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The dangers of sun exposure: practical approaches to skin cancer prevention

DIONA DAMIAN MB BS(Hons), PhD, FACD

In Australia, skin cancer is more common than all other cancers combined. Practical skin cancer prevention strategies are important and effective for older Australians as well as for young people, and are critically important for individuals chronically immune suppressed by their medications or by lymphoid malignancy.

Key points

- Skin cancer is four times as common in Australia as all other cancers combined.
- Ultraviolet (UV) radiation-induced DNA damage and suppression of the skin's antitumour immune defences are key pathways in skin carcinogenesis. Even very low doses of UV radiation can damage DNA and profoundly suppress skin immunity.
- Regular sunscreen use can substantially reduce the incidence of premalignant actinic keratoses, cutaneous squamous cell carcinoma, and possibly basal cell carcinoma and melanoma.
- Skin cancer prevention is effective and important in later life as well as in young people.
- Skin cancer prevention is especially important in immune-suppressed transplant recipients and those immune suppressed by chronic lymphoid malignancy.
- High-risk patients may require systemic chemo - prevention, usually with retinoids, such as acitretin, in addition to sun-protective behaviour, clothing, sunglasses and sunscreens.
- Oral nicotinamide (vitamin B_3) protects from UV immuno - suppression and is now being evaluated for its ability to reduce skin cancer incidence.

OUR MOST COMMON MALIGNANCY

In Australia, the lifetime risk of developing any skin cancer is 70% for men and 58% for women.[1] An estimated 2% of the NSW population develop a basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) each year, and the lifetime risk of melanoma is now one in 15 for men and one in 24 for women.[1,2] BCC and SCC account for 80% of all newly diagnosed cancers and are Australia's most expensive malignancy: about 9% of total cancer expenditure is spent on their diagnosis and treatment, and the incidence of BCC and SCC continues to increase in Australia's ageing population.[1,3]

Most nonmelanoma skin cancers (NMSCs) in Australia are BCCs (about 70%), with most of the remainder being SCCs. BCCs rarely metastasise, but can cause extensive tissue destruction if not treated promptly and appropriately, or if the tumour is a more aggressive subtype (e.g. micronodular, infiltrating or morphoeic; Figure 1). Of SCCs on the head and neck (Figure 2), 5% will metastasise, usually to regional nodes, although distant metastases can also occur.[4] Risk factors for metastasis include site (head and neck), depth of invasion and tumour differentiation.[4]

Actinic keratoses (AKs; Figure 3) are premalignant skin lesions that strongly predict the occurrence of NMSCs and can progress to invasive SCC.[5,6] In Australia, more than 50% of the population aged over 40 years have AKs.[5] The risk of subsequent NMSC is also

Professor Damian is Professor of Dermatology at the University of Sydney; and Clinical Academic Dermatologist at Royal Prince Alfred Hospital, Sydney, NSW.

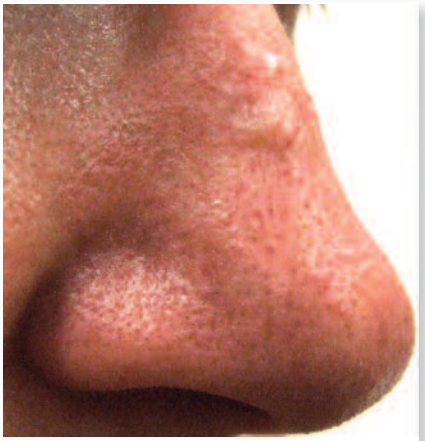

Figure 1. Infiltrating basal cell carcinoma. These lesions may have clinically ill-defined margins and can be resistant to nonsurgical therapies. Microscopically controlled excision (Mohs surgery) can enhance cure rates and optimise conservation of normal tissue at cosmetically sensitive sites.

