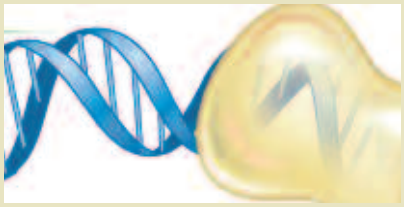
abstract



Accumulation of sun exposure is an important factor resulting in aging of the skin and development of cutaneous malignancy. Unfortunately, most people think of suntanning as a healthy, natural process, and damaging effects of the sun are not experienced until 15–20 years after the initial damage has been done. By the time we see patients in our clinic, the majority of our older clientele has extensive, irreversible photo damage and precursors of skin cancer. It is difficult to treat many of these patients as multiple lesions are frequently present, and patients are sometimes unwilling to initiate sun-protective measures, are not ideal surgical candidates, and may not comply with treatments suggested by the dermatologist due to financial burden. We emphasize the critical role of sun exposure as a cause of skin aging, benign stigmata of aging, and development of skin cancers. Treatment options including topical therapies, oral medications, surgery, and new-age technologies are discussed.

Key words: *photo-aging, therapy, skin cancer, dermatoheliosis, melanoma*

Malignant Photo Damage

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Introduction

Cumulative sun exposure remains the largest factor in aging skin, and is responsible for a large portion of the unwanted esthetic effects (Table 1). The ravages of the cumulative effects of sun exposure can be seen in later years as what we perceive as the clinical stigmata of old age. These include the premalignant lesions: rhytids, lentigines and various pigmentary changes, actinic keratoses, telangiectasia, fragility and ecchymoses, loss of translucency, and seborrheic keratoses. There is also associated atrophy, inelasticity, wrinkling, and redundant, dry, coarse, and yellow-coloured sallow skin. Malignant lesions associated with photo-aging include basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), lentigo maligna, and melanoma.[1,2]

Aging of the skin involves intrinsic (genetic) and extrinsic (photo-aging) factors. Extrinsic factors include ultraviolet and infrared radiation, oxygen, ozone, petrochemical pollutants, cold and wind, and alterations of humidity. Advancing age, immune status, hormonal cycles, and genetic predisposition also may modify or intensify the actual physical effects of these environmental stimuli. Solar radiation, composed of ultraviolet and infrared radiation, is the foremost environmental element that indisputably damages the skin.[1] Ultraviolet A (UVA) exposure to skin results in tanning, pigmentation, and collagen/elastin alteration. Ultraviolet B (UVB) results in erythema related to sunburns as well as development of various forms of skin cancer. By 18 years of age, we have been exposed to 80% of our lifetime ultraviolet exposure;[3] unfortunately, there is a delay of approximately 15–20 years before visible effects of photo-aging become apparent.[2]

Mechanism of Solar-Induced Skin Aging

Ultraviolet exposure to keratinocytes and melanocytes results in the formation of oxygen free radicals, which promote DNA mutation (via formation of thymine dimers) and damage of DNA repair proteins (Figure 1). This allows for an accumulation of DNA mutations and an inability to correct them. These free radicals are partially neutralized by antioxidants such as vitamin A, C, E, glutathione, beta-carotene, and bioflavinoids.[2]

Histological assessment of photo-damaged skin reveals epidermal atrophy with loss of rete ridges, resulting in increased skin fragility, wrinkles, and purpura.[4] As well, there is a loss of the barrier function of the epidermis, resulting in dryness and scaling.

The dermis is also altered over time with ultraviolet exposure. There is a loss of thickness due to a one percent loss of collagen per annum. The remaining collagen is coarser, with fibre disarray.[5] Loss of dermal blood vessels results in decreased wound healing ability and yellow, sallow discolouration of the skin. Elastic fibres are fragmented, calcified, and decreased in numbers resulting in solar elastosis (sagging skin).

