Sunscreens and Photoaging: An Update

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UV radiation (UVR) can lead to the development of nonmelanoma skin cancers (NMSCs) and premature skin aging. Sunscreens are safe and effective in protecting against photocarcinogenesis and photoaging. Many types of sunscreens are available, including organic and inorganic products, as well as those containing antioxidants and other additives that may enhance the protective qualities of a sunscreen. Additionally, the new US Food and Drug Administration (FDA) policy on sunscreen labeling and testing ensures that consumers are offered protection against both UVA and UVB radiation. If photodamage does occur, there are many treatments available to improve both the medical and cosmetic consequences of sun damage. Regular and appropriate sunscreen use minimizes the risk for developing skin cancer and slows the process of premature skin aging.

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Photoaging is the result of both the acute and chronic effects of exposure to UV radiation (UVR). Acute inflammatory changes include erythema, edema, and hyperpigmentation. Chronic effects include photoaging, photocarcinogenesis, and immunosuppression. Skin-damaging UV rays fall in the UVA (320–400 nm) or UVB (290–320 nm) spectrums. UVA causes immediate pigment darkening from the redistribution of melanin. UVB causes delayed tanning from an increase in melanocyte number and activity. Exposure to UVR from sunlight is associated with approximately 90% of nonmelanoma skin cancers (NMSCs). Additionally, up to 90% of skin changes attributed to premature aging are caused by UV damage.[1]

UVB is more potent in the induction of NMSC and actinic keratoses (AKs),[2] but both UVA and UVB radiation cause DNA damage. UVB has a direct effect by inducing the formation of cyclobutane pyrimidine dimers. The accumulation of C-to-T mutations results in oncogenesis. UVA generates reactive oxygen species (ROS), resulting in mutagenic oxidative products and carcinogenesis. Excessive exposure to UVR is thought to deplete the skin's natural stores of antioxidants that normally provide protection against ROS.[3] Additionally, repeated UVR exposure can cause mutations in the p53 gene, *TP53*, leading to skin cancer.[4,5] A study by Cui et al[6] showed that when p53 recognized DNA damage it stimulated the production of pro-opiomelanocortin. Pro-opiomelanocortin subsequently induces the production of melanocyte-stimulating hormone, which in turn increases the production of melanin and results in a tan. Tanning is the manifestation of a stress response in the skin and the result of the same DNA damage that leads to the formation of skin cancers.[4] Therefore, DNA damage is the first step for both tanning and photo-oncogenesis.

Clinically, photoaging manifests as wrinkles, roughness, dryness, irregular pigmentation, telangiectasia, sallowness, and brown spots. Actinic elastosis and Favre-Racouchot syndrome are specific phenotypes resulting from chronic sun exposure.[7] Wrinkles and telangiectasia are associated with an increased risk for AKs and NMSCs.[8-10] Risk factors

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for photoaging and skin cancer include fair skin, difficulty tanning, proneness to sunburns, sunburn before 20 years of age, use of tanning beds, and advanced age. Smoking is a moderate independent risk factor for wrinkling, telangiectasia, and squamous cell carcinoma.[11]

Histologically, photoaged skin may show a loss of epidermal polarity, increased keratinocyte atypia, and increased epidermal thickness. Photodamaged skin also has decreased amounts of types I and III collagen, with abnormal accumulation of elastin.[12,13] A study by Fisher et al[14] found that UVR increased the expression of matrix metalloproteinases, which likely contributes to the degradation of type I collagen. They also found that pretreatment with tretinoin inhibited the induction of these matrix metalloproteinases. Matrix metalloproteinase–mediated dermal damage is thought to contribute to wrinkling and may help explain the utility of tretinoin for photorejuvenation.[14]

SUNSCREENS

Sun avoidance is the single most effective method of skin cancer and photoaging prevention. Additional sun protection methods include sun-protective clothing and sunscreens. Sunscreens are an important first step in protecting against photocarcinogenesis and premature aging. Various organic and inorganic UV filters have been identified and developed to protect across the UV spectra, acting via absorption, reflection, and/or diffusion. Specifically, organic, or chemical ingredients, act as sponges to absorb UV rays. Examples of organic sunscreens, which mostly protect against UVB radiation, include *p*-aminobenzoic acid derivatives such as padimate O, avobenzone (Parsol 1789, DSM Nutritional Products Ltd), and oxybenzone. Inorganic, or physical ingredients, such as titanium dioxide and zinc oxide deflect UV rays.

