

Non-melanoma skin cancer

By Dr Luke Bereznicki

Learning objectives

After reading this article, the pharmacist should be able to:

- Discuss the incidence and impact of non-melanoma skin cancer (NMSC) on the Australian health care system.
- Broadly describe the characteristics of actinic keratoses and NMSC.
- Discuss the importance of prevention of NMSC.
- Discuss the available treatment options for actinic keratoses and NMSC.

Competencies addressed: 6.1.1, 6.1.2, 6.1.3, 6.3.1, 6.3.2

Introduction

Australia has the highest incidence of skin cancer in the world.¹ The estimated age-standardised rate of non-melanoma skin cancer (NMSC) in Australia is 1170 per 100,000 population, based on a 2002 national survey.² The three main forms of skin cancer occurring in Australia are basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma.^{2,3} Merkel cell lesions, Kaposi sarcoma and cutaneous lymphoma are other rare types of cancer which may occasionally affect the skin.⁴ Actinic (or solar) keratoses are the most common pre-malignant lesion seen by dermatologists, and have the potential to progress to SCCs.^{5,6} This article will provide an overview of NMSC and actinic keratoses, including their natural history, incidence, risk factors, clinical features, prevention and treatment.

Natural history

Basal cell and SCCs develop within the epidermis. BCCs develop in the basal layer of keratinocytes (the deepest cell layer of the epidermis) while SCCs arise from more superficial layers of keratinocytes.⁷ Repeated ultraviolet (UV) radiation exposure leads to keratinocyte damage, particularly in susceptible individuals. This damage may result in photoaging (dermatoheliosis), actinic keratoses and solar lentigo (freckles).⁷ The majority of SCCs begin as actinic keratoses.^{5,6}



Incidence and impact on the health care system

Actinic keratoses

It is estimated that 60% of predisposed persons over the age of 40 years have at least one actinic keratosis.⁸ Among white persons, the prevalence of actinic keratoses increases with age; from less than 10% in persons 20 to 29 years of age to 75% in those aged 80 to 89 years of age.^{9,10} Approximately 60% of SCCs are thought to arise from actinic keratoses.⁵ However, most actinic keratoses do not progress to cancer, and approximately one-quarter regress spontaneously within 12 months.¹¹ Estimates vary on the proportion of actinic keratoses that progress to SCCs. A longitudinal study found the risk of progression to be from 0.24% per year for each actinic keratosis.¹¹ As most patients have multiple actinic keratoses, another study used these data to determine that the 10-year risk of progression to SCC is 6.1% to 10.2% per person.¹² After progression to SCC, the risk of metastasis is estimated to be between 0.5% and 3.3%.^{13,14}



NMSC

NMSC is by far the most common cancer diagnosed in Australia;⁴ the incidence of treated NMSC in Australia in 2002 was more than five times the incidence of all other cancers combined.² NMSC only accounts for approximately 1% of cancer deaths in Australia,¹⁵ but imposes a large burden on the health care system. It is estimated that 70% of men and 58% of women will experience at least one NMSC by the age of 70 years.² Rates of NMSC have increased since 1985, with the greatest increase in those aged over 60 years.² The incidence rate for those younger than 60 years has stabilised over this time.² Even though NMSC can generally be managed in the primary care setting without hospitalisation, NMSC still accounts for more hospital admissions than any other cancer type.¹⁵ The Australian Institute of Health and Welfare published a report on NMSC in September 2008.⁴ Some of the key findings were:

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- Over 400,000 Australians were projected to be diagnosed with NMSC in 2008;
- 410 Australians died from NMSC in 2006;
- NMSC now results in almost 1,000,000 general practitioner encounters per year, and the number of encounters rose by 14% between 1998 and 2007;
- Inpatient separations where NMSC was the principal diagnosis more than doubled between 1993-4 and 2006-7 from 36,000 to 80,000; and
- Hospitalisation for NMSC was significantly more likely for Australian-born patients.