With aging, there is also loss of subcutaneous fat, with flattening of cheekbones, sunken lips, bulging infraorbital fat pads, and loss of the fullness and roundness of youth. Loss of subcutaneous fatty tissue results in contraction of

Figure 1:

Ultraviolet Radiation and Nucleotide Excision Repair

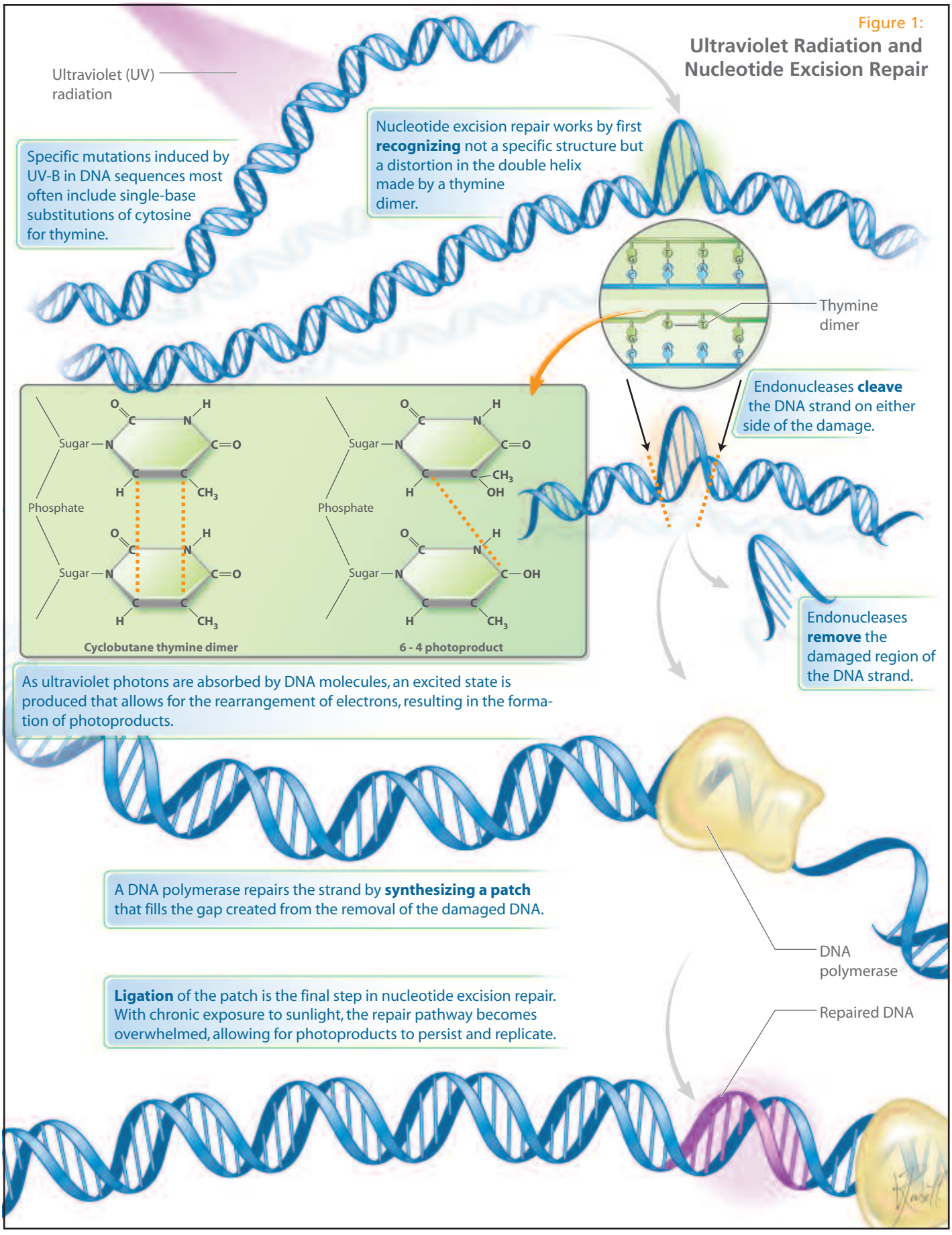

Table 1: Cutaneous Manifestations of Photo-aging

Wrinkling and/or furrowing
Coarseness
Sallowness
Hyperplasia of sebaceous glands
Persistent erythema and/or inflammation
Telangiesctasia
Atrophy
Irregular or mottled pigmentation
Dryness and/or roughness
Purpura, easy bruising, and stellate pseudoscars
Benign neoplasms
Premalignant neoplasms
Malignant neoplasms

Source: Calderone DC, Fenske NA. 1995.[63]

connective tissue, deepened lines of facial expression, and thermoregulatory impairment of older adults.[2]

Musculature also alters with the aging face. There is a prominent brow ptosis with age and the development of Crow's feet, frown lines, etc. Skin appendages (hair, sweat glands, and oil glands) decrease in number, size, and activity, presenting as dry skin with loss of size and numbers of hairs. Hair growth slows, with atrophy and fibrosis of blood vessels, resulting in thinned calibre of hair, loss of melanocyte numbers and activity, and greying/balding.

Malignant Photo Damage

Actinic keratosis (AK) occurs on sun-exposed sites (face, ears, hands, and forearms) and favours fair-skinned individuals, especially people with red hair and freckles. They present as flat to slightly raised red to brown scaling lesions with a sandpaper texture. Skin examination reveals this premalignant condition in 14% of patients in a dermatology clinic.[6] Approximately one percent of these transform yearly to squamous cell carcinoma. The average patient with sun-damaged skin has an average of 7.7% actinic keratosis and a 10.2% 10-year risk of squamous cell carcinoma.[7,8]