Until recently, most sunscreens were marketed according to their sun protection factor (SPF), which reflects the ratio of doses of UVR that result in erythema with protection to the doses that result in erythema without protection. Because UVB is responsible for inciting erythema, SPF largely does not measure a product's ability to protect against UVA radiation. Organic blockers that only protect against UVA typically are classified as SPF 3. Inorganic blockers provide a greater degree of both UVB and UVA protection but often are not cosmetically acceptable. The advent of micronized particles has improved the cosmetic elegance of many inorganic sunscreens. Many of today's sunscreen products contain a combination of organic and inorganic screens to yield broad-spectrum protection. Some recent concerns about specific sunscreen ingredients will be addressed in this article.

In 2006, a study conducted in Australia found that regular sunscreen use decreased the occurrence of squamous cell carcinoma by 38% and basal cell carcinoma by 25%.[15] A prospective study published in 2010 found that regular sunscreen use reduces the incidence of melanoma by 50% to 73%.[16] Protection from the sun at any age reduces the risk for AKs and squamous cell carcinoma as well as the progression of photoaging.[17-20] Animal studies suggest that sunscreens can repair preexisting sun damage in addition to providing photoprotection.[20] A human study showed that use of sunscreen with an SPF of at least 15 showed improvement of photodamage at 24 weeks compared to baseline.[21] Therefore, regular sunscreen use not only prevents sun damage but also has reparative effects.

It has been known for some time that sunscreens offer excellent protection against UVR, but appropriate usage of sunscreens still falls short.[22] The majority of users do not apply enough product with each application. The recommended dose per application of sunscreen is 2 mg/cm^2. Sun protection factor levels have a direct linear correlation to application densities. Additionally, most users do not apply sunscreen frequently enough. Reapplication is recommended every 2 hours. Fortunately, higher SPFs offer more protection and actually may compensate for the underapplication of sunscreens.[22]

Although sunscreens are considered effective for protection against photocarcinogenesis and photoaging, there is some concern about photostability. It is thought that certain UV filters may lose some of their protective abilities and/or degrade following exposure to UVR. For example, avobenzone, a potent UVA blocker, loses 50% to 60% of its photoprotective properties after 1 hour of sun exposure.[23] Much research has focused on improving the photostability of avobenzone. Methods include eliminating actives that can interact with and degrade avobenzone, such as octinoxate, and adding actives that can act as photostabilizers such as octocrylene or oxybenzone.[24,25]

The addition of antioxidants to sunscreens is another method of enhancing their photoprotective effects. The skin possesses a network of both enzymatic and nonenzymatic host antioxidants to fight ROS. Naturally occurring enzymatic antioxidants include superoxide dismutase, catalase, and glutathione peroxidase. Examples of nonenzymatic antioxidants include ascorbic acid, tocopherols, glutathione, and ubiquinone. Although naturally occurring antioxidants offer protection against free radicals, they are not able to neutralize the abundance of free radicals produced by UVR and other environmental stressors. Adding antioxidants to sunscreens helps overcome this deficit. Antioxidants are able to neutralize free radicals by donating an electron. They

also may provide reparative effects when the sunscreen's defense capability is overwhelmed.[26]

