Skin cancer

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Skin cancer can usefully be classified into two types on the basis of biological and clinical differences:

- melanoma skin cancer, arising from malignant transformation of the neural crest-derived melanocytes
- non-melanoma skin cancer (NMSC).

The majority of NMSCs are keratinocyte-derived tumours such as basal cell carcinomas (BCC) and squamous cell carcinomas (SCC). Other tumour types such as Kaposi sarcoma and cutaneous T cell lymphoma can also be included in this group, but they will not be considered further because they are relatively uncommon, and their biology and clinical behaviour are so different from other forms of NMSC.

The clinical contrast between melanoma and BCC and SCC could not be more striking. For many Caucasian populations, NMSC is the commonest human malignancy, outnumbering all other cancers combined; morbidity and mortality are low, and therapy usually straightforward and effective[1,2]. By contrast, melanoma incidence is one to two orders of magnitude lower, but case fatality is about 25%, and treatment of all but the earliest lesions dismal[3,4]. These tumour types, however, have at least two things in common, in that they are both related to sun exposure, and the necessary diagnostic suspicion relies almost entirely on clinical skills.

Causes of skin cancer

The evidence implicating sun exposure as the major determinant of NMSC is overwhelming:

- tumours are most common on exposed body sites
- they are more common in Caucasian populations living in areas of high ambient ultraviolet radiation (UVR) exposure
- migrant studies also implicate sun exposure[5].

Perhaps even more convincing is the evidence provided by genetics[6]. NMSC is at least 50 times less common in those with black skin, whereas individuals with xeroderma pigmentosa (who have a defect in a specific form of DNA repair required to correct UVR-induced damage) have a several thousand-fold greater risk of developing both NMSC and melanoma[6].

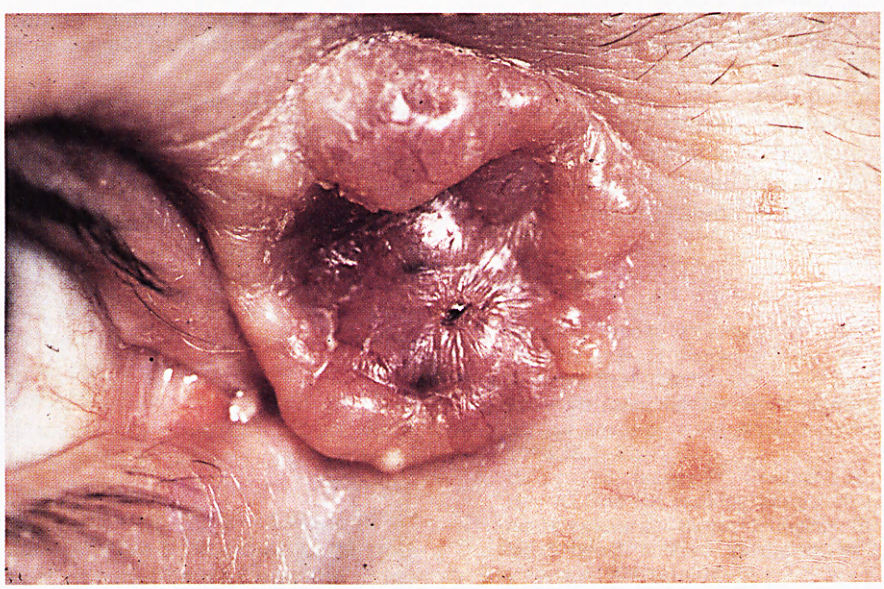
The carcinogenic effects of UVR act through several mechanisms. UVR is mutagenic, it can act as a tumour promoter and, at least in experimental systems, decreases the functioning of the cutaneous immune system. Ultraviolet radiation B (UVB) appears more carcinogenic than ultraviolet A (UVA) radiation but, since UVA exposure is greater, the attributable risk from UVA may still be important. The combination of psoralens and UVA (PUVA), as used in therapy for psoriasis, is also a cause of NMSC[1].