Basal cell carcinoma represents 80% of all skin cancers and 33% of all cancers in the US.[9] The incidence of BCC in Caucasian adults is 191/100,000 per year.[10] Common sites of involvement include the eyelids, ears, nose, and lips. Risks for BCC are light hair, fair complexion, freckles, skin type I/II, red hair, blond hair, and blue/green eyes. The typical lesion appears as a nonhealing papule or plaque with a translucent border and telangiectasia. Occupational risks are also evident, including fishing, farming, and other outdoor jobs. This form of cancer is relatively benign with five-year survival estimated at 95%.[11] Less than 0.1% of BCCs metastasize to other organs (nodes, liver, bone, or lungs).

Squamous cell carcinoma represents 20% of nonmelanoma skin cancer. These lesions can look like a patch of eczema or psoriasis but fail to respond to conventional therapy. This cancer is locally invasive and can metastasize. There has been a 50–200% increase in incidence in the last 20 years.[12,13] Risks of SCC include extrinsic (UV accumulation, arsenic, tobacco, HPV, radiation, and PUVA) and intrinsic (photo type I, chronic wound, albino, immunosuppression, and XP) factors.[14–24] Multiple AKs increase the risk of SCC progression 10- to 50-fold. The most important management is prevention by sun avoidance and use of sunscreen and sun-protective clothing.[25]

Melanoma incidence and mortality rates have been rising over the last 30 years. Over 54,000 new cases present each year. Multiple risk factors are well documented (fair skin, poor tanning, blue/green eyes, blond/red hair, dysplastic nevus, multiple nevi, history of nonmelanoma skin cancer, three or more blistering burns, three or more years of outdoor work during teen years, outdoor recreation/occupation, and equatorial living). One study of sunscreen use and sun avoidance in Australia showed that sunscreen use has resulted in a decreased incidence of malignant melanoma.[26] Unfortunately, nondermatologists are four-fold more likely to misdiagnose melanoma and multiple clinical variants exist. It is imperative to routinely self-examine skin to screen for changing moles. The treatment of choice is surgical excision deep to fat, with surgical margins varying, depending on the depth of tumour thickness.