Advances in technology and the development of more sophisticated sunscreens have led to several unsubstantiated concerns about the safety of certain sunscreens. Oxybenzone is a synthetic estrogen that has been used in sunscreens as a physical blocker since the 1980s. A 2001 rodent study showed systemic absorption and hormonal effects when applied in astronomical doses.[27] There is no evidence that oxybenzone has any adverse effects in humans, where it is excreted and not accumulated. Another unsupported concern is that retinyl palmitate actually leads to the generation of free radicals. Retinyl palmitate, a form of vitamin A, is another common sunscreen ingredient. Unpublished studies in rodents suggested that retinyl palmitate generates free radicals on exposure to UVR. Naturally occurring antioxidants can neutralize free radicals and there is no scientific evidence that retinyl palmitate causes cancer in humans.[28]

Concerns regarding nanoparticles and the risk for their absorption span beyond sunscreens. Micronizing the size of sunscreen particles, specifically zinc oxide and titanium dioxide, can maximize protection with a more appealing cosmetic appearance. It has been demonstrated that nanoparticles do not penetrate the skin and do not harm living tissue. A review conducted by the Australian government concluded that nanosized zinc oxide and titanium dioxide particles remain on the skin's surface without penetrating the stratum corneum.[29] Similar results have been found with confocal microscopy.[30] Despite this consensus, the issue of nanoparticles remains somewhat controversial. An animal study showed that nanoparticles can actually penetrate the skin and enter other organs, namely the liver, and cause damage when applied in extremely high quantities for long periods of time.[31]

NEW US FOOD AND DRUG ADMINISTRATION POLICY

In an ongoing effort to keep up with emerging scientific data, the US Food and Drug Administration (FDA) recently updated its policy on sunscreen development and marketing.[32] In 2011, the FDA joined the rest of the medical and scientific community in its public recognition of sunscreen's ability to prevent skin cancer and premature aging. A final rule was issued on how sunscreens must be tested and labeled, which came as an update to the 2007 proposed rule. All sunscreens, including cosmetics and moisturizers with SPF claims, must undergo and pass an established broad-spectrum test to be labeled as such. The broad-spectrum label indicates that a product provides UVA protection that is proportional to its UVB protection. The final rule also eliminated the proposed 2007 star system that graded a product's UVA protection on a scale of 1 to 4 stars.[32]

The purpose of the broad-spectrum test is to assure consumers that they are being protected from both UVA and UVB, not just UVB as indicated by the SPF.[32] Only products with a broad-spectrum SPF of 15 or higher are considered by the FDA to reduce the risk for skin cancer and premature skin aging. The higher the SPF (up to 50), the greater the protection from UVR afforded. Non–broad-spectrum sunscreens and those with an SPF of less than 15 can only claim protection from sunburn. Labeling provisions will require these products to include a warning that alerts consumers to these limitations.[32]

This final rule also eliminates the use of terms such as *waterproof*, *sweat proof*, and *sunblock*, as these terms overstate a product's effectiveness.[32] No sunscreen is waterproof because all sunscreens will eventually wash off. Sunscreens cannot claim to provide protection for more than 2 hours without reapplication and they cannot claim to provide immediate protection. Finally, products labeled *water resistant* must specify effectiveness for either 40 or 80 minutes while swimming or sweating, which is based on standard testing.[32]

In addition to the final rule for sunscreen testing and labeling, the FDA issued a proposed rule that would limit the maximum SPF value labeled on sunscreen to 50+ because there are not sufficient data to support that the use of higher SPF products affords greater sun protection. The FDA also reaffirmed that there are no safety issues with any of the active ingredients in sunscreens and concluded that nanoscale titanium dioxide and zinc oxide are safe and do not penetrate the skin.[33] The FDA is requesting data and information on different dosage forms of sunscreens. For sunscreen spray products, the agency requests additional data to establish effectiveness and to determine if they present a safety concern if unintentionally inhaled.[34]

TREATMENT OF PHOTOAGING

Treatment of photoaging is 2-fold; it must address both the medical concerns caused by photocarcinogenesis as well as the cosmetic concerns associated with photoaging. Many treatments address both effectively. Patients must be educated on the benefits and limitations of a treatment method to ensure realistic expectations. Various treatments have either localized or global effects. Topical therapies with global effects include sunscreen; retinols; antioxidants; microdermabrasion; and α-hydroxy acids, which are used as both cosmeceuticals and chemical peels. Photodynamic therapy (PDT) targets both the cosmetic and medical consequences of photoaging. Localized treatments include Q-switched lasers for lentigines; pulsed dye lasers for telangiectasia;

botulinum toxin for dynamic rhytides; and fillers for nondynamic wrinkles, folds, and volume loss.