Other causes of NMSC, such as X-irradiation, arsenic exposure, or Mendelian-inherited dermatoses[6], for example Gorlin's syndrome (multiple BCC, medulloblastoma, dysmorphic face and odontogenic cysts), are unimportant in comparison with UVR. Organ transplant patients receiving immunosuppression show a relative risk for NMSC of up to 200-fold, and the majority of these patients develop skin cancer or related lesions[7]. Recent studies suggest that the immunosuppressive regimen used may be important[8]. There is evidence that the immunological effects of a foreign organ *in situ* may also be relevant.

Non-melanoma skin cancer

Basal cell carcinoma. BCC is 5–10 times more common than SCC, with perhaps 5% of individuals developing one or more such tumours. Classically, they are slow growing, ulcerated lesions, with a pearly and telangiectatic edge (Fig 1) occurring on the face of an elderly individual[1,9,10]. This is a misleading description for many lesions. An increasing number occur on the trunk, the morphoeic type of BCC has an edge that is frequently

Figure 1. Basal cell carcinoma adjacent to the eye.



difficult to define, and superficial BCCs, which are common on the trunk, can be easily mistaken for Bowen's disease or even for a patch of eczema. BCCs are probably hair follicle-derived tumours (they are almost unheard of on the palms or soles), they are locally invasive but rarely metastasise (<1:4,000), and overall morbidity is low with fatality extremely rare. Nevertheless, invasion of underling structures such as bone or tumour tracking along nerves into the cranium can be a significant clinical problem. The morphoeic type of BCC, with poorly defined margins situated near the eye, is easily underestimated and inadequately treated.

Squamous cell carcinoma. The relation with cumulative sun exposure is stronger for SCC than for any other skin tumour. SCCs characteristically occur on the face, the scalp of balding men and the backs of the hands. Their appearance and clinical behaviour is highly variable, but typically these lesions are keratotic and 'untidy', occurring on sun-damaged skin, often ulcerated and sometimes secondarily infected. By definition, SCC is invasive and, unlike BCC, readily capable of metastasis which can occur in up to a few percent of cases in some series[1,11]. The aggressiveness of SCC depends on body site: keratinocyte-derived SCC of the lip or mouth and SCC arising in (thermal) burn sites or on the ear (debatably) are more aggressive than other cutaneous SCC[11].

Other related lesions. Intriguingly, BCC has no known precursor, whereas actinic keratoses (AK) (Fig 2) and Bowen's disease are thought to be pre-malignant precursors of SCC[12]. AKs are small, scaly red areas on sun-exposed sites characterised histologically by focal dysplasia. They are extremely common and frequently multiple; in some surveys, over half the population of Australia aged over 40 has one or more lesions. Their relation to SCC is still subject to enquiry. The rate of progression from an AK to an SCC has been estimated as one per 1,000 cases per year, with perhaps a quarter of AKs resolving without therapy each year, but many SCCs arise without an obvious precursor AK or Bowen's lesion[13]. It remains possible that AK is not an SCC precursor, but merely cognate, both lesions being caused by sun exposure. Bowen's disease may progress to SCC; clinically, it appears as a red scaly plaque on the lower legs of elderly women that might easily be misdiagnosed as a plaque of psoriasis (the predisposition for the lower leg is not entirely explained). Bowen's disease is more

Key Points

CAUSES OF SKIN CANCER:

- UVR is the major cause of both melanoma and NMSC. A causative role for UVB is proven; the jury is still out with respect to UVA
- UVR acts as a mutagen, tumour promoter and, at least experimentally, inhibits the cutaneous immune response
- The quantitative relation with UVR differs between tumour types
- PUVA used therapeutically causes NMSC
- Certain forms of immunosuppression (eg following organ transplantation) are associated with increased risk of NMSC
- Skin pigmentation is the major genetic risk factor for skin cancer
- The contribution of Mendelian disorders to skin cancer, such as Gorlin's syndrome (BCC) or familial melanoma, is small

NON-MELANOMA SKIN CANCER:

- NMSC is the commonest human malignancy
- There is low morbidity
- Treatment is highly effective, and usually straightforward, with choice of surgery, radiotherapy or cryotherapy. There are no adequate studies to dictate clinical practice
- Accurate clinico-histopathological diagnosis is important

MELANOMA:

- Incidence is increasing in most populations studied; some think that this is partly accounted for by increased sampling of lesions unlikely to progress
- Death is because of metastasis, and little progress has been made in treating metastatic disease
- Epidemiological studies suggest important birth cohort effects in some populations, with mortality declining for individuals born after mid-century
- Efficacy of population-based primary or secondary prevention is unproven

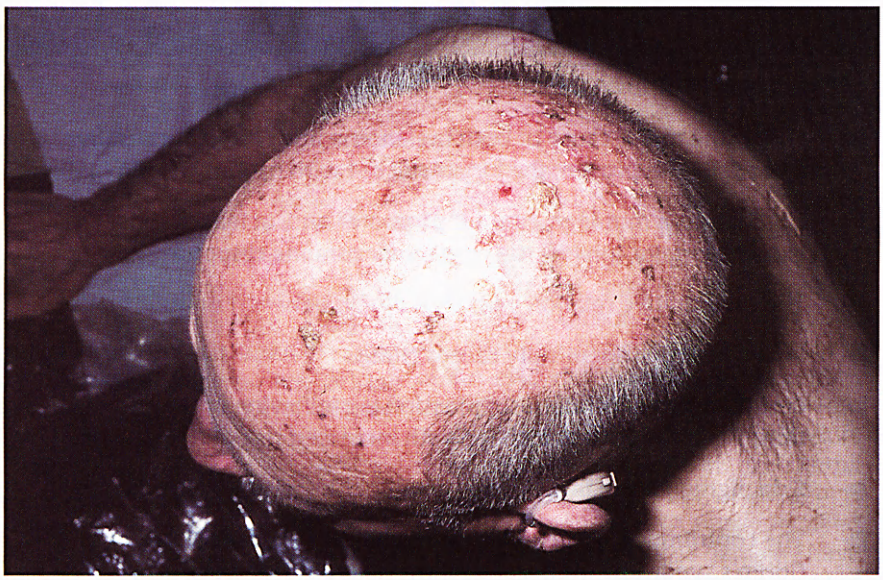


Figure 2. Multiple actinic keratoses on the background of heavily sun-damaged skin.

common in individuals with high sun exposure, and lesions are also common at other body sites. Histologically, Bowen's disease comprises full thickness dysplasia, and 'progression' to SCC is apparent in some biopsies.

Keratoacanthomas. These interesting lesions are clinically and histologically similar to SCC[14]. They appear rapidly over a 2–3 month period before involuting spontaneously, leaving a scar. Opinion is divided whether they are SCCs that regress either spontaneously or in response to the immune system, or are different *de novo* from SCC.

Treatment of non-melanoma skin cancer

Therapy for the majority of BCC and SCC is straightforward, relying on destruction of the tumour. BCC can be treated by excision, radiotherapy, curette and cautery, or cryotherapy. There are no satisfactory comparative clinical trials; in everyday practice, therapy is often dictated by local expertise (or the lack of it)[9–11]. Tumours near the eye merit particular attention. Recurrence rates of 5–10% are quoted for BCC after various types of therapy, but in most cases the recurrence can be easily re-excised[9,10]. It may seem counterintuitive, but histological evidence of incomplete excision does not mean a clinical recurrence will occur, and a wait and see policy is often pursued.

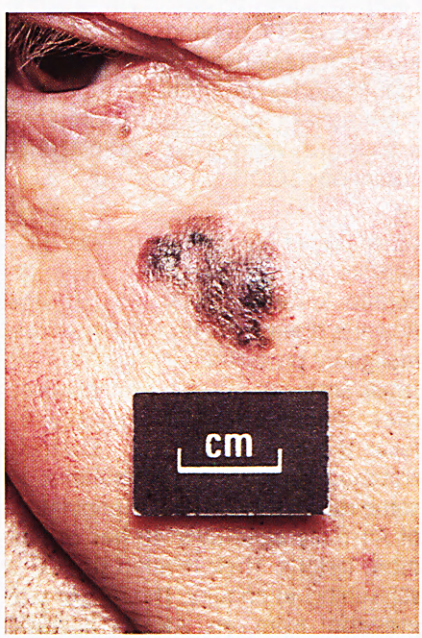
Various treatments may also be used for SCC[11]. The potential for metastasis, particularly from poorly differentiated tumours, necessitates prompt, accurate histological diagnosis, and treatment – usually with either excision or radiotherapy. Although treatment of either BCC or SCC is often straightforward, management is inappropriate by those unfamiliar with the various forms of treatment and, in particular, without dermatopathological expertise.