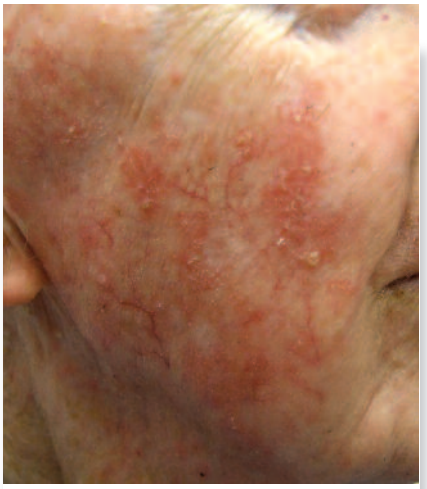

Figure 3. Actinic keratoses (AKs). AKs are premalignant lesions that provide a surrogate marker for nonmelanoma skin cancer risk. AKs can also serve as surrogate markers of skin cancer prevention in sunscreen or systemic chemoprevention trials. Many patients with widespread AKs will show marked reduction in their lesion counts, often within just a few months, with daily sunscreen use.

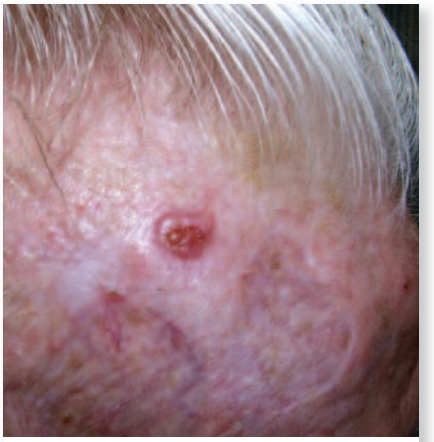

Figure 2. Squamous cell carcinoma on the head. These lesions can have high metastatic potential, especially in immune-suppressed individuals.

proportional to the number of previously diagnosed skin cancers. In a US study, the five-year risk of developing another skin cancer was estimated at greater than 60% for individuals with two previous skin cancers and at greater than 90% for individuals with four to five previous skin cancers; a third of this highest-risk group developed new skin cancers within 12 months.[7]

CUTANEOUS IMMUNITY AND EFFICIENT DNA REPAIR ARE KEY DEFENCES AGAINST SKIN CANCER

Exposure to ultraviolet (UV) radiation in sunlight is the major environmental risk factor for skin cancer; about 90% of NMSCs and at least 65% of melanoma can be attributed to solar UV exposure.[8] UV-induced genetic damage is a key mechanism of skin carcinogenesis.[9] Where DNA repair capacity is severely impaired, as in xeroderma pigmentosum, there is a 1000-fold increase in the risk of melanoma and NMSC.[10] Skin cancer incidence can be reduced in patients with xeroderma pigmentosum by the topical application of liposomal DNA repair enzymes.[11]

The skin's immune system is a critical defence against skin cancer formation; chronically immune-suppressed transplant recipients have rates of SCC that are 50- to 80-fold higher and rates of BCC that are about fivefold higher than those in the immunocompetent population.[12,13] These immune-suppressed patients also have higher rates of metastasis and death from skin cancer. Cardiac transplant recipients surviving 10 years post-transplant are at greater risk of death from skin cancer than from cardiac causes.[14]

Lymphoid malignancy: a risk factor for skin cancer development and metastasis

Lymphoid malignancy is a risk factor for skin cancer development and metastasis. Individuals who are chronically immune suppressed as a result of HIV infection, or immune suppressed because of non Hodgkin's lymphoma (NHL), are also at hugely elevated risk of skin cancer development and metastasis and both require regular and careful skin cancer surveillance.[15-17] Chronic lymphocytic leukaemia (CLL) is a subtype of NHL and comprises 25% of all leukaemias. It primarily affects the elderly, with an incidence in patients aged over 65 years that is about 15-fold higher than in younger patients.[16] Australia has a particularly high incidence of CLL, with an age-standardised incidence of 5.5 and 3.3 per 100,000 in men and women, respectively.[16] However, the true incidence may be even higher because many cases are asymptomatic. Patients with CLL have increased risks of developing NMSC, melanoma and also rare skin malignancies, such as Merkel cell carcinoma, adnexal carcinomas and atypical fibroxanthomas. Skin cancers in these patients with CLL tend to have peritumural infiltrates of immune suppressive, leukaemic B-cells and greater subclinical extension than comparable tumours in immunocompetent patients (reviewed in reference 17). More than 10% of CLL patients with SCC will die from metastatic skin cancer.[18]

