Skin cancer basics for pharmacy

Pharmacies are often the first port of call for people with a skin complaint. Rod Tucker describes types of skin cancer and precancerous lesions and explains what to look out for and treatment options.

Skin cancers are common. There are two main types: melanoma and non-melanoma. Data for 2006 showed that there were over 81,600 cases of non-melanoma skin cancer registered in the UK. However, this is probably an underestimate and the real number of cases is more likely to be around 100,000 because there is incomplete recording of data.

Non-melanoma skin cancer

Non-melanoma skin cancer is the most common cancer in Caucasians and accounts for more than 95 per cent of all skin cancer in the UK. Fortunately, survival rates for this type of skin cancer are over 95 per cent. Non-melanoma skin cancer can be divided into basal cell carcinoma and squamous cell carcinoma.

Basal cell carcinoma

Basal cell carcinomas (BCCs; see Figure 1) arise from the basal layer of the epidermis and account for about 80 per cent of all non-melanoma skin cancers. These tumours are most commonly found on the head and neck. They are slow growing and rarely metastasise. However, they are also often referred to as a “rodent ulcers” because lesions are locally invasive, effectively burrowing into the skin, causing local tissue destruction and resulting in disfigurement.

The precise cause of BCC remains unclear although several epidemiological studies suggest a strong link with exposure to ultraviolet light. On the other hand, it is suggested that increased exposure to UV radiation may be a poor predictor for the development of BCCs because these lesions rarely occur on other areas of the body that would be exposed to a high incidence of UV radiation, such as the backs of the hands.

Over 50 per cent of BCCs show a defect in p53, a tumour suppression gene that is activated by UV irradiation. Mutations in other genes may also impact on the development of BCCs. A number of other factors, such as increasing age, skin type and sunburn in childhood, have been linked to the pathogenesis. The risk of BCC development is also increased in patients who are immunosuppressed (eg, patients on renal dialysis are often educated about sun protection).

Clinically, BCCs can appear as several different types (eg, nodular, macular). In the early stages, patients might complain of a small, raised slow-growing lesion that bleeds and does not heal properly. Once developed, a BCC tends to have a raised border with a central ulcerated area. Stretching the skin will often highlight the border and closer inspection will usually reveal the presence of small blood vessels on the surface of the lesion (telangiectasias).

Squamous cell carcinoma

Squamous cell carcinoma (SCC; Figure 2), arises in the superficial layers of keratinocytes. This type of skin cancer tends to present as a non-healing ulcer or growth. About 70 per cent of SCCs occur on the head or neck. The pinnae and lower lip are high risk areas.

A small percentage (3–4 per cent) of SCCs metastasise — in 2006 there were 577 deaths from non-melanoma skin cancers.

The association between SCC and exposure to sunlight is fairly well established. SCCs can be preceded by actinic keratoses, which are dysplastic intraepidermal lesions that present as rough scaly skin (see Panel 1). Another potential precancerous lesion is Bowen’s disease, which is full thickness intraepidermal dysplasia (see Panel 1).

Although the precise cause of non-melanoma (and melanoma) skin cancers at the molecular level is unclear, evidence is emerging to link actinic keratosis and SCC to ageing or senescent cells becoming resistant to apoptosis in response to stress or damage.

Reflect on knowledge gaps

1. What is actinic keratosis and how can it be treated?
2. What treatment options are available for basal cell carcinoma?
3. What is the ABCDE of melanoma?

Before reading on, think about how this article may help you to do your job better.
Melanoma
Melanomas are cancerous growths of the melanocyte cells in the basal layer of the epidermis. Non-cancerous growth of melanocytes leads to the formation of benign melanocytic naevi (i.e., moles) or ephelides (freckles). The incidence of melanoma has quadrupled since the 1970s. UK figures show that in 2006 melanomas were diagnosed in 10,410 people, of which there were 2,042 deaths.

Most melanomas arise in the skin but they can also occur in mucosal surfaces (e.g., eyes, oral cavity, lips, vagina). There are four basic types of skin melanoma:

- **Superficial melanoma** Superficial melanomas are flat, irregularly pigmented lesions that grow laterally in the skin before becoming invasive. This type of melanoma is thinner than the other types and most common (around 80 per cent of melanomas). It often occurs in younger patients.