BCC is the most common malignancy in white people,¹⁶ and accounts for approximately two-thirds of NMSC in Australia.⁴ Most of the remaining NMSC in Australia is SCC. The age-standardised rates of BCC and SCC in Australia are 884 and 387 per 100,000 population, respectively.² BCC rarely metastasises to other organs, but can be highly invasive and cause destruction of local tissue.⁴ While mortality due to BCC is low, it causes significant morbidity and places a large burden on health care services. SCC is also invasive and possesses a greater potential to metastasise than BCC.⁴ Most SCC are thought to follow actinic keratoses, which result from excessive sun exposure.^{5,6}

Characteristics

BCC characteristically occurs in areas of the body exposed to the sun. It is most common on the head and neck (80% of cases) and the trunk (15% of cases) and the arms and legs.¹⁷ However, BCC may also arise in unusual sites, including the breasts, perianal area, genitalia, palms and soles.¹⁷ The most common presentation of BCC is nodular.¹⁷ Nodular BCCs commonly presents with a raised pearly pink and white nodule or papule with a smooth, shiny, translucent surface with overlying telangiectases and a rolled border, at times exhibiting central crusting or ulceration.¹⁸ Superficial BCC presents as a scaly erythematous patch or plaque. Nodular and superficial BCC may contain melanin, giving a brown, black or blue appearance to the lesions.¹⁷ The least common presentation of BCC is the sclerosing (or morpheic) type, and these lesions are typically ivory-coloured or colourless. The skin may be atrophic and indurated. Patients may also present with mixed subtypes, or with uncommon variants.

SCCs are most often found on the lips, ears and scalp.¹⁸ The lesions are papules or plaques that are firm, skin-coloured or pink, and smooth or hyperkeratotic.¹⁹ Ulceration may also be present.¹⁹ Patients may describe their lesions as itchy or painful nonhealing wounds that bleed when traumatised.¹⁹ Actinic keratoses are lesions that occur on UV-exposed areas of the body. They appear as rough, scaly patches that range in colour from normal skin tone to reddish brown.²⁰ They are usually between one and 2.5 centimetres in diameter, but may be larger. Patients may present with single or multiple lesions covering a large area of skin. Lesions may be asymptomatic or cause pruritis or a burning sensation.²¹

It is often difficult to determine the cell type and whether the lesion is malignant or not; in primary care settings, sensitivity of clinical examination for diagnosing skin cancer has been reported to range from 40% to 80%.^{22,23} Patients with suspicious lesions should be encouraged to present to an appropriate medical practitioner for further investigation.

Risk factors

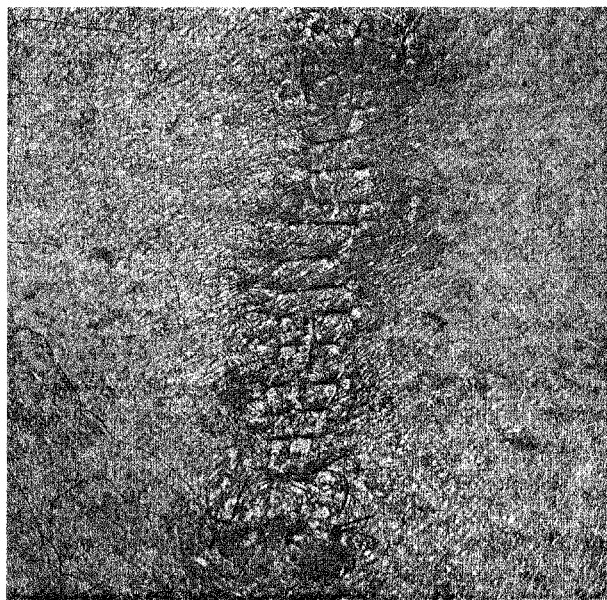
The most important risk factor for NMSC is exposure to UV radiation, particularly during childhood and adolescence.⁴ Risk factors for NMSC are also risk factors for actinic keratoses because of the direct relationship between actinic keratoses and SCC.²⁴ The majority of all skin cancers are thought to be caused by high intensity or cumulative exposure to UV radiation.²⁵ It is important to remember that there are no 'safe' UV rays: UVB is the primary carcinogen, while UVA is synergistic.²⁶

UV exposure is accepted as the major cause of NMSC,²⁷ although the relationship between it and UV exposure is complex.²⁸ The timing, pattern of exposure and amount of exposure are all important variables.¹⁷ The risk of NMSC is increased by recreational exposure to the sun during

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childhood and adolescence.²⁷ Intense intermittent exposure carries an increased risk of BCC compared to a similar degree of continuous exposure,²⁹ while the risk of SCC is strongly linked to cumulative sun exposure.²⁸ Advanced age is strongly linked to an increased incidence of actinic keratoses, because age is a proxy for total UV exposure.²⁵ Additional risk factors for NMSC include certain physical characteristics (fair complexion, red or blond hair and light eye colour), exposure to radiation and immunosuppression.³⁰ Compared to the general population, the risk of subsequent BCC is 10-times higher in patients who have a history of BCC.³¹



A 5cm excision in the arm, the result of an operation to remove a skin cancer.

