CHAPTER 1

# The epidemiology, aetiology and prevention of melanoma

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**OVERVIEW**

- Over the last three decades, incidence rates of melanoma in the UK have increased every year. Increments in mortality have been smaller, and melanoma accounts for 1–2% of total cancer deaths.
- Incidence of melanoma is greater in females, whereas mortality from melanoma is greater in males.
- Melanoma is a cancer seen predominantly in pale-skinned people and the dominant behavioural risk factor in Europe is acute intermittent sun exposure on sunny holidays.
- Risk factors for melanoma include red hair and freckles, skin which burns in the sun and a positive family history.
- The Atypical Mole syndrome is a phenotype associated with the presence of over 100 moles and two or more atypical moles. This is the most potent phenotypic risk factor for melanoma.
- Rare families exist in which multiple cases of melanoma occur and a proportion of these families have hereditary mutations in the *CDKN2A* gene.
- Behaviours that protect against strong sunlight should be encouraged among patients at risk of melanoma. A simple message is: 'don't burn, don't tan'.

Melanoma is the eighth most common malignancy in the UK. In 2003, there were 8114 new cases and 1777 deaths. Incidence rates have increased every year for the last three decades, faster than that of any other major cancer, making melanoma an increasing public health concern. Despite this, increments in mortality have been smaller, and melanoma accounts for only 1–2% of total cancer deaths in the UK. One-third of patients are under the age of 50, and approximately 15 years of life are lost for each death, placing melanoma amongst the top five cancer causes of lost life-years.

## Epidemiology

In the UK, the incidence of melanoma has more than tripled over the last 25 years to age-standardized rates of 11.1 per 100 000 in men and 12.6 per 100 000 in women in 2003 (Figure 1.1). The increase in incidence has been greatest for melanoma under 1 mm in Breslow thickness. It has been proposed that this increasing trend may be an epiphenomenon attributed to earlier detection, better surveillance and changes in diagnostic criteria. However, available evidence suggests much of the rising incidence is real.

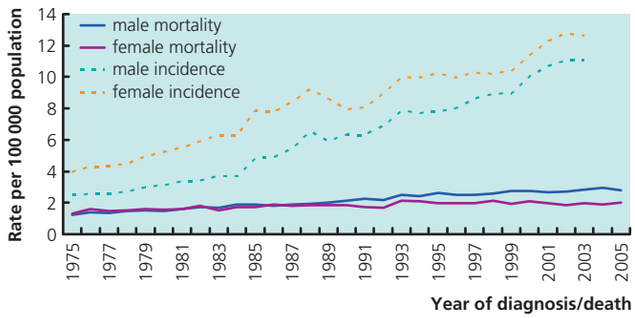


**Fig. 1.1** Age-standardized (European) incidence and mortality rates of melanoma by sex in Great Britain between 1975 and 2005.

Mortality rates have also significantly risen over the last 25 years (Fig. 1.1), but at a much slower pace as tumours < 1 mm in Breslow thickness have a good prognosis. In contrast to incidence, mortality is greater in men, with male deaths outnumbering female deaths almost twofold. The rise in melanoma mortality has been greatest among men aged > 65 years, who present late with thick (> 4 mm in Breslow depth) advanced tumours that have a poor prognosis. Reasons for this include the tendency for melanoma to be located on the back in males where they are hard to see, lack of self-examination and a tendency for not reporting changing moles.

## Risk factors

The most common types of primary cutaneous melanoma – superficial spreading melanoma (Fig. 9.3), nodular melanoma (Fig. 9.4) and lentigo maligna melanoma (Fig. 9.5) – are cancers of white-skinned people and are associated with a number of well-established risk factors (Table 1.1). Rarely, melanoma occurs on the palms and soles, nail apparatus and genital and sinonasal mucosa (Fig. 9.6). These rare subtypes are equally common in all ethnic groups irrespective of skin colour, and are of unknown aetiology.