Immune suppression can also significantly reduce the treatment response of NMSCs. Lower cure rates after photodynamic therapy have been documented in transplant recipients,[19] and 14-fold higher rates of BCC recurrence have been reported after Mohs microscopically controlled excision in patients with CLL than in controls.[20]

Ultraviolet radiation suppresses the skin's antitumour immune defences

UV radiation in sunlight can profoundly suppress cutaneous immunity in otherwise immunocompetent individuals, even at low doses that are substantially below the sunburn threshold.[21] Both UVB radiation (290 to 320 nm) and longwave UVA radiation (370 to 385 nm; abutting the visible spectrum) are highly immunosuppressive at doses equivalent to about four to five minutes and 10 to 15 minutes of summer sunlight, respectively.[21] Otherwise healthy people with previously diagnosed melanoma or NMSC have been shown to have a higher intrinsic susceptibility to this UV-induced immunosuppression than those without prior skin cancer.[22]

Men have a higher incidence of melanoma and NMSC in Australia, and also experience higher skin cancer mortality than women.[1,2] In part, this may reflect known gender differences in susceptibility to UV-induced immune suppression; testosterone enhances UV immune suppression in mice whereas oestrogen can be UV-protective.[23] There is also some evidence suggesting that men may be more susceptible to UV immune suppression than women.[24]

SUN-PROTECTIVE CLOTHING AND BEHAVIOUR

As well as avoidance of deliberate solar overexposure and avoidance of artificial UV from tanning beds, the use of sun-protective clothing and hats is essential in areas of high solar irradiance.[25] Human scalp hair has been estimated to confer an ultraviolet protection factor (UPF) of five to 17, so even in individuals without hair loss it is possible to obtain damaging UV doses to the scalp within relatively brief exposure times.[26] As a large proportion of UV radiation incident on the skin is diffuse (scattered and reflected) rather than direct, the UPF of shade structures is only about 1.5 to 5.[27] Similarly, hats cannot fully protect the lower face from diffuse UV radiation, and so sunscreen to the face is needed as well.

The eyes have it

Eye protection is important for reducing the risk of UV-associated ocular conditions such as pterygia and cataracts.[28] The eyelid margins, inner canthi and periocular skin are common sites of NMSC (Figure 4).[29] Treatment of skin cancers at these sites is generally surgical, and often requires complex surgical repair. Use of wraparound sunglasses with high UV protection is thus essential to reduce periocular as well as ocular UV exposure.

The frequency of NMSC at periocular sites, and the importance of early detection to achieve both cure and cosmetically and functionally acceptable surgical repair, means that careful skin examination must always include directed examination of these areas, using adequate lighting of the inner canthi, which tend to be shadowed by normal room lighting.

SUNSCREENS CAN REDUCE DNA DAMAGE, UV IMMUNE SUPPRESSION, AKS AND SKIN CANCER

Topical sunscreens reduce epidermal DNA damage following exposure to UVB and UVA and can also prevent UV-immunosuppression.[30,31] The degree of immune protection is proportional to the level of longwave UVA protection provided by the sunscreen.[32] Hence broadspectrum sunscreens will confer greater immune protection than sunscreens of the same sun protection factor (SPF) filtering only lower UV wavelengths.[31] Products offering a higher SPF

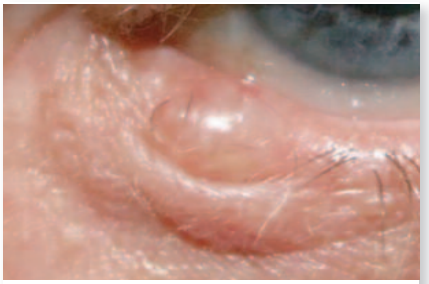

Figure 4. Nodular basal cell carcinoma (BCC). The periocular skin is a common site for nonmelanoma skin cancers; this nodular BCC at the lower lid margin had been unnoticed by this elderly patient.

