containing DHA, it is best to shave or wax, shower, and exfoliate the skin first because that will produce a more even tan.²³ It is also important to avoid moisturizing the application area because this can interfere with an even absorption of the DHA product. The exception to this is if there is a very dry area on the skin, in which case it is recommended that the user apply a very thin layer of moisturizer to that area. Applying the product to the body with a circular motion can help prevent a streaky look. DHA concentrations range from 1 to 15%. This concentration range allows users to adjust the intensity of their coloration as desired. Since they first hit the marketplace in the 1960s, DHA formulations have improved. This is due in part to purer supplies of DHA, better manufacturing, including ingredients that better complement DHA, and making the compounds more acidic. Newer products also contain lower concentrations of DHA. As mentioned above, DHA comes in multiple formulations, each having their own benefits. Lotions tend to last longer than sprays; however, sprays reduce the risk of blotching and streaking. Mousses and gels tend to have a faster drying time, and mousses contain less

moisture so they can be beneficial to users with more oily skin.

It is important to note that the United States Food and Drug Administration (FDA) has approved DHA only for topical application on the skin. DHA is not approved for use on non-skin areas, such as the eyes, lips, and mucous membranes. As a result, DHA has not been approved in the use of spray tanning booths due to the potential exposure to non-FDA approved sites, even when taking precautions, such as wearing nose plugs, goggles, or applying petroleum jelly to the lips. Reported side effects from DHA-containing spray tans include rashes, cough, dizziness, and fainting. Some physicians have expressed concern that chronic exposure to spray tans may increase the risk of pulmonary disease, including asthma, chronic obstructive pulmonary disease (COPD), and cancer. Users often also complain of an unpleasant odor after applying the tanner, which is a result of the chemical reaction taking place in the skin. Added fragrances can sometimes mask the smell; however, this may increase the likelihood of allergic reactions or worsen asthma symptoms. Some formulations contain parabens. Parabens are a chemical preservative in many cosmetics that can cause rosacea and allergic contact dermatitis in some users.²⁴ They have also been shown to be weak estrogens.²⁵ There has been no link found between parabens and the risk of breast cancer; however, more research is needed to explore their long-term safety.²⁶

Although DHA was previously thought to be limited in penetration to the dead outer layer of the skin, a report released by the FDA theorized that about 11 percent of the applied DHA penetrates into the living cells of the epidermis and dermis. In addition, a previous study done on cultured mouse cells showed that DHA induces DNA damage, cell-cycle block, and apoptosis in living cells.²⁷ Another study found that using a 9% DHA spray interfered with vitamin D production.²⁸ UVB radiation has been correlated with the reduction of roughly 20 types of cancer, and this benefit is thought to be due to the UV-induced production of vitamin D.²⁹ Another risk is that topical DHA in levels of 5% or greater have been shown to increase susceptibility to free-radical damage from sunlight for 24 hours after application.³⁰ This could be problematic for people applying DHA every day or every other day. The addition of topical antioxidants have been said to produce a more natural looking tan, and further study is needed to determine if they can decrease this free radical damage. It has also been shown that people who use sunless tanning products were more likely to report having had a sunburn.³¹ The tanning from DHA only provides a sun protection factor (SPF) of 3, and this effect is short-lived, thus it is extremely important to apply sunscreen after the tanner is applied.^{32,33}

Erythrulose is similar in composition to DHA. It is found naturally in red raspberries. Applied by itself, erythrulose takes longer to produce a tan, and the resulting tan fades quicker. The tan produced is also more red than brown in appearance. However, when combined with DHA, the tan reportedly lasts longer, fades better, and provides a more attractive tone. Erythrulose, however, has also been shown

to increase production of free radicals similar to the effect seen with DHA.³⁴

There are other topical products that are designed to complement tanning. Maximizers are moisturizers that contain antioxidant fruit extracts. Some of the formulations also contain bronzer extracts. Maximizers are designed to prevent uneven or premature exfoliation of the skin. They can be applied before or after the user tans. Tingles are another tanning product that contain benzyl nicotinate. This acts to increase microcirculation to the skin, exposing more oxygen to melanocytes.³⁵ It has the effect of making the user feel like their skin is burning or “tingling”. It is reported by the manufacturers to aid in UV tanning by increasing the production of melanin in the skin. Products known as optimizers or accelerators contain the protein tyrosine. Tyrosine can be synthesized endogenously or obtained from the diet. Tyrosine is a precursor to the production of melanin. The thought with topical tyrosine products is that by providing more of this substrate, this will aid in the production of melanin. There is no current evidence to support this claim.³⁶