Certain heritable traits such as red hair and freckles are associated with an increased relative risk for melanoma of about 3. The most potent risk factor, however, is the presence of increased numbers of moles (benign melanocytic naevi) and the presence of bigger moles with an irregular or ill-defined edge, known as atypical moles. Moles are acquired proliferative lesions, which appear from early childhood until mid-adult life, when they start to reduce in number. In-

**Table 1.1** Risk factors for melanoma. Note that many of these factors are interdependent and have not been subject to multivariate analysis, so cannot be used to compute the precise risk of melanoma for a given individual.

| Risk factor | Relative risk |
|---|---|
| *Physical characteristics* | |
| Fair skin (that burns easily and does not tan) | 1.4 |
| Light eye colour | 1.6 |
| Red or light-coloured hair | 1.4–3.5 |
| Freckles | 1.9–3.5 |
| *Number of benign melanocytic naevi (>2 mm)* | |
| 11–50 | 1.7–1.9 |
| 51–100 | 3.2–3.7 |
| >100 | 7.6–11 |
| *Number of atypical moles* | |
| 1–4 | 1.6–7.3 |
| >5 | 5.7–8.6 |
| *Family history* | |
| Melanoma in one first-degree relative | 2.4–3.0 |
| Melanoma in three or more first-degree relatives | 35–70 |
| *Others* | |
| Single blistering sunburn | 2.0–3.0 |
| Regular sunbed use (starting under the age of 35) | 1.8 |
| Higher social class | 3.0 |

dividuals living in hot countries, such as Australia, have more moles then those living in Europe, implying that they are induced by sun exposure. However, twin studies provide good evidence that the number of moles is also determined genetically. As large numbers of moles are a risk factor for melanoma, it is hypothesized that that mole genes are also low-risk melanoma susceptibility genes. Two per cent of the UK population have the Atypical Mole syndrome (Fig. 1.2, Box 1.1), which is a phenotype associated with both large numbers of moles (more than 100 moles >2 mm in diameter) and moles which are atypical (being larger than 5 mm in diameter with an irregular shape and colour). Patients with the Atypical Mole syndrome have a significantly increased risk of melanoma.

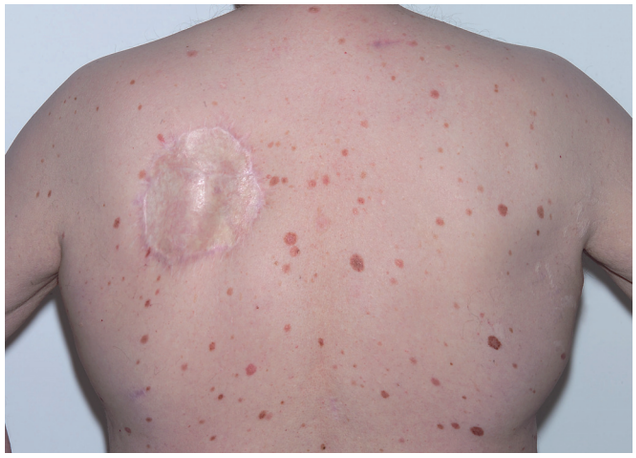

**Fig. 1.2** The back of a patient with Atypical Mole syndrome. Note the scar from wider excision of a melanoma.

Box 1.1 **Atypical Mole syndrome**

One definition of the Atypical Mole syndrome is the presence of two or more of the features listed here. Using this definition, 2% of the UK population have the Atypical Mole syndrome and are at a greater risk of developing melanoma.

- ≥100 naevi >2 mm (≥50 if aged <20 years or >50 years)
- 2 or more atypical naevi
- 1 or more naevi on the buttocks
- 2 or more naevi on the dorsal feet

## Sun exposure

Ultraviolet (UV) B accounts for 5% of the UV radiation in natural sunlight and is the major cause of skin cancer and sunburn. UVA accounts for 95% and is contributory. Melanoma is most common in people who are pale skinned and who tend to burn in the sun. This is evidence for sun exposure as its environmental cause. The incidence of melanoma is highest where fair-skinned people live at low latitudes such as Australia, which is further evidence for sun exposure as causal. The recent increase in incidence has been attributed to changes in social attitude and behaviour over the last century. Past social convention prevented exposure of much of the skin. This has now changed, with large proportions of the population exposing nearly all of their skin intermittently to sudden large doses of sunlight (Fig. 1.3). Epidemiological studies have supported the view that the key behavioural factor for melanoma is acute intermittent exposure to strong sunlight, such as on sunny holidays. Case–control data have also repeatedly identified sunburn as a risk factor for melanoma, especially in early life. Chronic low-dose over-exposure seen in outdoor workers does not appear to be so clearly related to melanoma risk in Europe, but may still be causal in a proportion of cases. This sort of over exposure is more closely related to the risk of cutaneous squamous cell carcinoma (SCC).