(i.e. a higher level of UVB protection) will provide greater protection against a given level of sun exposure than those with lower SPFs, although SPF number is in no way an indicator of the duration of 'safe' sun exposure. The 'real life' SPF of sunscreens tends to be one-third to half of the laboratory-measured SPF, largely as a result of differences in amount of product applied 'in the field' and the amount applied during formal sunscreen testing.[33] For example, the average amount of sunscreen applied by beach-goers is estimated to be only about one-third of the amount of lotion used in SPF testing.[33] Other contributing factors that can lower SPFs observed in real life are differences in the UV spectra of sunlight and laboratory UV sources.[34]

Patients taking photosensisitising medications, such as tetracyclines or thiazide diuretics, should be especially diligent in their use of sunscreens, in minimising their sun exposure and in their use of sun-protective hats and clothing. As drug-induced phototoxicity often results from exposure to longwave UVA (340 to 400 nm), sunscreens for these patients need to be broadspectrum with high-level UVA protection against these long wavelengths.[35]

Daily use of sunscreen has been shown to reduce the incidence of AKs and SCCs by up to 40%.[36,37] The number of new

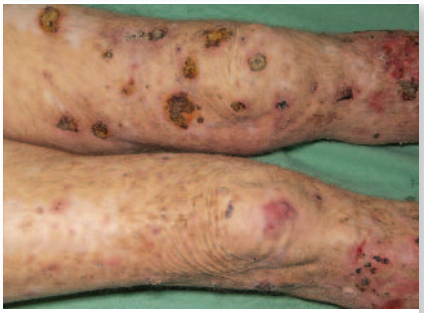

Figure 5. Squamous cell carcinoma (SCC). Patients with multiple nonmelanoma skin cancers, especially multiple SCC as seen on the legs of this 73-year-old man, may require systemic chemoprevention with retinoids, such as acitretin.

AKs can be reduced by about 30 to 40% within just a few months of daily facial sunscreen use;[38] for the face at least, daily use of sunscreen should be encouraged for all patients with AKs and for all patients at high skin cancer risk. Many patients with large numbers of AKs, who are initially candidates for field treatments such as topical 5-fluorouracil, will no longer require this treatment after two to three months using daily high-SPF sunscreen. There is also evidence suggesting that after prolonged follow up (eight to 10 years), the incidence of BCC and possibly melanoma may be lower with sunscreen use.[37,39] Hence interventions commenced in adulthood (even in middle age and beyond) have potential to reduce subsequent skin cancer risk. The use of broadspectrum, high-SPF sunscreen can also reduce AKs and NMSC in immune-suppressed transplant recipients.[40]

People practising rigorous sun protection will have the potential for vitamin D deficiency. About 50% of otherwise healthy skin cancer patients assessed at the author's institution were vitamin D deficient in winter.[41] Low, non-burning sun exposures of a few minutes daily – ideally to less cancer-critical body sites, such as arms and legs – may be appropriate for those at lower skin cancer risk.[42] In Australia, however, daily use of facial sunscreen should still be encouraged. For individuals at high skin cancer risk, vitamin D assessment and supplementation may be required.

SYSTEMIC CHEMOPREVENTION: WHEN SUNSCREENS AREN'T ENOUGH

Transplant recipients and individuals with large numbers of potentially dangerous skin cancers may sometimes require oral retinoids, such as acitretin, to reduce rates of NMSC. Retinoids can reduce SCC and BCC incidence but carry a side effect profile that includes drying of the skin, eyes and lips, potential abnormalities in liver function and lipid levels, osteoporosis, skin fragility, impaired wound healing and teratogenicity.[43] Acitretin is thus only appropriate for those at very high skin cancer risk (Figure 5).