Topical retinoids are considered by many to be first line in the field treatment of photoaging. Several studies have shown that retinoids improve fine wrinkling, mottled hyperpigmentation, and roughness.[35-37] In low concentrations, α- and β-hydroxy acids act as exfoliants but are used as peels in higher concentrations. The keratolytic and irritant effects of α- and β-hydroxy acids depend on the acid and concentration; they have been shown to improve pigmentation and roughness in photoaged skin but have little effect on AKs and wrinkles.[38,39] Microdermabrasion exfoliates and ablates the superficial epidermis and also activates a dermal wound-healing cascade, resulting in the production of type I procollagen messenger RNA.[40]

Photodynamic therapy is another field approach for the treatment of photodamage. Aminolevulinic acid combined with a light source has a comparable efficacy to topical therapies, such as 5-fluorouracil, in the treatment of actinic damage, while also providing photorejuvenation benefits. A recent study demonstrated global improvement of photodamage in 69% (33/48) of patients treated with methyl aminolevulinate plus red light. Improvement was noted in fine and coarse lines, mottled pigmentation, tactile roughness, sallowness, erythema, and sebaceous hyperplasia.[41] This dual benefit is not without its limitations. First, patients must be aware that not all AKs will respond to treatment; second, lentigines and seborrheic keratoses cannot be treated with PDT. Additionally, PDT may bring subclinical lesions to the surface,[42] and perhaps most importantly, patients should understand that the side effects of PDT, which include erythema and sun sensitivity, can result in substantial downtime.

Various lasers also can provide global cosmetic improvements. Lasers provide options for the destruction of pigmented and vascular lesions as well as dermal remodeling.[43] The 10,600-nm ablative fractional resurfacing laser, the 1550-nm nonablative erbium laser (Figure 1), and the 1927-nm thulium laser increase dermal collagen production and therefore are alternative options for photorejuvenation. Nonablative lasers are less effective than ablative therapies but result in less downtime. The thulium laser has the potential to effectively treat AKs, similar to other field treatments such as topical 5-fluorouracil or PDT (Figure 2). When compared to these other treatment modalities, the thulium laser has the advantages of relatively less downtime and concurrent aesthetic benefits, which may be beneficial to the patient.[44] Laser therapies may be an expensive option, however, for patients looking to treat only AKs, as the alternative options generally are covered by insurance. Cryosurgery and electrosurgery are less expensive than lasers and can lighten limited numbers of discrete pigmented lesions, such as seborrheic keratoses, as well as treat AKs.[45]

Current research is focused on the combination of various treatments for optimized results. For example, a prospective split-face study by Dover et al[46] demonstrated that the effects of treatment with 5-aminolevulinic acid followed by intense pulsed light were superior to intense pulsed light alone. Results of combination nonablative therapies are superior to a nonablative laser alone.[47-52] Additionally, combining topical therapies with lasers results in greater improvements in photoaging. A review by Tierney and Hanke[53] outlined the studies that have shown the benefits of these combination therapies.

