Photodamage, Part 1: Pathophysiology, Clinical Manifestations, and Photoprotection

Sonal Choudhary, MD; Jennifer Carol Tang, BS; Angel Leiva; Keyvan Nouri, MD

Photodamage is defined as changes in the skin that occur after prolonged exposure to solar irradiation. Photoaging is one of the results seen with photodamage, which is an alteration in the skin caused by sun exposure resembling the effects of age. Skin cancers are at the other end of the spectrum of photodamage. UV radiation (UVR) is the common entity that contributes to both. The derangements in the epidermis and dermis mainly are attributable to collagen degradation and remodeling. These biologic processes translate to the clinical manifestations of photodamage, including wrinkles, decreased skin elasticity, hyperpigmentation, telangiectasias, actinic keratoses (AKs), and neoplasms. Sunscreens and antioxidants are photoprotective agents that aim to minimize the effects of UVR. The therapeutic modalities for the management of photodamage include topical agents, mechanical exfoliation, and laser therapies. Topical remedies such as retinoids, α-hydroxy acids, and antioxidants commonly are used today. There is a wide gamut of laser and light devices, such as ablative lasers, nonablative lasers, fractional lasers, and radiofrequency ablation. In this review article, we discuss the different aspects of photodamage with a focus on photoaging, the possible mechanisms, and the available modalities of prevention and management.

Photodamage refers to the changes in the skin that occur after prolonged exposure to UV irradiation. Photoaging refers to alterations in the skin that resemble the effects of age caused by sun exposure. Aging is a constant and inevitable process, wherein intrinsic aging and photoaging are 2 independent clinically and biologically distinct processes that simultaneously affect the skin. Intrinsic aging is composed of slow, irreversible tissue degeneration while photoaging (extrinsic aging) is a result of exposure to outdoor agents, mainly UV irradiation. The effects of UV radiation (UVR) on skin are profound and are estimated to account for up to 90% of visible skin aging.[1,2] It has been studied and demonstrated that UV irradiation inhibits the synthesis of collagen and induces collagen degradation.[3,4]

Not only can excessive solar exposure accelerate and intensify skin aging, it also can lead to serious health risks such as cutaneous neoplasms. UV radiation is a

Drs. Choudhary and Nouri, Ms. Tang, and Mr. Leiva are from the Department of Dermatology and Cutaneous Surgery, University of Miami, Miller School of Medicine, Florida.

The authors report no conflict of interest in relation to this article.

Correspondence: Sonal Choudhary, MD, Department of Dermatology and Cutaneous Surgery, University of Miami, Miller School of Medicine, 1475 NW 12th Ave, Miami, FL 33136 (drsonalchoudhary@gmail.com).

complete carcinogen, as it not only initiates cancer through DNA mutation but also promotes cancer growth through the inflammatory processes inherent in cumulative UV exposure.[1,5] It is estimated that 90% of all skin cancers are directly related to sun exposure.[6] About 90% of skin cancers are diagnosed at 45 years of age or later.[7] Marked increases in all skin cancer rates have been observed in the past 2 decades, which coincides with the arrival of the "baby boomer" generation into middle age. Baby boomers are a generation produced by a post–World War II surge in the US birthrate between 1945 and 1965 and constitute a cohort of the American population that is believed to have fueled the development of commercial products that could reverse the signs of intrinsic skin aging. This can be attributed to the baby boomers' inclination to preserve their youthfulness and attitude of denial toward aging and death.[8]

But the sun-seeking behaviors of these baby boomers have been implicated in a surge in skin cancer rates.[9] The incidence of melanoma has doubled since 1985, and the incidence of nonmelanoma skin cancers such as basal cell carcinoma and squamous cell carcinoma has shown increases as high as 66% and 93%, respectively.[7,10] However, only 6% of dermatologic visits concern skin cancer.[11] Therefore, in addition to the cosmetic benefits, decreasing and managing the more serious aspects of aging skin require attention. In addition to photoaging and skin cancers, UVR possesses immunosuppressive effects.[12] The close association of photodamage and UVR indicates necessary sun protection.