The NSAID celecoxib inhibits the enzyme cyclo-oxygenase 2, which plays a key role in skin carcinogenesis. In a recent study in elderly immunocompetent patients, BCCs and SCCs were significantly reduced (rate ratio 0.41) following nine months of celecoxib use versus placebo. However, there was no significant effect of treatment on the development of AKs.[44] NSAIDs carry a side effect profile that includes increased gastrointestinal, renal and cardiovascular effects, reducing their suitability for the mostly elderly population at highest risk of skin cancer.[45]

Nicotinamide, the amide form of vitamin B3 (niacin), prevents skin cancer and photo-immunosuppression in mice, and replenishes cellular energy after UV exposure, which may enhance DNA repair.[46,47] Nicotinamide has been found to prevent UV immunosuppression in individuals when used topically, or orally (at doses of both 500 mg and 1500 mg, daily).[24,48,49] The drug protected individuals equally against longwave UVA and UVB.[48] A 1% lotion of nicotinamide applied twice daily to an elderly population at high risk of skin cancers was also shown to accelerate seasonal regression of AKs.[50] Unlike nicotinic acid (niacin), nicotinamide does not cause headaches or flushing, and is well tolerated even at high doses.[51] Clinical trials are currently in progress to determine whether oral nicotinamide can reduce NMSC incidence in high-risk patients.

FOLLOW UP

Regular follow up and patient education are essential components of the skin cancer prevention plan in high-risk patients. Follow-up visits allow regular reinforcement of the need for sunscreen use, sun-protective behaviour and self-surveillance, as well as increasing the chance of detecting lesions at an earlier, more curable stage. MT

REFERENCES

A list of references is available on request to the editorial office.

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DIONA DAMIAN MB BS(Hons), PhD, FACD