Nonsurgical Therapy for Malignant Lesions

Long-term ultraviolet radiation produces visible signs of photo aging and skin cancer. Eighty percent of these are basal cell carcinomas occurring *de novo* on sun-damaged skin, with 20% squamous cell carcinoma (actinic keratosis precursor) and 5% melanoma (50% dysplastic nevus precursor), as described.[27]

Surgical removal can cause significant disfigurement and functional impairment. As the population of older people continues to grow, a careful assessment of surgical risk factors will need to be taken into account both pre- and perioperatively. A majority of octogenarians are not optimal candidates for surgical intervention, and nonsurgical options may be a strong consideration as an alternate form of treatment.[27] Radiation therapy, chemotherapy, biologic response modifiers, retinoids, and cyclooxygenase inhibitors have all been utilized in the medical treatment of cutaneous malignancies.

Topical Chemotherapy

The most studied topical chemotherapeutic agent is fluorouracil (5-FU). This agent is an anti-DNA thymidine analog resulting in increased cell death. The most valuable role is its use in managing actinic keratosis, the precursors of SCC. However, limited data do support use in SCC *in situ* or in superficial BCC. Electrochemotherapy is used to increase the concentration of chemotherapy within tumour cells. Intralesional bleomycin, in combination with an electrical pulse, has demonstrated some efficacy in the treat-

ment of BCC, although routine use of these agents as the sole treatment for BCC or SCC is neither accepted nor recommended.[27]

Biologic Response Modifiers

Imiquimod promotes immunostimulation by binding to cell surface receptors such as Toll receptor[7] and stimulating the secretion of multiple cytokines. Significant activity has been shown with BCC, especially superficial subtypes. Off-label uses include treatment of lentigo maligna melanoma,[28] melanoma *in situ*, cutaneous metastases of melanoma and nonmelanoma skin cancers (SCC *in situ*, Bowenoid papulosis, extra mammary Paget's, and keratoacanthoma).[27,29]

Retinoids

Derivatives of vitamin A, retinoids, are evolving as potential tools in the prevention of new BCCs and SCCs. Isotretinoin is considered the most effective retinoid for the prevention of nonmelanoma skin cancer.[27] Topical tretinoin has been shown to decrease the number of solar keratoses and may prevent progression to carcinoma. Retinoids induce apoptosis, impede proliferation, and stimulate differentiation of cells. However, the response of established tumours to retinoids has been disappointing, with few remissions reported.

Cytokines

Intralesional injection of interferon alpha 2a/2b has shown some positive effects in the treatment of nonmelanoma skin cancers.[30]

Cox-2 Inhibitors

Topical nonsteroidal anti-inflammatories (three percent diclofenac) used twice daily have been shown to reduce numbers of AKs by 50% but are less effective than other chemical and destructive modalities.[31]

Dietary and Herbal Supplements

Vitamins and antioxidants combined with sunscreens are currently on the market. The administration of antioxidants in combination seems to provide greater efficacy than protection by any single antioxidant agent. Evidence suggests that beta-carotene reduces UV-induced photo-immunosuppression, although no decrease in incidence of nonmelanoma skin cancers has been shown. Vitamins C and E may increase the minimal erythema dose, with significant reduction in UV-induced erythema. A low-fat diet has been shown in several studies to reduce the incidence of actinic keratosis after eight to 12 months.[30] There is a growing body of evidence that polyphenols from black and green tea exhibit inhibitory properties against UV-induced photocarcinogenesis.[32] Finally, recent findings suggest that procyanidins, from grape seeds, exert antioxidant activity against UV-induced photo damage. Further randomized, double-blind, placebo-controlled studies are required to determine the benefits of diet and herbal therapy, if any, in the treatment of cutaneous neoplasia.[27]