PATHOPHYSIOLOGY

Photodamage derives from the derangements induced by UVR. The onslaught of biochemical reactions and photon-induced damage that occur in the epidermis and dermis translate to the visible manifestations of wrinkles and pigmentary abnormalities. The main facet of wrinkle formation is damage to and remodeling of the extracellular matrix caused by matrix metalloproteinases (MMPs) and other proteases. Matrix metalloproteinases are naturally existing molecules whose function is to remodel the extracellular matrix during times of skin development and wound healing.[13] Matrix metalloproteinases have affinities toward specific components of the dermis and epidermis. The constituents of the dermis include type I and III collagen, elastins, proteoglycans, and fibronectins. Collagen fibers contribute to most of the strength and elasticity of the skin.[14] Matrix metalloproteinases-9 preferentially degrades elastin and fibrillin while MMP-2 degrades collagen type III and components of the dermal-epidermal junction.[15,16] In addition, there are various proteolytic enzymes such as gelatinases and stromelysins that further degrade collagen after cleavage by collagenase.[16,17] Collagenase messenger RNA expression is up-regulated throughout the epidermis and dermis when exposed to UVR.[3] UVR also is able to increase MMP expression indirectly by activation of transcription factor activator protein 1, which increases transcription of MMP genes.[18,19] Coincidentally, activator protein 1 also stimulates the production of tissue inhibitor of MMP-1.[3] A substantial portion of MMPs are synthesized in the epidermis

---

TABLE 1

Physiologic Derangements in Photodamage

- Altered composition of dermal ECM with disorganized collagen fibers and imperfect repair, leading to wrinkle formation, decreased skin elasticity, greater skin fragility, and reduced wound healing

- Accumulation of dystrophic elastic fibers in dermis after alteration by MMPs and other proteases, leading to solar elastosis[22]

- Diminished number of collagen fibers in papillary dermis

- Reduced expression of fibrillin, an important component of oxytalan (connects superficial dermal elastic fibers to those in the deeper dermal layers)[23]

- Decreased type VII collagen, which weakens the connection between the lamina densa and papillary dermis[24]

Abbreviations: ECM, extracellular matrix; MMP, matrix metalloproteinase.

TABLE 2

Additional Components Involved in Photodamage

Factors Affecting Photodamage	Role	Mechanism or Action
TGF-β	Regulates cell differentiation, growth, and repair	UVR down-regulates number of TGF-β type II receptors[27]
	Aids the induction of procollagen and fibronectin synthesis in the dermis[26]	Repression of TGF-β binding to its receptor is seen in ~90% of photoaged skin[27]
ROS	Causes connective tissue degradation[28-30]	UVR generates ROS in the dermis and epidermis[32]
	Inactivates naturally occurring tissue inhibitors of metalloproteinases[31]	UVB radiation is most damaging to the epidermis[33,34]
		UVA radiation penetrates to the dermis, causing more oxidative stress[33,34]
		UVR depletes antioxidants[35]
		ROS create mutations in mtDNA, disrupt the function of the mitochondria, and induce MMPs[36-39]
		mtDNA mutations can persist for >1.5 years after generation and can be used as an extended marker of UVR[40]
Neutrophils and mononuclear cells	Causes inflammatory response due to release of ROS, cytokines, and MMPs[41]	Recruited into the epidermis and dermis in response to the damage caused by UVR[42]
	Potentially activates certain proteases, such as MMP-1 and MMP-9[42]	UVR-activated nuclear factor κB drives neutrophil attraction[43]
Estrogen	May be involved in the maintenance of the extracellular matrix through the increased production of hyaluronic acid and collagen[44,45]	
Smoking		Leads to altered wound healing and cancer advancement[46]
		Smokers have 4.7 times more risk for developing facial wrinkles compared with nonsmokers[47]
		Smoke extract is able to increase MMP expression in fibroblasts[48]

Abbreviations: TGF-β, transforming growth factor β; UVR, UV radiation; ROS, reactive oxygen species; mtDNA, mitochondrial DNA; MMP, matrix metalloproteinase.

and then migrate further down toward the dermis.[3] There is an observation of a temporal pattern of the level of MMP expression, such that it seems to be maximal after multiple UVR exposures.[3] A hypothesis regarding MMP-induced collagen fragments states that photodamage can lead to the further suppression of collagen synthesis by fibroblasts.[20,21] It has been suggested that the presence of damaged collagen may act in some way to down-regulate collagen synthesis by cells that are inherently capable of making collagen[20,21] (Tables 1 and 2).