- **Lentigo maligna melanoma** Lentigo maligna melanomas arise from pigmented lesions that often occur on sun exposed areas.

- **Nodular melanoma** Nodular melanomas are the most aggressive type of melanoma. They present as rapidly growing, pigmented nodules that bleed or ulcerate. (Both nodular and lentigo maligna melanomas tend to arise in older people.)

- **Acral lentiginous melanoma** Acral lentiginous melanomas arise as pigmented lesions, often on non sun exposed areas, such as the soles of the feet, palms of the hands or under nails.

Melanoma skin cancer is the most serious form of skin cancer with a much higher mortality than non-melanoma skin cancer. Once a melanoma starts to develop, it undergoes a phase of horizontal growth (i.e., spread). In later stages, growth is vertical and this is dangerous because the cancer can then spread from the dermis, via the lymphatic system to local lymph nodes or through the bloodstream to other organs (i.e., metastasis).

The mean age of presentation of melanomas is 55 years. The most common sites are the trunk (in men) and the legs (in women).

Despite the large increase in the incidence of skin cancer, it should be remembered that melanoma is rare. Moreover, evidence suggests that mortality has remained relatively stable over the past 30 years and has even begun to fall in some countries. Incidence may have increased due to greater reporting of early lesions. Although there are more melanomas reported in younger patients, these lesions tend to be thinner and associated with a better prognosis.

Panel 1: Precancerous lesions

**Actinic keratosis**
An actinic keratosis is often a marker for cumulative sun-induced skin damage and some authors suggest that these lesions are the precursors of up to 60 per cent of squamous cell carcinomas. Actinic keratoses can present in different ways. They might be flat or thick and can be flesh coloured or red. In general, they tend to have an erythematous base covered with scale (hyperkeratosis) and occur predominantly on the backs of the hands, the face, scalp and forehead. Patients often have multiple lesions.

The incidence of actinic keratosis is not known because it is not generally recorded. Nevertheless, it is higher in people with light skin and blue eyes and generally higher in men than in women. This gender difference is suggested to be due to the greater tendency for men to have outdoor occupations and hence receive greater sun exposure. It is suggested that in Australia, which has the highest level of skin cancers, 40–60 per cent of people over the age of 40 years have actinic keratosis.

Although more common with increasing age (reflecting cumulative UV exposure), the conversion rate of actinic keratoses into SCC is low (0.1 to 10 per cent) even in a high risk population. The risk in the general population is estimated to be less than 0.1 per cent.

Because actinic keratosis (and Bowen’s disease) is precancerous it is often treated. Fluorouracil or imiquimod are used (see main text). Topical diclofenac 3 per cent gel (Solaraze) is gaining popularity in primary care although efficacy has only been demonstrated in placebo-controlled studies. Its mechanism of action in actinic keratosis is unknown but may be related to reduced prostaglandin E2 synthesis. The gel should be smoothed into the skin twice a day. A pea-sized amount (0.5g) is suitable for a 3cm² area. No more than 8g should be used daily. The product is usually used for between 60 and 90 days, with maximum efficacy observed with longer duration. The manufacturer claims that a 30-day regimen gives complete resolution in 14 per cent of patients compared with 90 per cent with a three-month regimen. Lesions continue to improve once treatment is stopped. The most reported side effects include contact dermatitis, erythema, inflammation, irritation, pain and blistering.

**Bowen’s disease**
Bowen’s disease often presents as a slow growing single lesion on sun exposed areas. The lesion is erythematous with a sharply demarcated but irregular border which becomes hyperkeratotic. It should be noted that Bowenoid lesions can sometimes be misdiagnosed due to their resemblance to eczematous or psoriatic patches. The risk of conversion of a Bowenoid lesion to SCC is relatively low (3–5 per cent).

Melanoma risk factors
The precise cause of melanoma is still unclear. The presence of moles is the biggest risk factor. In particular, the atypical mole syndrome — a familial condition associated with a large number of atypical melanocytic naevi — is known to give rise to a significant increase in melanoma risk. For example, it is estimated that if a person has more than 100 moles they have as much as a 20-fold increased risk of developing melanoma. However, the rate of transfer from a
mole into a cutaneous melanoma is low and has been estimated at less than one in 200,000 for people under 40 years and one in 33,000 for men over 60 years.