## Sunbeds

There is strong evidence to suggest that exposure to sunbeds increases the risk of melanoma and SCC. A recent systematic review concluded the relative risk for melanoma was 1.8 among regular

**Fig. 1.3** The type of sun exposure which is held to be most likely to produce melanoma in Europe is short, intense exposure in fair-skinned indoor workers, of the type seen on sunny holidays, rather than chronic cumulative sun exposure.

users of sunbeds who start before the age of 35. This is concerning, as up to 7% of the UK population may use sunbeds. Proponents of the cosmetic tanning industry continue to argue that sunbed use is required to maintain adequate vitamin D levels and an indoor tan protects against sunburn from subsequent exposure to sunlight. Although winter vitamin D levels may be inadequate in some individuals, alternative sources of vitamin D are more appropriate. Furthermore, skin that has been tanned using sunbeds (which emit a greater UVA to UVB ratio than natural sunlight) is less protected from sunburn than an equivalent natural tan.

## Family history and melanoma susceptibility genes

A positive family history of melanoma is also a risk factor for melanoma. A study from the Swedish Cancer Registry estimated the standardized incidence ratio (approximating to relative risk) for melanoma to be 2.4 for offspring if one parent had a melanoma and 3.0 for a sibling. Rare families exist in which large numbers of cases of melanoma occur, and the majority of these families have hereditary mutations in a gene called *CDKN2A*, which codes for two proteins, P16 and P14ARF. Even rarer families have mutations in a gene coding for *CDK4*. Other high-risk genes remain to be identified.

In most *CDKN2A* mutation-positive families in the UK and Australia, family members appear to be at increased risk of melanoma alone. In families with *CDKN2A* mutations living in North America and in some parts of Europe, there is also an increased risk of pancreatic cancer (Fig. 1.4). The frequency of CDKN2A mutations is 20–40% in families where there are three or more affected first-degree relatives, and < 5% if there are only two. This means that hereditary mutations are responsible for a very small proportion of melanoma. The penetrance of CDKN2A mutations, and factors which moderate the penetrance, are poorly understood. Gene testing for mutations is therefore of limited clinical utility at present and is best restricted to the research setting.

## Racial variation

Although melanoma occurs most commonly in individuals with white skin, it can occur in all races. Recent American data have shown the age-adjusted incidence of melanoma per 100 000 in different ethnic subtypes to be 18.9 in Whites, 4.0 in Hispanics, 1.5 in Far East Asians and 1.0 in Blacks. The lower incidence of melanoma in ethnic groups is attributed to the protective effects of epidermal melanin against UV radiation, which, in very dark black skin, affords a Sun Protection Factor (SPF) equivalent to 13.4. The majority of melanoma in non-White populations occurs on sun-protected sites such as the palms, soles and mucosal surfaces. However, some data have shown that lighter-skinned Hispanics tend to develop melanoma on sun-exposed sites in a similar distribution to Whites compared with dark-skinned Hispanics. This suggests that the degree of pigmentation in ethnic groups may influence the site and incidence of melanoma. This is of particular relevance given the increasing proportion of mixed races who have intermediate pigmentation in Western countries.