CLINICAL MANIFESTATIONS

Photodamage from UVR leads to physical manifestations that cause much distress to patients. Photoaging, which is photodamage superimposed on natural aging, has characteristic, sharp features that present in the younger population. Contrastingly, intrinsic aging has qualities that are more subtle and present in older individuals. In intrinsic aging, the skin becomes dry and pale. In addition, there are fine wrinkles with dermal atrophy. However, these changes are in the context of otherwise smooth and unblemished skin.[49] Photodamage manifests as rough skin, mottled hyperpigmentation, and decreased elasticity and recoil.[50,51] The skin becomes more lax, atrophic, and susceptible to bruising.[52] In addition, the skin may contain telangiectasias (mainly on the nose and cheeks), AKs, purpura, fibrotic depigmented areas, lentigines, and eventually premalignant and malignant neoplasms.[53,54] The skin also may have an overall leathery appearance.[55] Irregular pigmentation due to hyperplasia of melanocytes is a hallmark of photodamage.[56] Solar elastosis, which is yellowing and coarsening of the skin, also becomes evident in fair skin, especially in the temporal region.[56] In darker-skinned patients, the effects of photodamage usually are less severe and present at a later age.[56] Melasma is a common pigmentary disorder associated with sun exposure and is characterized by well-defined lesions of hyperpigmentation.[56] Although melasma is related to sun exposure, it also is commonly seen in the young population, who may or may not be greatly sun exposed.

The wrinkles of photodamage are coarse and usually on the forehead and periorbital and perioral areas.[56] These wrinkles also are particular because they do not efface when the skin is stretched, while effacement is seen in fine wrinkles.[56] Other lesions associated with chronic sun exposure are seborrheic keratoses, spider nevi, superficial varicose veins, and acne rosacea.[52]

Clinically, the effects of photodamage can be classified into 2 distinct types: Milian's citrine skin type and atrophic, telangiectatic phenotype.[57] The Milian's citrine skin type is described as deep wrinkles, decreased tautness, leathery skin, blister eruption, decreased wound healing, and cutis rhomboidalis nuchae on the back of the neck. The atrophic phenotype contains telangiectasias and has relatively less wrinkle formation.[57]

PHOTOPROTECTION
Sunscreen Applications and Covariables

Sunscreens provide protection against UVR and are measured in sun protection factor (SPF). The SPF refers to the total amount of UVR required to create 1 minimal erythema dose on protected skin consisting of a 2-mg/cm^2 area divided by the total amount of UVR required to create 1 minimal erythema dose on unprotected skin. The application of SPF 30 with a 2-mg/cm^2 thickness film distributed evenly over the body allows maximum protection against the harmful effects of UVB (290–320 nm) and UVA (320–340 nm) radiation.[58] Daily outdoor occupations and lifestyles may lead to excessive exposure to UVR. Clinicians recommend photoprotection through the use of sunscreens and sun avoidance. Reducing the amount of UVR absorbed by the skin decreases the likelihood of obtaining AKs, solar elastosis, and squamous cell carcinoma.[59,60] Sun protection factor 15 provides excellent protection against UVB radiation by application on the skin every 40 to 80 minutes, but it does not provide the same results against UVA radiation.

Sunscreen should be applied 15 to 30 minutes before sun exposure to obtain maximum effect, and it should cover the back of the neck, the ears, and hairless regions of the scalp. Greater protection against the sun and longer exposure times can be maintained with higher SPF products, though they must not solely be relied on. Enhanced cosmetic appearance can be achieved by applying sunscreen with a high SPF in combination with topical agents such as lipstick and makeup that also contain a sunscreen. Clothing also can protect against the sun and further prevent photodamage. In general, fabric must be tightly woven to decrease sunlight penetration. Also, a hat with a 4-inch circumference is enough to cover the entire face and neck.[61,62]

From physiologic and pathologic points of view, the effects of visible light are different from the effects of UVR. The sensitivity of visible light on the skin can lead to diseases such as porphyria, solar urticaria, polymorphous light eruption, and other idiopathic photodermatoses. A study suggests that visible light exposure may increase pigmentation in people with