REFERENCES

1. Staples MP, Elwood M, Burton RC, Williams JL, Marks R, Giles GG. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. Med J Aust 2006; 184: 6-10.
2. Australian Institute of Health and Welfare. Cancer in Australia: actual incidence and mortality data from 1982 to 2007 and projections to 2010. Asia-Pacific J Clin Oncol 2011; 7: 325-338.
3. Goodwin M, Zhou J, Shukla S, Meere D, Chen C, Harding J. Non-melanoma skin cancer: general practice consultations, hospitalisation and mortality. Canberra: Australian Institutes of Health and Welfare and Cancer Australia; 2008.
4. Mourouzis C, Boynton A, Grant J, et al. Cutaneous head and neck SCCs and risk of nodal metastasis - UK experience. J Craniomaxillofac Surg 2009; 37: 443-447.
5. Frost C, Williams G, Green A. High incidence and regression rates of solar keratoses in a Queensland community. J Invest Dermatol 2000; 115: 273-277.
6. Alam M, Ratner D. Primary care: cutaneous squamous-cell carcinoma. N Engl J Med 2001; 344: 975-983.
7. Karagas MR, Stukel TA, Greenberg R, Baron JA, Mott LA, Stern RS. Risk of subsequent basal cell carcinoma and squamous cell carcinoma of the skin among patients with prior skin cancer. JAMA 1992; 267: 3305-3310.
8. Armstrong BK, Kricker A. How much melanoma is caused by sun exposure? Mel Res 1993; 3: 395-401.
9. Halliday GM. Common links among the pathways leading to UV-induced immunosuppression. J Invest Dermatol 2010; 130: 1209-1212.
10. Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum. Cutaneous, ocular, and neurologic abnormalities in 830 published cases. Arch Dermatol 1987; 123: 241-250.
11. Yarosh D, Klein A, O'Connor A, Hawk J, Rafal E, Wolf P. Effect of topically applied T4 endonuclease V in liposomes on skin cancer in xeroderma pigmentosum: a randomised study. Xeroderma Pigmentosum Study Group. Lancet 2001; 357: 926-929.
12. Moloney FJ, Comber H, O'Lorcain P, O'Kelly P, Conlon PJ, Murphy GM. A population-based study of skin cancer incidence and prevalence in renal transplant recipients. Br J Dermatol 2006; 154: 498-504.
13. Carroll RP, Ramsay HM, Fryer AA, Hawley CM, Nicol DL, Harden PN. Incidence and prediction of nonmelanoma skin cancer post-renal transplantation: a prospective study in Queensland, Australia. Am J Kidney Dis 2003; 41: 676-683.
14. Ong C, Keogh AM, Kossard S, Macdonald PS, Spratt PM. Skin cancer in Australian heart transplant recipients. J Am Acad Dermatol 1999; 40: 27-34.
15. Wilkins K, Turner R, Dolev JC, LeBoit PE, Berger TG, Maurer TA. Cutaneous malignancy and human immunodeficiency virus disease. J Am Acad Dermatol 2006; 54: 189-206.
16. Redaelli A, Laskin BL, Stephens JM, Botteman MF, Pashos CL. The clinical and epidemiological burden of chronic lymphocytic leukemia. Eur J Cancer Care 2004; 13: 279-287.
17. Otley CC. Non-Hodgkin lymphoma and skin cancer: a dangerous combination. Australas J Dermatol 2006; 47: 231-236.
18. Mehrany K, Weenig RH, Lee KK, Pittelkow MR, Otley CC. Increased metastasis and mortality from cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia. J Am Acad Dermatol 2005; 53: 1067-1071.
19. Dragieva G, Prinz BM, Hafner J, et al. A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients. Br J Dermatol 2004; 151: 196-200.
20. Mehrany K, Weenig RH, Pittelkow MR, Roenigk RK, Otley CC. High recurrence rates of basal cell carcinoma after Mohs surgery in patients with chronic lymphocytic leukemia. Arch Dermatol 2004; 140: 958-988.
21. Damian DL, Matthews YJ, Phan TA, Halliday GM. An action spectrum for ultraviolet radiation-induced immunosuppression in humans. Br J Dermatol 2011; 164: 657-659.
22. Yoshikawa T, Rae V, Bruins-Slot W, Van den Berg JW, Taylor JR, Streilein JW. Susceptibility to effects of UVB radiation on induction of contact hypersensitivity as a risk factor for skin cancer in humans. J Invest Dermatol 1990; 95: 530-536.