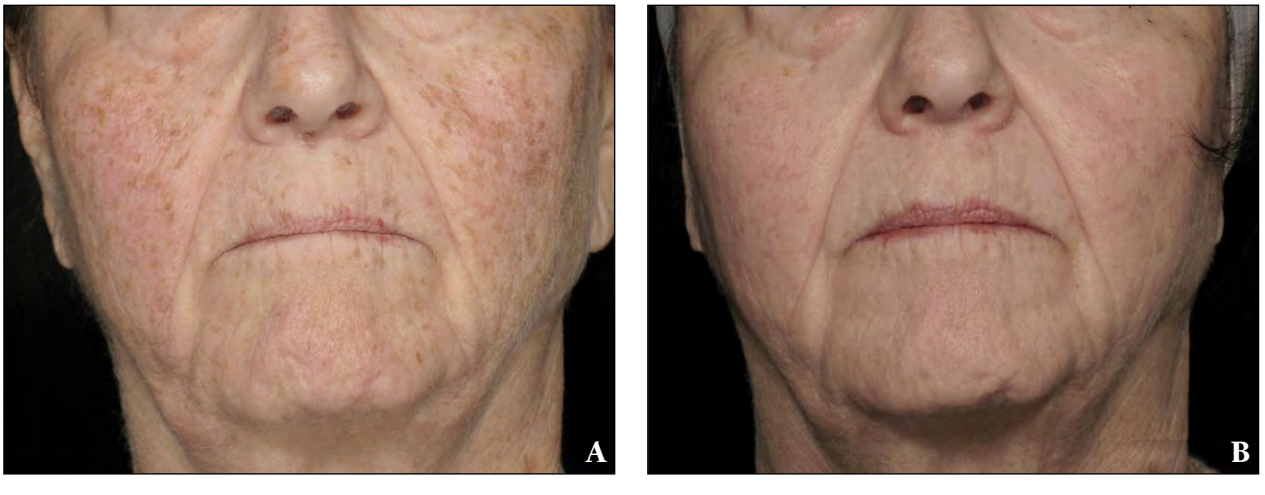

Figure 1. A patient before (A) and after treatment of photoaging, including fine lines and dyspigmentation, with a 1550-nm nonablative erbium laser (B).

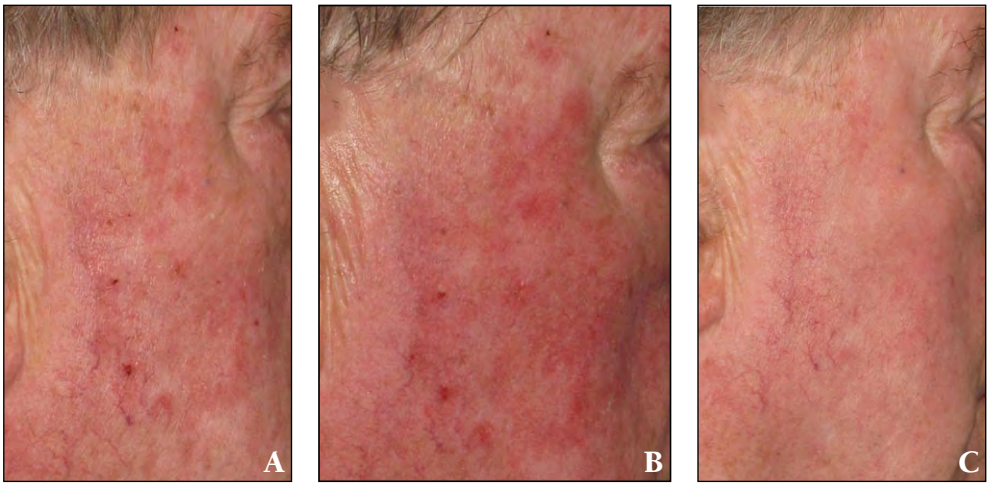

Figure 2. A patient before treatment (A), immediately posttreatment (B), and 4 months following treatment of actinic keratoses and photoaging using a 1927-nm thulium nonablative fractional resurfacing laser (C).