Fitzpatrick skin types IV to VI.[63] Darker-skinned patients with postinflammatory hyperpigmentation and melasma must use a protecting agent against visible light. Inorganic sunscreen agents (iron oxide, titanium dioxide, zinc oxide) are less susceptible to sensitivity and have better light-blocking effects than organic sunscreen agents.[63,64]

Although sunscreens are the "gold standard" for UVR protection and consist of chemicals that prevent erythema, reliable skin protection is never attained. Controlled studies[65,66] testing the efficacy of sunscreen have shown that the total surface area to which it is applied actually is less than 0.5 mg/cm^2. The application of sunscreen still causes negative biologic effects in DNA damage, as noticed in thymine dimer formation and 8-hydroxy-2-deoxyguanosine formation. Also, suberythemal levels of irradiation cause the p53 gene induction and UV immunosuppression.[67] The ingredients found in sunscreen contain free radicals that, when activated by UVR, are absorbed by the skin, hence they can cause harm.[68] Antioxidants naturally protect the skin from polluting chemicals and UVR.[69] Both enzymatic and nonenzymatic antioxidative interactions act in conjunction to protect both the intracellular and extracellular tissues within the skin. Nonenzymatic antioxidants include liquid-phase L-ascorbic acid, glutathione (GSH) in the cellular compartment, vitamin E in membranes, and ubiquinol in mitochondria. Based on molarity, L-ascorbic acid is a predominant antioxidant in the skin. The acidic concentration is 15-fold greater than that of GSH, 200-fold greater than vitamin E, and 1000-fold greater than ubiquinol and ubiquinone.[70] Notably, people with AKs or basal cell carcinoma have lower plasma levels of L-ascorbic acid, α-tocopherol, and GSH.[71] The application of topical antioxidants to protect the skin against oxidative stress is necessary when the skin is exposed to sunlight. Direct application is the preferred method versus oral and diet supplementations for targeting specific areas of the skin that are deficient in antioxidants.

Antioxidants that are naturally used by the body are considered great for topical use. These include vitamin C, vitamin E, ubiquinol, and GSH.

Plants also synthesize several antioxidants (eg, vitamins C and E, flavonoids) to avoid excessive oxidative damage. Topical flavonoids, such as the silybin extract of silymarin, have potent photoprotective properties capable of preventing photodamage to the skin. Studies have shown that silymarin promotes antioxidant reactions, which cause tumor inhibition. Although the mechanisms of action are unknown, studies have demonstrated considerable efficacy.[72,73]

SPF Scale Ratings
The US Food and Drug Administration has implemented new SPF safety ratings (ie, low, medium, high, highest UV protection). This system is based on results obtained from both in vitro and in vivo UVA testing. Two tests determine the protection grade of SPF: the first measures the resistance to UVA radiation, and the second measures the overall ratio of tanned to healthy skin.[60]

This is the first in a 2-part series on photodamage. Part 2 will appear in a future issue of Cosmetic Dermatology®.