Melanoma (Figs 3 & 4)

Melanoma incidence appears to have increased in most Caucasian populations surveyed, with a doubling over the last 20 years, case fatality remains high at about 25%, and the initial enthusiasm for primary or secondary prevention has not yet led to studies demonstrating its efficacy[3,15–17]. Recent progress has centred less on improvements in therapy – in general, there have not been any – but more on understanding the genetics of inherited predisposition to melanoma, and the relation between melanoma incidence and sun exposure. The mainstay of clinical management remains early diagnosis, based on a high level of clinical suspicion, and adequate excision (although trials continue to determine what is 'adequate'). Once the tumour has metastasised, therapy is largely palliative, although research approaches based on the new biology show considerable promise[18].

Up to 5% of melanomas in some series are familial and follow an autosomal dominant pattern with incomplete inheritance[19]. Mutations in the p16 tumour suppressor gene[20] or its physiological complement, the oncogene cyclin-dependent kinase 4, underlie the inherited predisposition in some of these families[21]. In some kindreds, apart from showing a high incidence of melanoma, the phenotype is characterised by large numbers of atypical naevi (>100), including naevi on such sites as the scalp, buttocks, palms and soles. A similar phenotype can also be seen sporadically or without a history of melanoma, although its quantitative

Figure 3. Lentigo maligna melanoma.



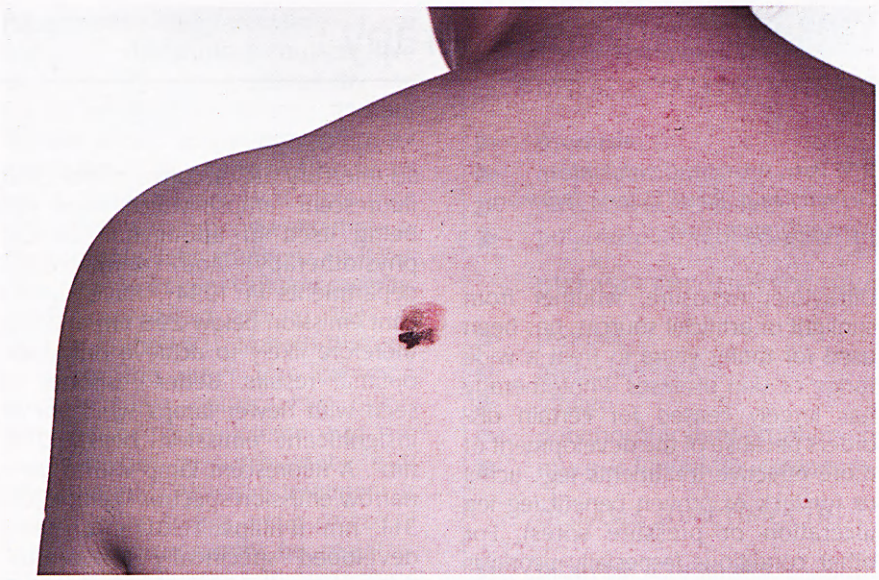


Figure 4. Malignant melanoma developing in pre-existing melanocytic nevus.

significance is unclear in the absence of a family history of melanoma. These patients require dermatological assessment, including a detailed family history and preferably examination of other family members.

UVR is a major determinant of melanoma, but the position is not as straightforward as for SCC. Although melanoma is more common in Australia than the UK, and migrant studies implicate early childhood exposure, the body site incidence of melanoma suggests either other co-factors or a different dose-response with UVR. This, together with a higher incidence in those intermittently exposed to UVR rather than in those with higher cumulative doses of UVR, has led to the idea that intermittent sun exposure is important. The emphasis on 'burning' as a cause rather than as a risk factor, though receiving wide coverage, may be misplaced[4,15].