Surgical Therapy of Skin Malignancy

Laser resurfacing has been successfully used in several types of solar damage. This technique can recover skin from elastotic changes, comedomes, and acne cysts in the condition of Favre-Racouchot; flatten fine wrinkles; and aid in the treatment of extensive actinic keratosis.[33] However, the older the patient is, the more difficult the treatment due to decreased skin hydration.[34]

Photodynamic therapy is a combination therapy based on topical application of a photosensitizer followed by irradiation with either laser, light emitting diodes, IPLs, or other light sources to increase the effects of nonablative photo rejuvenation.[35] Actinic keratosis and skin cancers preferentially uptake 5-amino levulinic acid (5-ALA) as they are highly metabolically active cells. This chemical is converted to protoporphyrin IX, a strong photosensitizer, with destruction of cells by free oxygen radical species generated from tissue oxygen in the presence of protoporphyrin IX and visible light. Treatment is aimed at extensive solar keratosis in patients, with several studies showing benefit in superficial basal cell and squamous cell carcinoma.[36–39]

Mohs Micrographic Surgery

Mohs micrographic surgery (MMS) offers a 95–99% cure rate of BCC at five-year follow-up. Indications for MMS include lesions >1.5 cm, anatomic location, histological subtypes, recurrence, and cosmetically sensitive areas.[40–42] Mohs surgery for high-risk SCC lesions and cosmetically sensitive areas can provide cure rates of up to 97%.[40,42] Mohs surgery offered to select cases of melanoma offers a 99.5% cure rate.[43–45]

Microdermabrasion

This technique is ideally suited for lesions on the surface of the skin or in the upper third of the dermis. Dermabrasion reduces shadows of scars and breaks up the base of depressed scars. It may be effective as prophylaxis against SCC and BCC in actinically damaged skin. Potential complications include bleeding, erythema, milia, eczematization, altered pigment, hypertrophic healing, and enlarged pore size.[46] It is effective in treating sun-damaged skin, fine rhytides, age spots, and enlarged pores.

Cryosurgery Cryotherapy

Cryosurgery cryotherapy, which offers 98.8% cure rates[47] for AKs, can be used for superficial BCCs with five-year recurrences up to 7.5%.[48] Cryosurgery in the very old, whose light-exposed atrophic skin is very thin, should be undertaken with caution, especially over the skull where the skin may fail to heal, leaving exposed bone. The ideal tumours to treat are well-defined BCCs of nodular or superficial type and noninvasive SCC; these tumours should be under two centimetres in diameter. Less favourable results are achieved in morphemic BCC, lesions around the ear, nasolabial fold, scalp invasive SCC, and lesions previously treated by any other modality.[49] Recurrence rates are approximately 1–10% for low-risk BCC, and 10% for SCC.[49] The scar produced by this method is far superior to that following radiotherapy, and cryotherapy is extremely cost

effective. Unfortunately, there is no surgical specimen to indicate adequacy of removal. Cryotherapy has also been used successfully in lentigo maligna in an older patient deemed unsuitable for surgical modality.[50]

Excision, Curettage

Therapy of BCCs includes destructive and chemical modalities. Excision with saucerization followed by electrodessication and curettage is one common and effective method of therapy. Excision alone provides a cure rate of 95–97% if two millimetre margins are ensured perilesion.[51] The majority of treatment modalities for SCC are destructive. Excision with shave biopsy for low-risk lesions and deep wide resection for high-risk lesions are effective.[40] Electrodesiccation and curettage or liquid nitrogen cryotherapy for small, low-risk lesions provides a 96% cure rate.[40,52]

Radiation

Radiation is a useful treatment of BCCs in older adults and patients unable to sit through surgery. Radiation also offers the benefit of treating multiple lesions in a radiation field.[53] Radiation may be offered to poor surgical candidates or in patients with nonresectable tumours or metastases.[40] This therapy remains a good option in selected patients with Bowen's disease and other nonmelanoma skin cancer, but caution should be exercised before selection of patients with lesions in poor healing areas, such as the lower extremity.[54,55]