Prevention

The most critical aspect of skin cancer management is prevention. The stabilisation in the rate of NMSC in Australians under the age of 60 years is encouraging,² because it suggests that exposure to national skin cancer prevention programs in childhood and adolescence has been effective in curbing the increasing incidence of NMSC in this age group. However, the overall incidence of NMSC is rising worldwide, particularly in the elderly population.^{2,32}

The 'Slip! Slop! Slap!' and SunSmart campaigns are credited with changing the attitudes and behaviours of Australians regarding sun protection and skin cancer by delivering a consistent and continuous message for more than 25 years.³³ Avoidance of the sun and protection against exposure are essential primary and secondary preventive measures against NMSC.³⁴ Although no randomised controlled trials (RCTs) have shown any effect of the use of sunscreen on the incidence of BCC, they have shown a protective effect on the development of actinic keratoses and SCC.³⁵⁻³⁷ Daily use of sunscreen to the head, neck, arms, and hands seems to reduce the incidence of actinic keratoses more than

discretionary use.³⁶ Pharmacists are well placed to promote the prevention of skin cancer through sun avoidance and regular surveillance to assist with early detection of skin cancers. The Cancer Council website (www.cancer.org.au/cancersmartlifestyle/SunSmart.htm) is a useful resource for both health professionals and consumers.

Treatment

Actinic keratoses

Actinic keratoses may be treated for a variety of purposes: for cosmetic reasons, for relief of associated symptoms or, most importantly, to prevent SCC. Treatment options include ablative (destructive) therapies or topical therapies in patients with multiple lesions.²⁰ Cryotherapy (using liquid nitrogen, compressed nitrous oxide or carbon dioxide) is commonly used to treat actinic keratoses.²⁰ The cure rate for cryotherapy is high, with reported cure rates between 75 and 99%.³⁸⁻⁴¹ Cryosurgery can be performed in the office setting, and is well tolerated.²⁰ Curettage (mechanically scraping away abnormal tissue) is also highly effective for actinic keratoses. It is useful for treating a limited number of lesions, especially those that are thick and hyperkeratotic.²⁰ Photodynamic therapy involves the application of a photosensitising agent (e.g. methyl aminolevulinate) to each lesion, followed by exposure to light of a specific wavelength. Various treatment protocols have been investigated, but photodynamic therapy is generally well tolerated, has excellent cosmetic results and is highly effective (cure rates between 69% and 93%).^{38,42,43} In RCTs comparing cryotherapy and photodynamic therapy for actinic keratoses, both treatments were effective, but patients preferred photodynamic therapy, mainly because of improved cosmetic outcomes.^{40,41}

The currently available topical therapies (including photodynamic therapy) for actinic keratoses are shown in Table 1. Topical therapies are useful for field treatment of multiple lesions.²⁰ Actinic keratoses on the face may respond more quickly to topical treatment than lesions on the scalp and other areas. There is limited comparative data between topical treatments, and it is unknown whether they prevent invasive skin cancer.⁴⁴ Regular emollient use is also effective for mild lesions.^{45,46} Salicylic acid possesses keratolytic effects, and may also be useful.⁴⁷ In addition to preventing actinic keratoses, sunscreens may lead to remission for some actinic keratoses.^{35,48}

BCC

There are a variety of treatment options for BCC (see Box 1). The choice of treatment depends on a number of factors, including the overall risk of recurrence (see Box 2). Additional considerations include the age of the patient, their general health, their treatment preferences, access to primary or secondary care and cost.⁴⁴ Few RCTs have

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Table 1. Topical therapies for actinic keratoses. Modified from NPS News 61, 2008.⁴⁴