Melanoma mortality has increased by 5–10% per year in most Caucasian populations surveyed[4]. These changes are reasonably attributed to changes in sun exposure patterns, although objective evidence of changes in individuals' sun exposure to support such a correlation is not available. Cohort analysis of Australian mortality data shows that mortality for successive birth cohorts has been declining for the last 50 years[22]. The interpretation of these data is speculative; whilst changes in detection and earlier presentation may have contributed, studies favour some as yet unknown change in the environment decreasing melanoma risk for those born in the last half century.

More recently, large annual increases in melanoma incidence of 15–40% have been reported from some centres. These changes have been largely unaccompanied by a rise in mortality or a decrease in incidence of thicker tumours, and are thought to represent an increased sampling of lesions which, whilst having the histological features of malignant melanomas, follow a benign clinical course ('non-metastasising melanoma')[4,16]. Time will tell whether this interpretation is correct; for the present, lesions showing the histological features of melanoma must continue to be managed as aggressive tumours with a propensity to early metastasis.

Secondary prevention of melanoma relies on early detection and biopsy of suspicious lesions. Changes in a pre-existing mole such as itching, increase in size, change in colour, or the development of an irregular edge are all sensitive markers for melanoma, but they have a low specificity and, despite wide attention, are unlikely to be appropriate for population-wide screening[18]. In everyday clinical practice, a high level of suspicion for melanoma is required, particularly opportunistic detection, coupled with prompt referral and, if necessary, excision biopsy. Interpretation of pigmented lesion histology requires specialist dermatopathological expertise if related but benign lesions such as Spitz naevi are not to be inappropriately labelled as melanomas.

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Ultraviolet phototherapy

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Ultraviolet exposure, whether from sunlight or artificial sources, has been used for many years to treat a wide range of skin diseases. Phototherapy has largely ceased for certain disorders because of the development of more effective treatments (eg acne) or for lack of proven benefit (eg leg ulceration or pressure sores). For other conditions (especially psoriasis and eczema), various forms of phototherapy are used more widely, and with greater effect, as more is understood about the action of different wavelengths. There is increased use of phototherapy in the hospital setting, and at home with the use of sunbeds by patients and those with normal skin, despite continuing advice from dermatologists about the harmful effects of ultraviolet radiation (UVR) on the skin and the desirability of minimising exposure to sunlight.

The ultraviolet region of the electromagnetic spectrum is subdivided by wavelength:

- UVA: 420–320 nm
- UVB: 320–290 nm
- UVC: 290–200 nm

Wavelengths below about 295 nm are not found in terrestrial sunlight.

Ultraviolet B phototherapy

Psoriasis

The improvement in psoriasis that frequently follows exposure to natural sunlight led to the development of treatment with UV-emitting lamps, often used in combination with tar (Goeckerman regimen) or dithranol (Ingram regimen). Psoriasis does not improve if treated with wavelengths below 296 nm (UVC and short wavelength UVB), even though erythema (sunburn) is easily achieved[1]. Lamps used traditionally for treating psoriasis (mercury arc or conventional UVB fluorescent lamps), which were still being used in about half of UK physiotherapy and dermatology departments in 1994[2], have significant emission below 296 nm and are therefore likely to achieve only suboptimal results. Better response is seen with newer lamps which have insignificant emission below 296 nm[3]. A fluorescent lamp with a very narrow emission spectrum centred on 311 nm (Philips TL-01) has been developed specifically for phototherapy of psoriasis[4]. No randomised trials using clearance of psoriasis as the end-point have been published, but several reports[4,5] suggest that better results are achieved with these 'narrow-band' lamps than with conventional UVB lamps, and that they may even be as effective as psoralen and UVA (PUVA) therapy.

No association has been demonstrated between UVB phototherapy for psoriasis and melanoma or non-melanoma skin cancer, although there have been no large epidemiological studies. Studies in mice suggest that the new narrow-band UVB lamp is likely to be more carcinogenic than conventional lamps, but it has been argued that the faster response to treatment reduces any risk to that equivalent to, or even less than, that of conventional phototherapy[6].

Other disorders

Atopic dermatitis. Phototherapy is also used increasingly in atopic dermatitis, with the intention of reproducing the benefit reported by many patients following sun exposure. Several studies have documented improvement of atopic dermatitis with UVA[7], conventional[8] or narrow-band UVB[9]. It is, however, difficult to assess disease severity in atopic dermatitis, and there have been few placebo-controlled trials.