REFERENCES
1. Martini FH. *Fundamentals of Anatomy and Physiology*. 7th ed. San Francisco, CA: Benjamin Cummings; 2004.
2. Südel KM, Venzke K, Mielke H, et al. Novel aspects of intrinsic and extrinsic aging of human skin: beneficial effects of soy extract. *Photochem Photobiol*. 2005;81:581-587.
3. 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.
4. Fisher GJ, Datta S, Wang ZQ, et al. c-Jun-dependent inhibition of cutaneous procollagen transcription following ultraviolet irradiation is reversed by all-*trans* retinoic acid. *J Clin Invest*. 2000;106:663-670.
5. Green BG, Bluth J. Measuring the chemosensory irritability of human skin. *J Toxicol Cutan Ocul Toxicol*. 1995;14:23-48.
6. Gallagher RP. Sunscreens in melanoma and skin cancer prevention. *CMAJ*. 2005;173:244-245.
7. Surveillance Epidemiology and End Results. *Program Public Use Data, Cancer Surveillance Research Program (1973-98)*. Bethesda, MD: Cancer Statistics Branch, National Cancer Institute; 2001.
8. Fitzpatrick RE, Rostan EF. Double blind, half-face study comparing topical vitamin C and rejuvenation for photodamage. *Dermatol Surg*. 2002;28:231-236.
9. Edlich RJ, Cox MD, Becker EG, *et al*. Revolutionary advances in sun-protective clothing—an essential step in eliminating skin cancer in our world. *J Long Term Eff Med Implants*. 2004;14:95-106.
10. Almahroos M, Kurban AK. Ultraviolet carcinogenesis in nonmelanoma skin cancer. Part I: incidence rates in relation to geographic locations and in migrant populations. *Skinmed*. 2004;3:29-35.
11. Bergfeld WF. The aging skin. *Int J Fertil Womens Med*. 1997;42:57-66.
12. Murphy GM. Ultraviolet radiation and immunosuppression. *Br J Dermatol*. 2009;161(suppl 3):90-95.
13. Birkedal-Hansen H. Catabolism and turnover of collagens: collagenases. *Methods Enzymol*. 1987;144:140-171.
14. Uitto J. Collagen. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al, eds. *Dermatology in General Medicine*. 4th ed. New York, NY: McGraw-Hill; 1993:299-314.
15. Berton A, Godeau G, Emonard H, et al. Analysis of the ex vivo specificity of human gelatinases A and B towards skin collagen and elastic fibers by computerized morphometry. *Matrix Biol*. 2000;19:139-148.
16. Birkedal-Hansen H, Moore WG, Bodden MK, et al. Matrix metalloproteinases: a review. *Crit Rev Oral Biol Med*. 1993;4:197-250.
17. Nagase H, Woessner JF Jr. Matrix metalloproteinases. *J Invest Dermatol*. 1972;58:347-361.
18. Crawford HC, Matrisian LM. Mechanisms controlling the transcription of matrix metalloproteinase genes in normal and neoplastic cells. *Enzyme Protein*. 1996;49:20-37.

19. Gack S, Vallon R, Schaper J, et al. Phenotypic alterations in fos-transgenic mice correlate with changes in Fos/Jun-dependent collagenase type I expression. regulation of mouse metalloproteinases by carcinogens, tumor promoters, cAMP, and Fos oncoprotein. *J Biol Chem*. 1994;269:10363-10369.

20. Fligiel SE, Varani J, Datta SC, et al. Collagen degradation in aged/photodamaged skin in vivo and after exposure to matrix metalloproteinase-1 in vitro. *J Invest Dermatol*. 2003;120:703-707.

21. Varani J, Perone P, Fligiel SE, et al. Inhibition of type I procollagen production in photodamage: correlation between presence of high molecular weight collagen fragments and reduced procollagen synthesis. *J Invest Dermatol*. 2002;119:122-129.

22. Mitchell RE. Chronic solar dermatosis: a light and electron microscopic study of the dermis. *J Invest Dermatol*. 1967;43:203-230.

23. Watson RE, Griffiths CE, Craven NM, et al. Fibrillin microfibrils are reduced in photoaged skin: distribution and abundance at the dermal-epidermal junction. *J Invest Dermatol*. 1999;112:782-787.

24. Craven NM, Watson RE, Jones CJ, et al. Clinical features of photodamaged human skin related to reduction in collagen VII. *Br J Dermatol*. 1997;137:344-350.

25. Tsoureli-Nikita E, Watson R, Griffiths C. Photoaging: the darker side of the sun. *Photochem Photobiol Sci*. 2006;5:160-164.

26. Ignotz RA, Endo T, Massague J. Regulation of fibronectin and type I collagen mRNA levels by transforming growth factor-β. *J Biol Chem*. 1987;262:6443-6446.

27. Quan T, He T, Kang S, et al. Solar ultraviolet irradiation reduces collagen in photoaged human skin by blocked transforming growth factor-beta type II recept/Smad signaling. *Am J Pathol*. 2004;165:741-751.

28. Scharffetter-Kochanek K, Wlaschek M, Brenneisen P, et al. UV-induced reactive oxygen species in photocarcinogenesis and photoaging. *Biol Chem*. 1997;378:1247-1257.

29. Jurkiewicz BA, Buettner GR. EPR detection of free radicals in UV-irradiated human skin: mouse versus human. *Photochem Photobiol*. 1996;64:918-922.