23. Widyarini S, Domanski D, Painter N, Reeve VE. Estrogen receptor signaling protects against immune suppression by UV radiation exposure. Proc Natl Acad Sci USA 2006; 103: 12837-12842.
24. Damian DL, Patterson CRS, Stapelberg M, Park J, Barnetson RS, Halliday GM. Ultraviolet radiation-induced immunosuppression is greater in men and prevented by topical nicotinamide. J Invest Dermatol 2008; 128: 447-454.
25. IARC working group on artificial ultraviolet light and skin cancer. The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers. Int J Cancer 2006; 120: 1116-1122.
26. Parisi AV, Smith D, Schouten P, Turnbull DJ. Solar ultraviolet protection provided by human head hair. Photochem Photobiol 2009; 85: 250-254.
27. Turnbull DJ, Parisi AV, Sabburg J. Scattered UV beneath public shade structures during winters. Photochem Photobiol 2003; 78: 108-183.
28. Coroneo M. Ultraviolet radiation and the anterior eye. Eye Contact Lens 2011; 37: 214-224.
29. Raasch B, Maclennan R, Wronski I, Robertson I. Body site specific incidence of basal and squamous cell carcinoma in an exposed population, Townsville Australia. Mutat Res 1998; 422: 101-106.
30. Bissonauth V, Drouin R, Mitchell DL, Rhainds M, Claveau J, Rouabhia M. The efficacy of a broad-spectrum sunscreen to protect engineered human skin from tissue and DNA damage induced by solar ultraviolet exposure. Clin Cancer Res 2000; 6: 4128-4135.
31. 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.
32. Poon TS, Barnetson RS, Halliday GM. Prevention of immunosuppression by sunscreens in humans is unrelated to protection from erythema and dependent on protection from ultraviolet A in the face of constant ultraviolet B protection. J Invest Dermatol 2003; 121: 184-190.
33. Wulf HC, Stender IM, Lock-Anderson J. Sunscreens used at the beach do not protect agaginst erythema: a new definition of SPF is proposed. Photodermatol Photoimmunol Photomed 1997; 13: 129-132.
34. Damian DL, Halliday GM, Stc Barnetson R. Sun protection factor measurement of sunscreens is dependent on minimal erythema dose. Br J Dermatol 1999; 141: 502-507.
35. Lim DS, Murphy GM. High-level ultraviolet A protection is needed to prevent doxycycline phototoxicity: lessons learned from East Timor. Br J Dermatol 2003; 149: 193-227.
36. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. N Engl J Med 1993; 329: 1147-1151.
37. van der Pols JC, Williams GM, Pandeya N, Logan V, Green AC. Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. Cancer Epidemiol Biomarkers Prev 2006; 15: 2546-2548.
38. Darlington S, Williams G, Neale R, Frost C, Green A. A randomized controlled trial to assess sunscreen application and beta carotene supplementation in the prevention of solar keratoses. Arch Dermatol 2003; 139: 451-455.
39. Green AC, Williams GM, Logan V, Strutton GM. Reduced melanoma after regular sunscreen use: randomized trial follow-up. J Clin Oncol 2011; 29: 257-263.
40. Ulrich C, Jurgensen JS, Degen A, et al. Prevention of non-melanoma skin cancer in organ transplant patients by regular use of a sunscreen: a 24 months, prospective, case-control study. Br J Dermatol 2009; 161: 78-84.
41. McCombie A-M, Mason RS, Damian DL. Vitamin D deficiency in Sydney skin cancer patients. Med J Aust 2009; 190: 102.
42. Diamond TH, Eisman JA, Mason RS, et al. Vitamin D and adult bone health in Australia and New Zealand: a position statement. Med J Aust 2005; 182: 281-285.
43. Marquez C, Bair SM, Smithberger E, Cherpelis BS, Glass LF. Systemic retinoids for chemoprevention of non-melanoma skin cancer in high-risk patients. J Drugs Dermatol 2010; 9: 753-758.
44. Elmets CA, Viner JL, Pentland AP, et al. Chemoprevention of nonmelanoma skin cancer with celecoxib: a randomized, double-blind, placebo-controlled trial. J Nat Cancer Inst 2010; 102: 1-10.
45. Mathew ST, Devi G, Prasanth VV, Vinod B. Efficacy and safety of COX-2 inhibitors in the clinical management of arthritis: mini review. ISRN Pharmacol 2011; 2011: 480291.
46. Gensler HL, Williams T, Huang AC, Jacobson EL. Oral niacin prevents photocarcinogenesis and photoimmunosuppression in mice. Nutr Cancer 1999; 34: 36-41.
47. Park J, Halliday GM, Surjana D, Damian DL. Nicotinamide prevents ultraviolet radiation-induced cellular energy loss. Photochem Photobiol 2010; 86: 942-948.
48. Sivapirabu G, Yiasemides E, Halliday GM, Park J, Damian DL. Topical nicotinamide modulates cellular energy metabolism and provides broad-spectrum protection against ultraviolet radiation-induced immunosuppression in humans. Br J Dermatol 2009; 161: 1357-1364.
49. Yiasemides E, Sivapirabu G, Halliday GM, Park J, Damian DL. Oral nicotinamide protects against ultraviolet radiation-induced immunosuppression in humans. Carcinogen 2009; 30: 101-105.
50. Moloney FJ, Vestergaard ME, Radojkovic BL, Damian DL. Randomised, double-blinded, placebo controlled study to assess the effect of topical 1% nicotinamide on actinic keratoses. Br J Dermatol 2010; 162: 1138-1139.
51. Knip M, Douek IF, Moore WP, et al. Safety of high-dose nicotinamide: a review. Diabetologia 2000; 43: 1337-1345.