Chemical Peels

Chemical peels, both superficial (salicylic acid, Jessner's solution, and glycolic acid) and deep chemical peels (phenol), can be useful for treatment of AKs.[56,57] Chemical acid peels are an excellent modality for treatment of actinic keratosis, actinic dermatitis, seborrheic dermatitis, and solar lentigos. Improvement of rhytides, tone, and texture can be impressive.[58,59] More recently, TCA peels have been used in combination with dermabrasion for prophylaxis of cutaneous carcinoma development on the skin of xeroderma pigmentosum patients.[60] The goal is to cause an organized regeneration of skin. The depth of wounding depends on the strength of agent employed, skin site, preparation prior to peeling operator technique, and experience.[59]

Other Therapies

Other adjuvant therapies for melanoma metastases include chemotherapy, interleukin/interferon, vaccines, and immunotherapy, with little improvement on overall survival or quality of life.[41,42,61] Lymph node dissection is offered to determine prognosis and risk of metastatic disease.

Conclusion

After one century of sunbathing we have to face the consequences and be aware of the innate dangers of overexposure to sunlight or UV, such as dermatoheliosis, premature aging of the skin, epidermal precancers, skin carcinoma, and melanoma.[62] As aging progresses, patients will move from the least invasive techniques, such as nonablative resurfacing, radio frequency skin tightening, and botulinum toxin injections, to fillers, followed by traditional resurfacing and surgical interventions for treatment of benign dermatoheliosis. Multiple modalities are available to treat both benign and malignant sequelae of photo-aging and are divided into topical, oral, and surgical/ablative techniques. It is important to have knowledge of the multiple therapies available to your aging patient, especially in the face of a rapidly growing field of photo-rejuvenation and eradication of cutaneous malignancy. ◆

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References

1. Benedetto AV. The environment and skin aging. Clin Dermatol 1998;16:129–39.
2. Glogau RG. Systematic evaluation of the aging face. In: Bologna J, Jorizzo, Rapini, eds. Dermatology. Mosby Publications, 2001.
3. Lamberg L. Dermatologists call for massive cover-up. JAMA 1998; 279:1426–1427.
4. Contet-Audonneau JL, Jeanmaire C, Pauly G. A histological study of human wrinkle structures: comparison between sun exposed areas of the face, with or without wrinkles, and sun-protected areas. Br J Dermatol 1999;140:1038–47.
5. Montagna W, Carlisle K. Structural changes in aging human skin. J Invest Dermatol 1979;73:47–53.
6. Gupta AK, Cooper EA, Feldman SR. A survey of office visits for actinic keratoses as reported by NAMCS, 1990–1999. Cutis 2002;70(2 Suppl):S8–13.
7. Jeffes EW, Tang EH. Actinic keratosis: current treatment options. Am J Clin Dermatol 2001;1:167–79.
8. Marks R, Foley C, Goodman G. Spontaneous remission of solar keratoses: the case for conservative management. Br J Dermatol 1986;115:649.
9. Garner KL, Rodney WM. Basal and squamous cell carcinoma. Dermatology 2000;27: 447–58.
10. American Cancer Society. www.cancer.org.
11. Leong GK, Stone JL, Farmer ER. Nonmelanoma skin cancer in Japanese residents of Kauai, Hawaii. J Am Acad Dermatol 1987;17:233–8.
12. Glass A, Hoover R. The emerging epidemic of melanoma and squamous cell carcinoma. JAMA 1989;262:2097–100.
13. Gallagher R, Ma B, McLean D. Trends in basal cell carcinoma, squamous cell carcinoma, and melanoma of the skin from 1973 through 1987. Ja Am Acad Dermatol 1990;23:413–21.
14. Johnson T, Rowe D, Nelson B. Squamous cell carcinoma of the skin (excluding lip and oral mucosa). J Am Acad Dermatol 1992;26:467–84.
15. Everall J, Dowd P. Influence of environmental factors excluding ultraviolet radiation on the incidence of skin cancer. Bull Cancer 1978;65:241–8.
16. Markey A. Etiology and pathogenesis of squamous cell carcinoma. Clin Dermatol 1995;13:537–43.
17. Kettler A, Rutledge M, Tschen J. Detection of human papillomavirus in nongential Bowen's disease by the situ DNA hybridization. Arch Dermatol 1990;126:777–81.
18. Rowell N. A follow-up study of superficial radiotherapy for benign dermatoses: recommendations for the use of x-rays in dermatology. Br J Dermatol 1973;88:583–90.
19. Chuang T, Heinrich L, Schultz. PUVA and skin cancer. J Am Acad Dermatol 1992;26:173–7.
20. Foote J, Harris R, Giuliano AR. Predictors of cutaneous basal- and squamous- cell carcinoma among actinically damaged adults. Int J Cancer 2001;95:7–11.
21. Hahn S, Kim D. Clinical study of Marjolin's ulcer. Yonsei Med J 1990;31:234–41.
22. Bootsma D, Kraemer K, Cleaver J. Nucleotide excision repair syndromes: xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy. In: Vogelstien B, Kinzler K, Eds. The genetic basis of human cancer. New York: McGraw-Hill 1998:245–74.