CONCLUSION

Photoprotection is a primary means of preventing skin cancer and premature skin aging. Sunscreens are safe and effective in reducing development of future skin cancers and in preventing photoaging. Products with added antioxidants may further mitigate UV damage. The FDA supports regular sunscreen use and continually regulates product testing and marketing to improve both consumer knowledge and photoprotective benefits. If photodamage occurs, many treatments exist to improve both the medical and cosmetic effects of UVR. Preventing further damage with regular sunscreen use is key to diminishing the chance of developing future skin cancers as well as to slow the process of premature skin aging.

REFERENCES

1. Gilchrest BA. *Skin and Aging Processes.* Boca Raton, FL: CRC Press, Inc; 1984.
2. Kligman LH, Akin FJ, Kligman AM. The contributions of UVA and UVB to connective tissue damage in hairless mice. *J Invest Dermatol.* 1985;84:272-276.
3. Fuchs J, Kern H. Modulation of UV-light-induced skin inflammation by D-alpha-tocopherol and L-ascorbic acid: a clinical study using solar simulated radiation. *Free Radic Biol Med.* 1998;25:1006-1012.
4. Lim HW, James WD, Rigel DS, et al. Adverse effects of ultraviolet radiation from the use of indoor tanning equipment: time to ban the tan. *J Am Acad Dermatol.* 2011;64:893-902.
5. Bukhari MH, Niazi S, Khaleel ME, et al. Elevated frequency of p53 genetic mutations and AgNOR values in squamous cell carcinoma [published online ahead of print August 18, 2008]. *J Cutan Pathol.* 2009;36:220-228.
6. Cui R, Widlund HR, Feige E, et al. Central role of p53 in the suntan response and pathologic hyperpigmentation. *Cell.* 2007;128:853-864.
7. Lewis KG, Bercovitch L, Dill SW, et al. Acquired disorders of elastic tissue: part I. increased elastic tissue and solar elastotic syndromes. *J Am Acad Dermatol.* 2004;51:1-21; quiz 22-24.
8. Holman CD, Armstrong BK, Evans PR, et al. Relationship of solar keratosis and history of skin cancer to objective measures of actinic skin damage. *Br J Dermatol.* 1984;110:129-138.
9. Memon AA, Tomenson JA, Bothwell J, et al. Prevalence of solar damage and actinic keratosis in a Merseyside population. *Br J Dermatol.* 2000;142:1154-1159.
10. Brooke RC, Newbold SA, Telfer NR, et al. Discordance between facial wrinkling and the presence of basal cell carcinoma. *Arch Dermatol.* 2001;137:751-754.
11. Kennedy C, Bajdik CD, Willemze R, et al; Leiden Skin Cancer Study. The influence of painful sunburns and lifetime sun exposure on the risk of actinic keratoses, seborrheic warts, melanocytic nevi, atypical nevi, and skin cancer. *J Invest Dermatol.* 2003;120:1087-1093.
12. Lavker RM, Zheng PS, Dong G. Morphology of aged skin. *Clin Geriatr Med.* 1989;5:53-67.
13. El-Domyati M, Attia S, Saleh F, et al. Intrinsic aging vs. photoaging: a comparative histopathological, immunohistochemical, and ultrastructural study of skin. *Exp Dermatol.* 2002;11:398-405.
14. Fisher GJ, Wang ZQ, Datta SC, et al. Pathophysiology of premature skin aging induced by ultraviolet light. *N Engl J Med.* 1997;337:1419-1428.
15. van der Pols JC, Williams GM, Pandeya N, et al. Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use [published online ahead of print November 28, 2006]. *Cancer Epidemiol Biomarkers Prev.* 2006;15:2546-2548.
16. Green AC, Williams GM, Logan V, et al. Reduced melanoma after regular sunscreen use: randomized trial follow-up [published online ahead of print December 6, 2010]. *J Clin Oncol.* 2011;29:257-263.
17. Darlington S, Williams G, Neale R, et al. A randomized controlled trial to assess sunscreen application and beta carotene supplementation in the prevention of solar keratoses. *Arch Dermatol.* 2003;139:451-455.
18. Kligman LH, Akin FJ, Kligman AM. Prevention of ultraviolet damage to the dermis of hairless mice by sunscreens. *J Invest Dermatol.* 1982;78:181-189.
19. Boyd AS, Naylor M, Cameron GS, et al. The effects of chronic sunscreen use on the histologic changes of dermatoheliosis. *J Am Acad Dermatol.* 1995;33:941-946.