Topical therapy	PBS/RPBS listing for actinic keratoses	Administration	Reported efficacy	Possible side-effects
5-fluorouracil 5% (<i>Efudix</i>)	RPBS listed	Once- or twice-daily until there is a marked inflammatory response. Initial course of therapy is usually 3 to 4 weeks but may be longer	84% to 98% complete clearance in comparative trials (30 days post-treatment and 6-month follow-up)	Temporary pain, burning, redness, blistering and cracking of the skin in the treated area; usually resolve on treatment cessation
Imiquimod 5% (<i>Aldara</i>)	Not listed	3 times a week for up to 16 weeks	45% to 84% complete clearance of lesions on the face and scalp (2 to 8 weeks post-treatment)	Local skin reactions (itching, burning, pain, erythema, flaking, scaling, dryness, scabbing, crusting, erosion and ulceration) are common and can be severe
Photodynamic therapy using methyl aminolevulinate (<i>Metvix</i>)	Not listed	Treatment consists of 1 session	78% to 91% complete response in short-term comparative trials (after 3 to 6-months follow-up)	Temporary pain, burning, erythema, oedema and crusting
Diclofenac 3% (<i>Solaraze</i>)	Not listed	Twice-daily, usually for 60 to 90 days	50% complete clearance vs 20% with placebo (30 days follow-up post-treatment)	Contact dermatitis, erythema, rash, inflammation, irritation, pain, itching, tingling or blistering in the treated area

evaluated the range of treatment options for BCC, making it difficult to stratify treatments based on effectiveness.⁴⁹ Excisional surgery appears to be the preferred treatment, and similar response rates at one-year post treatment have been reported for excisional surgery, curettage plus cryotherapy and photodynamic therapy.⁵⁰ The five-year recurrence rate for surgical excision of primary BCC has been reported to be less than 2%.⁵¹ Other treatments may be useful if surgical excision is contraindicated or poses an unacceptable risk (e.g. bleeding, scarring).⁵⁰ Excisional surgery is associated with fewer adverse effects compared to photodynamic therapy and curettage plus cryotherapy.⁵⁰ Photodynamic therapy has been reported to have better cosmetic outcomes than surgery for nodular BCC, but the five-year response to treatment is lower.⁵² Cryotherapy, with or without curettage, and curettage and cautery may also be effective treatments in the short-term (up to one year post-treatment).⁵⁰ For high-risk BCC, surgical excision, radiotherapy and Mohs' micrographic surgery are suitable options; other treatments are generally used for low-risk lesions.³²

Topical therapies (e.g. imiquimod applied five times weekly) are reserved for superficial BCC with a low risk of recurrence.³² Topical imiquimod may also be useful for primary nodular BCC,³² although it is not approved for this

Box 1. Treatments for BCC. Taken from Telfer *et al.*, 2008.³²

Treatment modality
Surgical
Curettage and cautery
Cryotherapy
Excision
Laser destruction
Mohs' micrographic surgery
Nonsurgical
Imiquimod 5% (<i>Aldara</i>)
Photodynamic therapy
Radiotherapy

indication in Australia. There is limited data on the efficacy of 5-fluorouracil for BCC, and it is not approved for this indication.⁴⁴

SCC

Most cutaneous SCCs are easily treated, and the cure rate is high.¹⁹ However, there is still a risk of recurrence or metastasis. There is limited data on the relative



Box 2. Risk factors for recurrence of BCC.
Modified from Telfer *et al.*, 2008.³²

- Larger tumour size
- Tumour site (particularly lesions on the central face)
- Poorly defined lesion borders
- Morphoeic, infiltrating and micronodular histological subtype
- Recurrent lesion(s)
- Immunosuppression

effectiveness of the various treatment options for SCC. In general, the treatment modalities for BCC can be used for SCC.⁷ Surgical excision, curettage with cautery, cryotherapy, 5-fluorouracil, imiquimod and Mohs' surgery may be used.⁷ Electrodesiccation and curettage, excision or cryosurgery can eliminate up to 90% of local tumours with a low risk of metastasis.⁵³

Conclusion

NMSC is largely preventable. Pharmacists should continue to promote sun avoidance and protection from sunlight, beginning in childhood, to minimise the risk of skin cancer. They can align their counselling and health promotional activities with public programs such as the 'Cancer Smart Lifestyle' and 'SunSmart' from the Cancer Council of Australia. The incidence of NMSC is rising, particularly in those over 60 years of age, and it is important that the public are educated to regularly have their skin checked to enable early detection of actinic keratoses and NMSC. For patients with actinic keratoses or NMSC, pharmacists can provide advice and counselling regarding the available treatment options.

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