TANNING PILLS

Tanning pills are non-prescription formulations that are readily available to customers for purchase over the Internet. The most common active ingredient is canthaxanthin. This is a naturally occurring carotenoid found in such things as mushrooms, bacteria, crustaceans, sea trout, and algae. Canthaxanthin is FDA approved in small quantities for use as a coloring agent in food. The effect of ingesting canthaxanthin, and subsequent deposition in the epidermis and subcutaneous fat, is the formation of an orange-brown appearance of the skin. The FDA has banned canthaxanthin-containing tanning pills due to their significant adverse effects when ingested in large quantities. Some of the side effects include gastrointestinal disturbance, urticaria, hepatitis, retinopathy, and potentially fatal aplastic anemia.³⁷⁻³⁹

Another common ingredient in tanning pills is beta-carotene, a different carotenoid. Beta-carotene is obtained through the dietary consumption of fruits and vegetables, and it contributes to the yellow pigment found in human skin. Its deposition in the skin is thought to contribute to photoprotection, guarding against the deleterious effects of both natural and artificial UV light exposure, and raising the minimum amount of UVR exposure required to cause a sunburn.⁴⁰⁻⁴³ It has been shown that individuals with higher daily intakes of fruit, vegetables, and beta-carotene have yellower skin. It has also been shown, however, that high doses of synthetic beta-carotene are associated with an increased risk of lung cancer among those who smoke, calling into question its potential use as an antioxidant.⁴⁴

Another type of tanning pill contains tyrosine. As mentioned above, tyrosine is a protein that has been said to aid in the production of melanin. Oral tyrosine pills have not been shown to work.⁴⁵ The FDA considers them to be potentially dangerous and as a result they are not approved in the United States.

ALPHA-MELANOCYTE STIMULATING HORMONE ANALOGUES

Initial research involving medicinal applications of alpha-melanocyte stimulating hormone (MSH) analogues started in the 1980s. They work by binding to melanocortin type 1 receptors on melanocytes, which signal the melanocytes to produce eumelanin. Afamelanotide ([Nle4-D-Phe7]-alpha-MSH) is the first of these analogues to be developed for medical skin disorders. Afamelanotide is a subcutaneous implant administered once a month. It has been approved for erythropoietic protoporphyria in Europe.⁴⁶ It is also currently in Phase 2 clinical trials for vitiligo and Hailey-Hailey disease in Europe. A recent article by Fabrikant et al⁴⁵ contained updates on afamelanotide and its current clinical trials.⁴⁵ Afamelanotide has demonstrated *in vitro* and *in vivo* to potentiate the tanning effects of UV light exposure while also reducing sunburns and thymine dimer formation. Alpha-MSH analogues have been shown to enhance repair of UV-induced DNA damage of melanocytes.

The protective effects of endogenous alpha-MSH has widely been demonstrated. It has been shown that alpha-MSH aids in the phosphorylation of p53, helping to enhance its function against DNA damage. This ultimately results in a reduction of oxidative stress, which may decrease the risk of malignant transformation of melanocytes.⁴⁶ Another study demonstrated that pre-treating melanocytes with alpha-MSH reduced certain free radicals that are known to induce DNA damage as well as increase levels of the enzyme catalase, which helps to control free radical formation.⁴⁷ In addition, the loss of function of the melanocortin type 1 receptor has been linked with certain melanoma patients.⁴⁸

Other analogues of alpha-MSH, Melanotan I and II, are available and unregulated to enhance skin pigmentation for cosmetic tanning. They are not equivalent to afamelanotide. They have been reported to cause side effects, such as satiety, hypertension, and penile erections. Other risks include the potential to transmit blood-borne infections, rhabdomyolysis, encephalopathy, and renal dysfunction. These side effects have not been reported with the controlled-release subcutaneous afamelanotide implant that is undergoing clinical trials. They can be purchased from the Internet, tanning salons, gyms, and spas. Some web stores make unsubstantiated claims regarding clinical trials proving the effectiveness of the alpha-MSH analogues. Due to the unknown origin and methods of synthesis of Melanotan I and II, the FDA has issued warnings to the public regarding the safety of these synthetic analogues.

REFERENCES

1. Sahn RE, McIlwain MJ, Magee KH, et al. A cross-sectional study examining the correlation between sunless tanning product use and beliefs and behaviors. *Arch Dermatol.* 2012;148(4):448–454.
2. Fisher DE, James WD. Indoor tanning-science, behavior, and policy. *N Engl J Med.* 2010;363(10):901–903.
3. Dennis LK, Lowe JB, Snetselaar LG. Tanning behavior among young frequent tanners is related to attitudes and not lack of

knowledge about the dangers. *Health Educ J.* 2009;68(3):232–243.