30. Masaki H, Atsumi T, Sakurai H. Detection of hydrogen peroxide and hydroxil radicals in murine skin fibroblasts under UV irradiation. *Biochem Biophys Res Commun*. 1995;206:474-479.

31. Kahari VM, Saarialho-Kere U. Matrix metalloproteinases in skin. *Exp Dermatol*. 1997;6:199-213.

32. Yaar M, Gilchrest BA. Ageing and photoageing of keratinocytes and melanocytes. *Clin Exp Dermatol*. 2001;26:583-591.

33. Gilchrest BA, Soter NA, Hawk JL, et al. Histologic changes associated with ultraviolet A-induced erythema in normal human skin. *J Am Acad Dermatol*. 1983;9:213-219.

34. Parrish JA. Responses of skin to visible and ultraviolet radiation. In: Goldmith LA, ed. *Biochemistry and physiology of the skin*. New York: Oxford University Press; 1983:713-735.

35. Clydesdale GJ, Dandie GW, Muller HK. Ultraviolet light induced injury: immunological and inflammatory effects. *Immunol Cell Biol*. 2001;79:547-568.

36. Koivukangas V, Kallioinen M, Autio-Harmainen H, et al. UV irradiation induces the expression of gelatinases in human skin in vivo. *Acta Dermatol Verneol*. 1994;279-282.

37. Fisher GJ, Datta SC, Talwar HS, et al. Molecular basis of sun-induced premature skin ageing and retinoid antagonism. *Nature*. 1996;379:335-339.

38. Scharffetter K, Wlaschek M, Hogg A, et al. UVA irradiation induces collagenase in human dermal fibroblasts in vitro and in vivo. *Arch Dermatol Res*. 1991;283:506-511.

39. Berneburg M, Kamenisch Y, Krutmann J. Repair of mitochondrial DNA in aging and carcinogenesis. *Photochem Photobiol Sci*. 2006;5:190-198.

40. Berneburg M, Plettenberg H, Medve-Konig A, et al. Induction of the photoaging associated mitochondrial common deletion in vivo in normal human skin. *J Invest Dermatol*. 2004;122:1277-1283.

41. Borregaard N, Cowland JB. Granules of the human neutrophilic polymorphonuclear leukocyte. *Blood*. 1997;89:3503-3521.

42. Rijken F, Kiekens R, van den Worm E, et al. Pathophysiology of photoaging of human skin: focus on neutrophils. *Photochem Photobiol Sci*. 2006;5:184-189.

43. Pinnell S. Cutaneous photodamage, oxidative stress, and topical antioxidant protection. *J Am Acad Dermatol*. 2003;48:1-19.

44. Jensen EV, DeSombre ER. Mechanism of action of the female sex hormones. *Annu Rev Biochem*. 1972;41:203-230.

45. Wahl LM, Blaundau RJ, Page RC. Effect of hormones on metabolism and collagenase activity in the public symphysis ligament of the guinea pig. *Endocrinology*. 1977;100:571-579.

46. Freiman A, Bird A, Metelitsa AI, et al. Cutaneous effects of smoking. *J Cutan Med Surg*. 2004;8:415-423.

47. Kadunce DP, Burr R, Gress R, et al. Cigarette smoking: risk factor for premature facial wrinkling. *Ann Int Med*. 1991;114:840-844.

48. Yin L, Morita A, Tsuji T. Tobacco smoke extract induces age-related changes due to modulation of TGFβ. *Exp Dermatol*. 2003;12:51-56.

49. Tsoureli-Nikita E, Watson RE, Griffiths CE. Photoageing: the darker side of the sun. *Photochem Photobiol Sci*. 2006;5:160-164.

50. Varani J, Warner RL, Gharaee-Kermani M, et al. Vitamin A antagonizes decreased cell growth and elevated collagen-degrading matrix metalloproteases and stimulates collagen accumulation in naturally aged human skin. *J Invest Dermatol*. 2000;114:480-486.

51. Oikarienen A. The aging of the skin: chronoaging versus photoaging. *Photodermatol Photoimmunol Photomed*. 1990;7:3-4.