20. Kligman LH, Akin FJ, Kligman AM. Sunscreens promote repair of ultraviolet radiation-induced dermal damage. *J Invest Dermatol.* 1983;81:98-102.
21. Phillips TJ, Gottlieb AB, Leyden JJ, et al; Tazarotene Cream Photodamage Clinical Study Group. Efficacy of 0.1% tazarotene cream for the treatment of photodamage: a 12-month multicenter, randomized trial. *Arch Dermatol.* 2002;138:1486-1493.
22. Ouyang H, Stanfield J, Cole C, et al. The relevance of high SPF products: high SPF sunscreens help compensate for under-application. Poster presented at: American Academy of Dermatology 69th Annual Meeting; February 4-8, 2011; New Orleans, LA.
23. Bouillon C. Recent advances in sun protection. *J Dermatol Sci.* 2000;23(suppl 1):S57-S61.
24. Sayre RM, Dowdy JC. Darkness at noon: sunscreens and vitamin D3. *Photochem Photobiol.* 2007;83:459-463.
25. Chatelain E, Gabard B. Photostabilization of butyl methoxydibenzoylmethane (avobenzone) and ethylhexyl methoxycinnamate by bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S), a new UV broadband filter. *Photochem Photobiol.* 2001;74:401-406.
26. Samuels L. The truth about sunscreen and effective patient education. *Practical Dermatol.* March 2011:27-32.
27. Schlumpf M, Cotton B, Conscience M, et al. In vitro and in vivo estrogenicity of UV screens. *Environ Health Perspect.* 2001; 109:239-244.
28. Morison WL, Wang SQ. Sunscreens: safe and effective? Skin Cancer Foundation Web site. http://www.skincancer.org/prevention/sun-protection/sunscreen/sunscreens-safe-and-effective. Accessed April 11, 2012.
29. Australian Government Department of Health and Ageing Therapeutic Goods Administration. A review of the scientific literature on the safety of nanoparticulate titanium dioxide or zinc oxide in sunscreens. http://www.tga.gov.au/pdf/review-sunscreens-060220.pdf. Published July 2009. Accessed July 28, 2011.
30. Stamatas GN, Mack MC, Horowitz P. Micronized sunscreen particles were not shown to penetrate beyond the stratum corneum on human skin in vivo. Poster presented at: American Academy of Dermatology 69th Annual Meeting; February 4-8, 2011; New Orleans, LA.
31. Wu J, Lui W, Xue C, et al. Toxicity and penetration of TiO2 nanoparticles in hairless mice and porcine skin after subchronic dermal exposure [published online ahead of print June 6, 2009]. *Toxicol Lett.* 2009;191:1-8.
32. Labeling and effectiveness testing; sunscreen drug products for over-the-counter human use. *Fed Regist.* 2011;76(117):35620-35665. To be codified at 21 CFR §201 and 310.
33. Revised effectiveness determination; sunscreen drug products for over-the-counter human use. *Fed Regist.* 2011;76(117):35672. To be codified at 21 CFR §201.
34. Sunscreen drug products for over-the-counter human use; request for data and information regarding dosage forms. *Fed Regist.* 2011;76(117):35669-35672. To be codified at 21 CFR §352.
35. Weiss JS, Ellis CN, Headington JT, et al. Topical tretinoin in the treatment of aging skin. *J Am Acad Dermatol.* 1988;19(1 pt 2): 169-175.
36. Griffiths CE, Russman AN, Majmudar G, et al. Restoration of collagen formation in photodamaged human skin by tretinoin (retinoic acid). *N Engl J Med.* 1993;329:530-535.