23. Odom R, James W, Berger T. Albinism. In: James, Berger, Elston, eds. Andrews' diseases of the skin. California: WP Saunders, 2000: 1069–71.
24. Jensen P, Hansen S, Moller B. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol 1999;40:177–86.
25. Naylor M, Boyd A, Smith D. High sun protection factor sunscreens in the suppressions of actinic neoplasia. Arch Dermatol 1995;131:170–5.
26. Martin RH. Relationship between risk factors, knowledge, and preventative behavior relevant to skin cancer in general practice patients in south Australia. Br J Gen Pract 1995;45:365–7.
27. Chakrabarty A, Geisse JK. Medical therapies for non-melanoma skin cancer. Clin Dermatol 2004;22:183–8.
28. Kupfer-Bessaguet I, Guillet G, Misery L. Topical imiquimod treatment of lentigo maligna: clinical and histologic evaluation. J Amer Acad Dematol 2004;51:635–9.
29. Gupta A, Davey VA. Evaluation of the effectiveness of imiquimod and 5-Fluorouracil. J Am Acad Dematol 2005;52:147.
30. DJ Goldberg. Photodamaged skin, basic and clinical dermatology. Marcel Dekker, Inc, 2004: 208.
31. Wolf JE, Taylor JR, Tschen E. Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses. Int J Dermatol 2001;40:709–13.
32. Syed TA, Wong WH. Phase II, Clinical evaluation of 2% polyphenone (green tea extract) in a hydrophilic gel to assess improvement in damaged and premature aged facial skin. J Am Acad Dematol 2004;50:P25.
33. Kaufmann R, Beier C. Laser kin ablation: an update on aesthetic and medical indications. Med Laser Application 2004;19:212–22.
34. R Neumann. Experiences with CO2 laser skin-resurfacing of actinic elastosis. J Eur Acad Dermatol Vener 1998;1 (2 Suppl):S139.
35. Kaufmann R. Lasers in dermatology. Medical Laser Application 2005;20:103–9.
36. Bjerring P. Photorejuvenation – an overview. Med Laser Application 2004;19:186–95.
37. Piacquadio DJ, Chen DM, Farber HF, et al. Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp. Arch Dermatol 2004;140:41–6.
38. Haller JC, Cairnduff F, Slack G, et al. Routine double treatments of superficial basal cell carcinomas using aminolaevulinic acid-based photodynamic therapy. Br J Dermatol 2000;143:1270–4.
39. Wang I, Bendsoe N, Klinteberg CA, et al. I. Photodynamic therapy vs cryosurgery of basal cell carcinomas: results of a phase III clinical trial. Br J Dermatol 2001;144:832–40.
40. Rowe D, Carroll R, Day C. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. J Am Acad Dermatol 1992;26:976–90.
41. Coates AS. Systemic chemotherapy for malignant melanoma. World J Surg 1992;16:277–81.
42. Buzaid AC, Grimm EA, Ali-Osman F. Mechanism of the anti-tumor effect of biochemotherapy in melanoma: preliminary results. Melanoma Res 1994;4:327–30.
43. Zitelli JA, Mohs FE, Larson P. Mohs micrographic surgery for melanoma. Dermatol Clin 1989;7:833–43.