52. Taylor C, Stern R, Leyden J, et al. Photoaging/photodamage and photoprotection. *J Am Acad Dermatol*. 1990;22:1-15.

53. Bernhard JD, Pathak MA, Kochevar IE, et al. Abnormal responses to ultraviolet radiation. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al. eds. *Dermatology in General Medicine*. 3rd ed. New York, NY: McGraw-Hill; 1987:1481-1507.

54. Jansen C. The polymorphic phototest reaction. *Arch Dermatol*. 1982;118:638-642.

55. Gilchrest BA. Skin aging and photoaging: an overview. *J Am Acad Dermatol*. 1989;21(3 pt 2):610-613.

56. Hegedus F, Diecidue R, Taub D, et al. Non-surgical treatment modalities of facial photodamage: practical knowledge for the oral and maxillofacial professional. *Int J Oral Maxillofac Surg*. 2006;35:389-398.

57. Ma W, Wlaschek M, Tantcheva-Poor I, et al. Chronological ageing and photoageing of the fibroblasts and the dermal connective tissue. *Clin Exp Dermatol*. 2001;26:592-599.

58. Hexsel CL, Bangert SD, Hebert AA, et al. Current sunscreen issues: 2007 Food and Drug Administration sunscreen labeling recommendations and combination sunscreen/insect repellent products. *J Am Acad Dermatol*. 2008;59:316-323.

59. Naylor MF, Farmer KC. The case for sunscreens. A review of their use in preventing actinic damage and neoplasia. *Arch Dermatol*. 1997;133:1146-1154.

60. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. *N Engl J Med*. 1993;329:1147-1151.

61. Nash JF. Human safety and efficacy of ultraviolet filters and sunscreen products. *Dermatol Clin*. 2006;24:35-51.

62. Gilchrest BA. The a-B-C-ds of sensible sun protection. *Skin Therapy Lett*. 2008;13:1-5.

63. Mahmoud BH, Hexsel C, Lim H, et al. Impact of long wavelength UVA and visible light on melanocompetent skin. *J Invest Dermatol*. 2010;130:2092-2097.

64. Moyal D. Prevention of ultraviolet-induced skin pigmentation. *Photodermatol Photoimmunol Photomed*. 2004;20: 243-247.

65. Autier P, Boniol M, Severi G, et al. Quantity of sunscreen used by European students. *Br J Dermatol*. 2001;144:288-291.

66. Wulf HC, Stender IM, Lock-Andersen J. Sunscreens used at the beach do not protect against erythema: a new definition of SPF is proposed. *Photodermatol Photoimmunol Photomed.* 1997;13: 129-132.

67. Damian DL, Halliday GM, Barnetson RS. Broad-spectrum sunscreens provide greater protection against ultraviolet-radiation-induced suppression of contact hypersensitivity to a recall antigen in humans. *J Invest Dermatol.* 1997;109:146-151.

68. Xu C, Green A, Parisi A, et al. Photosensitization of the sunscreen octyl p-dimethylaminobenzoate by UVA in human melanocytes but not in keratinocytes. *Photochem Photobiol.* 2001;73: 600-604.

69. Thiele JJ, Dreher F, Packer L. Antioxidant defense systems in skin. In: Eisner P, Maibach HI, eds. *Cosmeceuticals: Drugs vs Cosmetics.* New York, NY: Marcel Dekker; 2000:145-187.

70. Shindo Y, Witt E, Han D, et al. Enzymic and non-enzymic antioxidants in epidermis and dermis of human skin. *J Invest Dermatol.* 1994;102:122-124.

71. Vural P, Canbaz M, Selçuki D. Plasma antioxidant defense in actinic keratosis and basal cell carcinoma. *J Eur Acad Dermatol Venereol.* 1999;113:96-101.

72. Zhao J, Lahiri-Chatterjee M, Sharma Y, et al. Inhibitory effect of a flavonoid antioxidant silymarin on benzoyl peroxide-induced tumor promotion, oxidative stress and inflammatory responses in SENCAR mouse skin. *Carcinogenesis.* 2000;21:811-816.

73. Singh RP, Tyagi AK, Zhao J, et al. Silymarin inhibits growth and causes regression of established skin tumors in SENCAR mice via modulation of mitogen-activated protein kinases and induction of apoptosis. *Carcinogenesis.* 2002;23:499-510. ■