Other factors that increase the risk for melanoma include age, being male, light hair and previous history of melanoma. Genetic factors have also been identified as impacting on the development of melanomas, particularly sunlight-induced cases. For example, a study of hospital patients with cutaneous malignant melanomas found that those with lesions on sun exposed sites had reduced DNA repair capacity compared with patients with melanomas on non-exposed sites. Between 5 and 10 per cent of patients with a melanoma have a family history of the condition.

The role of sunlight in the development of melanoma is not well understood but several epidemiological studies suggest a link. The basis for the association arises from the simple fact that the incidence is three to four times higher in sunny countries, such as Australia, than in the UK.

Studies have also looked at exposure patterns. A recent study found an increased risk in people who spent their childhood in sunny climes but risk is reduced if they arrived in such locations at an older age. In addition, a meta-analysis suggested that risk with intermittent sun exposure was higher than the risk with chronic sun exposure. There was also a strong association between higher risk and a history of sunburn. Measurement of sun exposure is difficult. Recording and coding methods vary considerably between studies and retrospective assessment of sun exposure is subject to recall bias. Nevertheless, the role of intermittent sun exposure as a risk factor has been shown to be a major factor in another review.

The relationship between the site of a mole and exposure to sunlight has also been investigated and it has been suggested that melanoma of the head and neck is associated with chronic sun exposure while trunk melanoma is associated with intermittent exposure.

The relationship between sun exposure and melanoma is also complicated by the fact that melanoma is rare in albinos. The role of sunlight has been further questioned recently and it has been suggested that genetic predisposition and other factors may play a larger role.

The relationship between the use of indoor tanning beds and melanoma is unclear.

In summary, there is good evidence from epidemiological studies that sun exposure is associated with an increased risk of melanoma, particularly in light-skinned patients. However, 80 per cent of melanomas in dark-skinned individuals are the rarer acral lentigious melanomas, which occur on the sole of the foot. This type of melanoma also occurs in those with intermediate pigmented skin such as Chinese, Japanese and Indian people and exposure to UV radiation is clearly not a factor.

**Prognosis of melanoma is directly related to tumour thickness**

**Recognising melanoma** For malignant melanoma, early detection and treatment is crucially important because once a lesion has metastasised, the cancer is often fatal.

A variety of aids have been developed to assist in the diagnosis of melanoma, including a simple seven-point checklist with major and minor factors (Panel 2) and an ABCDE mnemonic (Panel 3). These tools only apply to melanomas because these are the most serious type of skin cancers and need a higher level of vigilance.

Many melanomas can arise de novo although up to 50 per cent of these lesions may arise from a pre-existing naevus. Members of the public who present to pharmacists describing changing moles should be referred to the GP for further assessment. However, differential diagnosis of melanoma is difficult for GPs (who often have little training in dermatology) and there are a number of benign lesions that may be confused with a melanoma, including pigmented naevi, basal cell papilloma and pigmented dermatofibromas. The recent National Institute for Health and Clinical Excellence skin cancer guidelines recommend that all suspicious pigmented lesions should be referred for urgent specialist assessment via the two week suspected skin cancer referral pathway.

The use of biopsy for melanoma is not appropriate — the procedure may trigger metastasis.

**Treatment of skin cancers** Although malignant melanomas are the most serious form of skin cancers, non-melanoma cancers can be problematic. For instance, BCCs are associated with significant morbidity because they can cause local tissue destruction. Treatment of SCC lesions is necessary to avoid metastasis.

Non-melanoma skin cancers are not subjected to staging (see below). Diagnosis is based on clinical signs but differentiating between benign and malignant lesions can be difficult, requiring referral to a specialist. Non-melanoma skin cancers can be treated with a number of different approaches, but these all aim to remove or destroy the lesion.
Surgical excision is the most effective and, generally, the preferred method because tumours can be completely removed and this can be confirmed by subsequent histology. Curettage and cautery involves scraping away the lesion and cauterising bleeding points. Cryotherapy (directing a stream of liquid nitrogen at –190°C for up to 30 seconds and repeating the process after a few seconds) can also be used but may need to be repeated after six weeks. Photodynamic therapy is a relatively new option. It involves topical application of 5-aminolevulinate (Metvix) and irradiation of the area. This agent releases reactive oxygen species (free radicals) which lead to cellular destruction and hence resolution of the tumour. The technique is suitable for superficial SCCs and actinic keratoses. Its mode of action essentially involves activation of the immune system to release cytokines, such as alpha interferon, which mount a defence against viruses — hence its use in the treatment of warts. Imiquimod is also known to induce apoptosis of tumour cells at higher doses.