44. Bricca GM, Brodland DG, Ren D. Cutaneous head and neck melanoma treated with Mohs micrographic surgery. J Am Acad Dematol 2005;52:92–100.
45. Dalton SR, Gardner TL. Contiguous lesions in lentigo maligna. J Am Acad Dematol 2005;52:859–62.
46. Orentreich N, Orentreich DS. Dermabrasion: as a complement to dermatology, Clin Plast Surg 1998;25:63.
47. Lubritz RR, Smolewski SA. Cryosurgery cure rate of actinic keratoses. J Am Acad Dermatol 1982;7:631–2.
48. Rowe DE, Carroll RJ, Day CL. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications or patient follow-up. J Dermatol Surg Oncol 1989;15:317.
49. August PJ. Cryotherapy of non-melanoma skin cancer. Clin Dermatol 1995;13:589–92.
50. Davalbhakta A, Hamilton S, Grant JW. Spread of a recurrent lentigo maligna into a graft: a case for conservative treatment. Br J Plast Surg 2001;54:253–6.
51. Lallo MT, Sood S. Head and neck basal cell carcinoma: treatment using a 2mm clinical excision margin. Clin Otolaryngol 2000;25:370–3.
52. Motley R, Kersey P, Lawrence C. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. Br J Dermatol 2002;146:18–25.
53. Caccialanza M, Piccinno R, Grammatica A. Radiotherapy of recurrent basal and squamous cell skin carcinomas: as study of 249 re-treated carcinomas in 229 patients. Eur J Dermatol 2001;11:25–8.
54. Dupree MT, Kiteley RA, Weismantle K, Radiation therapy for Bowen's disease: lessons for lesions on the lower extremity. J Am Acad Dematol 2001;45:401–4.
55. Choo R, Woo T, Assaad D, What is the microscopic tumor extent beyond clinically delineated gross tumor boundary in non-melanoma skin cancers? Int J Radiation Oncology Biol Phys 2005;62:1096–9.
56. Demas PN, Bridenstine JB, Braun TW. Pharmacology of agents used in the management of patients having skin resurfacing. J Oral Maxillofac Surg 1997;55:1255–8.
57. Kitzmiller WJ, Visscher MO, MacLennan S. Comparison of a series of superficial chemical peels with a single midlevel chemical peel for the correction of facial actinic damage. Aesthetic Surg Journal 2003;23:339–44.
58. Collins PS. The chemical peel. Clin Dermatol 1987;5:57–74.
59. Nelson BR, Fader DJ, Gillard M. Pilot histologic and ultra structural study of the effects of medium-depth chemical facial peels on dermal collagen in patients with actinically damaged skin. J Am Acad Dematol 1995;32:472–8.
60. Nelson BR, Fader DJ, Gillard M. The role of dermabrasion and chemical peels in the treatment of patients with xeroderma pigmentosum. J Am Acad Dematol 1995;32:623–6.
61. Kirkwood JM. Systemic adjuvant treatment of high-risk melanoma: the role of interferon alpha-2b and other immuno-therapies. Eur J Cancer 1998;34(3 Suppl):S12–7.
62. Holubar K. Sun and society. J Eur Acad Dermatol Venereol 1995;5:S30.
63. Calderone DC, Fenske NA. The clinical spectrum of actinic elastosis. J Am Acad Dermatol 1995;32:1017.