37. Kang S, Leyden JJ, Lowe NJ, et al. Tazarotene cream for the treatment of facial photodamage: a multicenter, investigator-masked, randomized, vehicle-controlled, parallel comparison of 0.01%, 0.025%, 0.05%, and 0.1% tazarotene creams and 0.05% tretinoin emollient cream applied once daily for 24 weeks. *Arch Dermatol.* 2001;137:1597-1604.
38. Stiller MJ, Bartolone J, Stern R, et al. Topical 8% glycolic acid and 8% L-lactic acid creams for the treatment of photodamaged skin. a double-blind vehicle controlled trial. *Arch Dermatol.* 1996;132:631-636.
39. Thibault PK, Wlodarczyk J, Wenck A. A double-blind randomized clinical trial on the effectiveness of a daily glycolic acid 5% formulation in the treatment of photoaging. *Dermatol Surg.* 1998;24: 573-577; discussion 577-578.
40. Karimipour DJ, Kang S, Johnson TM, et al. Microdermabrasion: a molecular analysis following a single treatment. *J Am Acad Dermatol.* 2005;52:215-223.
41. Sanclemente G, Medina L, Villa JF, et al. A prospective split-face double-blind randomized placebo-controlled trial to assess the efficacy of methyl aminolevulinate + red-light in patients with facial photodamage. *J Eur Acad Dermatol Venereol.* 2011;25:49-58.
42. Karen JK, Hale EK. Rapid progression of a basal cell carcinoma after photodynamic therapy [published online ahead of print June 24, 2010]. *Dermatol Surg.* 2010;36:1328-1331.
43. Tanzi EL, Lupton JR, Alster TS. Lasers in dermatology: four decades of progress. *J Am Acad Dermatol.* 2003;49:1-31; quiz 31-34.
44. Kaufman J, Hale EK. Thulium-based beauty. *Dermatology Times.* October 1, 2010. http://www.highbeam.com/doc/1P3-2188542301.html. Accessed April 17, 2012.
45. Stern RS, Dover JS, Levin JA, et al. Laser therapy versus cryotherapy of lentigines: a comparative trial. *J Am Acad Dermatol.* 1994;30:985-987.
46. Dover JS, Bhatia AC, Stewart B, et al. Topical 5-aminolevulinic acid combined with intense pulsed light in the treatment of photoaging. *Arch Dermatol.* 2005;141:1247-1252.
47. Sadick NS, Alexiades-Armenakas M, Bitter P Jr, et al. Enhanced full-face skin rejuvenation using synchronous intense pulsed optical and conducted bipolar radiofrequency energy (ELOS): introducing selective radiophotothermolysis. *J Drugs Dermatol.* 2005;4:181-186.
48. Berlin AL, Hussain M, Phelps R, et al. Treatment of photoaging with a very superficial Er:YAG laser in combination with a broadband light source. *J Drugs Dermatol.* 2007;6:1114-1118.
49. Lee MW. Combination 532-nm and 1,064-nm lasers for noninvasive skin rejuvenation and toning. *Arch Dermatol.* 2003;139: 1265-1276.
50. Tan MH, Dover JS, Hsu TS, et al. Clinical evaluation of enhanced nonablative skin rejuvenation using a combination of a 532 and a 1,064 nm laser. *Lasers Surg Med.* 2004;34:439-445.
51. Hantash BM, De Coninck E, Liu H, et al. Split-face comparison of the erbium micropeel with intense pulsed light [published online ahead of print March 3, 2008]. *Dermatol Surg.* 2008;34:763-772.
52. Jørgensen GF, Hedelund L, Haedersdal M. Long-pulsed dye laser versus intense pulsed light for photodamaged skin: a randomized split-face trial with blinded response evaluation. *Lasers Surg Med.* 2008;40:293-299.
53. Tierney EP, Hanke CW. Recent advances in combination treatments for photoaging: review of the literature. *Dermatol Surg.* 2010;36:829-840.