For BCC, the product should only be used where diagnosis has been confirmed by biopsy. GPs could, for example, perform a punch biopsy, where a probe is used to remove a sample of skin to send to the laboratory. The cream is applied before bedtime once a day for five days of the week for between six and 12 weeks. It should be left on overnight (eight hours) and washed off in the morning with soap and water. Any unused cream in the individual sachets should be discarded after use.

For actinic keratosis, the cream should be applied twice a week for up to 16 weeks. Application can increase the sensitivity of the skin to sunlight so patients should use a sunscreen every day (factor 15 would be sufficient). In some patients, imiquimod can cause local side effects such as erythema, scaling, erosion, scabbing and crustng of the skin. If these effects are severe or cause discomfort, treatment should be stopped for a few days. A rest period can help the skin to recover.

Panel 2: Seven point checklist screening tool for melanomas

<table>
<thead>
<tr>
<th>Major features</th>
<th>Minor features</th>
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<tbody>
<tr>
<td>Change in size</td>
<td>Diameter ≤ 6mm</td>
</tr>
<tr>
<td>Change in colour</td>
<td>Sensory changes</td>
</tr>
<tr>
<td>Change in shape</td>
<td>Oozing, crustning or bleeding</td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
</tr>
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If a pigmented lesion displays any of the three major signs or three minor ones, this should raise suspicion of a melanoma.

Panel 3: ABCDE checklist for melanomas

- **Asymmetry** A mole that, when divided in half, does not look the same on both sides
- **Border irregularity** A mole with wavy or jagged edges
- **Colour variation** Changes in colour of a mole, including darkening, spread of colour, loss of colours or the appearance of multiple colours
- **Diameter** The commonly used expression is a mole larger than a pencil eraser, although melanomas can be smaller (Generally, >6mm would warrant suspicion.)
- **Elevation** A previously flat mole that protrudes

Other signs of melanoma include moles that bleed, are fast growing, or that itch or hurt, a scaly or crusty growth on the skin and a sore that will not heal.

Topical therapies

Topical therapies include fluorouracil (Efudix) and imiquimod (Aldara). Efudix is licensed for the treatment of superficial BCCs as well as actinic keratoses and Bowen’s disease. The summary of product characteristics for Efudix points out it is not suitable for the treatment of deeper, nodular BCCs or SCC. Fluorouracil is an anti-metabolite and inhibits DNA and RNA synthesis, hence destroying any tissue that is rapidly proliferating (ie, tumour cells). The cream should be applied twice daily for at least six weeks (although 12 weeks might be needed in some cases). Hands should be washed after application. The cream gives rise to rather unsightly effects which generally follow a sequence of initial erythema, vesiculation, tenderness, erosion and necrosis before re-epithelisation. If patients find that their skin has become tender the prescriber may recommend the application of a steroid cream such as hydrocortisone or clobetasone.

Aldara is licensed for the treatment of superficial BCCs and actinic keratoses. Its mode of action essentially involves activation of the immune system to release cytokines, such as alpha interferon, which mount a defence against viruses — hence its use in the treatment of warts. Imiquimod is also known to induce apoptosis of tumour cells at higher doses.

For BCC, the product should only be used where diagnosis has been confirmed by biopsy. GPs could, for example, perform a punch biopsy, where a probe is used to remove a sample of skin to send to the laboratory.

The cream should be applied twice a week for up to 16 weeks. Application can increase the sensitivity of the skin to sunlight so patients should use a sunscreen every day (factor 15 would be sufficient). In some patients, imiquimod can cause local side effects such as erythema, scaling, erosion, scabbing and crustng of the skin. If these effects are severe or cause discomfort, treatment should be stopped for a few days. A rest period can help the skin to recover.