4. American Cancer Society. Cancer Facts & Figures 2013. <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-036845.pdf>. Accessed March 24, 2014.
5. Rogers, Howard. “Your new study of nonmelanoma skin cancers.” E-mail to The Skin Cancer Foundation. March 31, 2010.
6. Squamous Cell Carcinoma. American Academy of Dermatology. <http://www.aad.org/skin-conditions/dermatology-a-to-z/squamous-cell-carcinoma>. Accessed March 24, 2014
7. Rogers HW, Weinstock MA, Harris AR, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. *Arch Dermatol.* 2010;146(3):283–287.
8. Jerant AF, Johnson JT, Sheridan CD, Caffrey TJ. Early detection and treatment of skin cancer. *Am Fam Physician.* 2000;62(2):357–368, 375–376, 381–382.
9. Little EG, Eide MJ. Update on the current state of melanoma incidence. *Dermatol Clin.* 2012;30(3):355–361.
10. Yaar M, Gilchrist BA. Photoageing: mechanism, prevention and therapy. *Br J Dermatol.* 2007;157(5):874–887.
11. Fisher GJ, Kang S, Varani J, et al. Mechanisms of photoaging and chronological skin aging. *Arch Dermatol.* 2002;138(11):1462–1470.
12. Benjamin CL, Ullrich SE, Kripke ML, Ananthaswamy HN. p53 tumor suppressor gene: a critical molecular target for UV induction and prevention of skin cancer. *Photochem Photobiol.* 2008;84(1):55–62.
13. Schwarz T. 25 years of UV-induced immunosuppression mediated by T cells—from disregarded T suppressor cells to highly respected regulatory T cells. *Photochem Photobiol.* 2008;84(1):10–18.
14. Wirz-Justice A, Graw P, Krauchi K, et al. “Natural” light treatment of seasonal affective disorder. *J Affect Disord.* 1996;37(2-3):109–120.
15. Woo DK, Eide MJ. Tanning beds, skin cancer, and vitamin D: an examination of the scientific evidence and public health implications. *Dermatol Ther.* 2010;23(1):61–71.
16. Ladizinski B, Lee KC, Ladizinski R, Federman DG. Indoor tanning amongst young adults: time to stop sleeping on the banning of sunbeds. *J Gen Intern Med.* 2013;28(12):1551–1553.
17. Talwar HS, Griffiths CE, Fisher GJ, et al. Reduced type I and type III procollagens in photodamaged adult human skin. *J Invest Dermatol.* 1995;105(2):285–290.
18. Miyamura Y, Coelho SG, Wolber R, et al. Regulation of human skin pigmentation and responses to ultraviolet radiation. *Pigment Cell Res.* 2007;20(1):2–13.
19. US House of Representatives Committee on Energy and Commerce Minority Staff. False and misleading health information provided to teens by the indoor tanning industry, 2012. <http://www.democrats.energycommerce.house.gov/sites/default/files/documents/False-Health-Info-by-Indoor-Tanning-Industry-2012-2-1.pdf>. Accessed September 1, 2013.
20. Boniol M, Autier P, Boyle P, Gandini S. Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. *BMJ.* 2012;345:e4757.