Treatment options for malignant melanomas are limited — prognosis can be poor. Survival from melanoma depends, as described, mainly on the Breslow thickness of the tumour. In terms of deciding how to treat a melanoma, it is important to know the extent of the lesion (ie, staging). There are five levels of staging. At stage 0 the lesion remains in the epidermis; at stages 1 and 2 the lesion has spread to surrounding tissue; at stage 3 there is regional lymph node involvement; and at stage 4 there are distant metastases.

If the melanoma remains in the epidermis it is easily cured by excision. Lesions should be excised with a 2mm margin of normal skin to allow for confirmation of the diagnosis by histology. After surgical excision, there is some weak evidence that adjunctive therapy with interferon alpha increases the chance of survival although the results from further trials are needed to confirm this benefit.

Once a malignant melanoma has produced metastases, treatment with chemotherapy is warranted.
Future treatments There have been some reports in the literature of patients who spontaneously recover from melanoma, suggesting that host immunity factors are somehow important. As a result, several studies have been undertaken using interferon alpha. Other studies have used another cytokine, interleukin 2. A recent meta-analysis of trials that involved either interferon alpha and standard chemotherapy or interleukin 2 for patients with metastatic melanoma, found that although inclusion of the cytokine improved the response rate to chemotherapy, there was no increase in survival. Interferon has been used in trials to determine whether it can prevent recurrence of melanoma once it has been surgically removed. The results so far have been disappointing.

Another avenue explored is the use of a melanoma vaccine. The principle is the same as conventional vaccine therapy, that is, it stimulates the immune system to produce antibodies to the antigens present on the surface of melanoma cells. Research suggests that vaccines can slow the growth of melanomas and, in some cases, the tumour will shrink. Unfortunately, it is still too early to provide any definitive answers on the effectiveness of vaccines and some of the phase III trials have been disappointing. Other potential therapies include the use of monoclonal antibodies.

A role for pharmacy
Pharmacists, who are often the first point of call for many patients with a skin problem, have an important public health role to play in helping patients to recognise the important signs and changes in moles that warrant referral. Early diagnosis can be life-saving.

In 2006, Superdrug introduced high street mole clinics where patients could have their moles checked for signs of malignancy. The clinics are run by specialist nurses and use digital dermoscopy to identify moles showing early signs of skin cancer. This technique illuminates and magnifies a lesion to highlight changes in it. However, concerns have been expressed about these services by the Drug and Therapeutics Bulletin. In an editorial (March 2009), it noted that nurses involved in the clinics had little training in the diagnosis of skin lesions and that there have been no studies to demonstrate that this service is comparable to that provided in hospitals by dermatologists. Clearly, the aim of the clinics is to provide an alternative to the norm and, ideally, primary care organisations in the future would commission services. In a further editorial (January 2010) the DTB reported evidence from a systematic review which found that although digital dermoscopy alone and digital dermoscopy with artificial intelligence are equally effective in the diagnosis of melanoma there is a lack of evidence that such techniques are suitable for use by non-experts. In 2008, the All-Party Parliamentary Group on Skin questioned whether such mole clinics could replace examination by a dermatologist. The DTB concluded that PCOs should not commission these services until robust evidence of the performance of these techniques in real-world settings exists.

Nevertheless, pharmacists can still play an important role in skin cancer, be it counselling on the use of 3 per cent diclofenac gel or advising someone to see a GP about a mole. They can also take part in educational campaigns, such as SunSmart, to raise public awareness of the potential dangers of overexposure to the sun and encourage people to examine their skin for signs that might indicate a cancerous lesion. Sun protection strategies were discussed in previous CPD articles (PJ, 28 March, 2009, pp347–50 and 11 April, 2009, pp419–22).

References
5. Menzies SW. Sun exposure is a major cause of melanoma. British Medical Journal 2008; 337:204

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CPD articles are commissioned by The Pharmaceutical Journal and are not peer reviewed.

Act: practice points
Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist’s CPD portfolio.
1. Make sure you are prepared to advise on the effects of Efudix — visit the BBC website for pictures and a description of the changes induced by fluourouracil by BBC Radio Nottingham’s John Holmes.
2. Display a poster about skin cancer or the SunSmart campaign (available to download at www.cancer researchuk.org).
3. Make sure your immunocompromised patients have been advised on sun protection.

Evaluate
For your work to be presented as CPD, you need to evaluate your reading and any other activities. What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

Record
Consider making this activity one of your nine CPD entries this year.