21. Cust AE, Armstrong BK, Goumas C, et al. Sunbed use during adolescence and early adulthood is associated with increased risk of early-onset melanoma. *Int J Cancer*. 2011;128(10):2425–2435.
22. Pagoto SL, Schneider KL, Oleski J, et al. Design and methods for a cluster randomized trial of the sunless study: a skin cancer prevention intervention promoting sunless tanning among beach visitors. *BMC Public Health*. 2009;9:50.
23. Sunless tanning: what you need to know. <http://www.mayoclinic.org/healthy-living/adult-health/in-depth/sunless-tanning/art-20046803?pg=2>. 24 Sep 2013.
24. Nagel JE, Fuscaldo JT, Fireman P. Paraben allergy. *JAMA*. 1977;237(15):1594–1595.
25. Byford JR, Shaw LE, Drew MG, et al. Oestrogenic activity of parabens in MCF7 human breast cancer cells. *J Steroid Biochem Mol Biol*. 2002;80(1):49–60.
26. Golden R, Gandy J, Vollmer G. A review of the endocrine activity of parabens and implications for potential risks to human health. 2005. *Crit Rev Toxicol*. 2005;35(5):435–458.
27. Petersen AB, Wulf HC, Gniadecki R, Gajkowska B. Dihydroxyacetone, the active tanning ingredient in sunless tanning lotions, induces DNA damage, cell-cycle block and apoptosis in cultured HaCaT keratinocytes. *Mutat Res*. 2004;560(2):173–186.
28. Armas LA, Fusaro RM, Sayre RM, et al. Do melanoidins induced by topical 9% dihydroxyacetone sunless tanning spray inhibit vitamin d production? A pilot study. *Photochem Photobiol*. 2009;85(5):1265–1266.
29. Grant WB. Update on evidence that support a role of solar ultraviolet-B irradiance in reducing cancer risk. *Anticancer Agents Med Chem*. 2013;13(1):140–146.
30. Jung K, Seifert M, Herrling Th, Fuchs J. UV-generated free radicals (FR) in skin: their prevention by sunscreens and their induction by self-tanning agents. *Spectrochim Acta A Mol Biomol Spectrosc*. 2008;69(5):1423–1428.
31. Brooks K, Brooks D, Dajani Z, et al. Use of artificial tanning products among young adults. *J Am Acad Dermatol*. 2006;54(6):1060–1066.
32. Faurschou A, Wulf HC. Durability of the sun protection factor provided by dihydroxyacetone. *Photodermatol Photoimmunol Photomed*. 2004;20(5):239–242.
33. Petersen AB, Na R, Wulf HC. Sunless skin tanning with dihydroxyacetone delays broad-spectrum ultraviolet photocarcinogenesis in hairless mice. *Mutat Res*. 2003;542(1–2):129–138.
34. Jung K, Seifert M, Herrling T, Fuchs J. UV-generated free radicals (FR) in skin: their prevention by sunscreens and their induction by self-tanning agents. *Spectrochim Acta A Mol Biomol Spectrosc*. 2008;69:1423–1428.
35. Kristl J, Abramović Z, Sentjurc M. Skin oxygenation after topical application of liposome-entrapped benzyl nicotinate as measured by EPR oximetry *in vivo*: influence of composition and size. *AAPS PharmSci*. 2003;5(1):E2.
36. Agin PP, Wilson DK, Shorter GG, Sayre RM. Tyrosine does not enhance tanning in pigmented hairless mice. *Photochem Photobiol*. 1983;37(5):559–564.
37. Rousseau A. Canthaxanthine deposits in the eye. *J Am Acad Dermatol*. 1983;8(1):123–124.
38. Harnois C, Cortin P, Samson J, et al. Static perimetry in canthaxanthin maculopathy. *Arch Ophthalmol*. 1988;106(1):58–60.
39. Bluhm R, Branch R, Johnston P, Stein R. Aplastic anemia associated with canthaxanthin ingested for “tanning” purposes. *JAMA*. 1990;264(9):1141–1142.
40. Stahl W, Sies H. β -Carotene and other carotenoids in protection from sunlight. *Am J Clin Nutr*. 2012;96(5):1179–1184.
41. Stahl W, Heinrich U, Aust O, et al. Lycopene-rich products and dietary photoprotection. *Photochem Photobiol Sci*. 2006;5(2):238–242.
42. Stahl W, Heinrich U, Wiseman S, et al. Dietary tomato paste protects against ultraviolet light-induced erythema in humans. *J Nutr*. 2001;131(5):1449–1451.
43. Stahl W, Sies H. Carotenoids and protection against solar UV radiation. *Skin Pharmacol Appl Skin Physiol*. 2002;15(5):291–296.
44. Gallicchio L, Boyd K, Matanoski G, et al. Carotenoids and the risk of developing lung cancer: a systematic review. *Am J Clin Nutr*. 2008;88(2):372–383.
45. Fabrikant J, Toulouei K, Brown SM. A review and update on melanocyte stimulating hormone therapy: afamelanotide. *J Drugs Dermatol*. 2013;12(7):775–779.
46. European Medicines Agency. (2014). Scenese recommended for rare disease that causes intolerance to sunlight [Press release]. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/10/news_detail_002195.jsp&mid=WC0b01ac058004d5c1.
47. Kadekaro AL, Chen J, Yang J, et al. Alpha-melanocyte-stimulating hormone suppresses oxidative stress through a p53-mediated signaling pathway in human melanocytes. *Mol Cancer Res*. 2012;10(6):778–786.
48. Song X, Mosby N, Yang J, et al. alpha-MSH activates immediate defense responses to UV-induced oxidative stress in human melanocytes. *Pigment Cell Melanoma Res*. 2009;22(6):809–818.
49. de Torre C, Garcia-Casado Z, Martínez-Escribano JA, et al. Influence of loss of function MC1R variants in genetic susceptibility of familial melanoma in Spain. *Melanoma Res*. 2010;20(4):342–348. ●