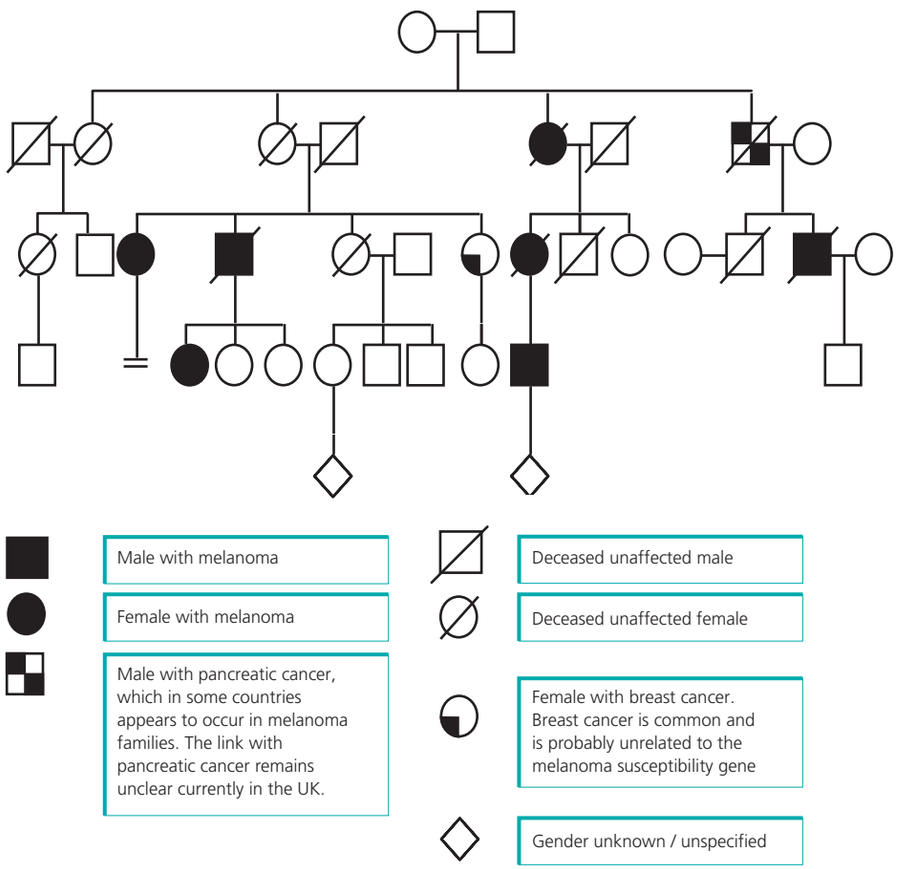


**Fig. 1.4** This family tree illustrates the pattern of cancer seen in families with hereditary mutations in the *CDKN2A* gene, which are transmitted in a dominant fashion with incomplete penetrance.

## Primary prevention

It is likely that the incidence of melanoma can be reduced by widespread reduction in exposure to strong sunlight, particularly by children and young adults. Complete sun avoidance is clearly impractical – a simple message to patients is 'don't burn, don't tan'. This can be achieved by following the SunSmart Code (Box 1.2). When a sunscreen is used, a broad-spectrum product that protects against UVA and UVB, with an SPF rating of ≥30 should be chosen.

### Sunscreens

Case-controlled studies into sunscreens have not consistently supported their beneficial effects in reducing melanoma. This is probably because many of these studies are subjected to significant confounding and bias, and were conducted before newer, more efficacious and better accepted sunscreens were introduced. The SPF rating of a sunscreen is the factor by which it protects from UVB erythema (early sunburn) and is based on controlled phototesting of untanned skin at an even application thickness of 2 mg/cm$^2$. For example, a product with an SPF of 15 allows an untanned individual to withstand 15 times the amount of UVB before developing erythema. In reality, most individuals do not use enough sunscreen, typically applying only 0.5–1.0 mg/cm$^2$. Application thickness is often uneven, may decrease after water exposure, and re-application may be inadequate. Consequently, the effective SPF of a sunscreen may be one-third of the nominal SPF. When sunscreens were first popularized in the early 1980s, the median SPF was 4–6. Some older sunscreens permitted high levels of UVA exposure to facilitate tanning and avoid burning, which might paradoxically have increased risk of skin cancer. Current sunscreens are more effective, protecting against UVA as well as UVB with typical SPF values of ≥20. The impact of these newer sunscreens on melanoma prevention may take several decades to be demonstrated.

Box 1.2 **The SunSmart Code – from SunSmart, the UK's national skin cancer prevention campaign (http://info.cancerresearchuk.org/healthyliving/sunsmart). The authors and editors would advise that if a sunscreen is used, it should block ultraviolet (UV) A and UVB with a Sun Protection Factor of ≥30.**

**S**pend time in the shade between 11 and 3
**M**ake sure you never burn
**A**im to cover up with a t-shirt, hat and sunglasses
**R**emember to take extra care with children
**T**hen use factor 15+ sunscreen

Also, report mole changes or unusual skin growths promptly to your doctor.

### Sun-protective clothing

The degree to which clothing impedes penetration of UVR is known as the Ultraviolet Protection Factor (UPF) and is based on the fibre content and weave, colour, finishing process and the presence of additives. Almost 90% of summer clothing has a UPF of >10, and 80% has a UPF of >15. Clothing is therefore a reliable and effective method of photoprotection, and should be encouraged.

## Further reading


Bishop JA, Wachsmuth RC, Harland M *et al*. Genotype/phenotype and penetrance studies in melanoma families with germline CDK2NA mutations. J Invest Dermatol 2000; 114:28–33.

Cancer Research UK. UK Malignant Melanoma statistics. Available at http://info.cancerresearchuk.org/cancerstats/types/melanoma/?a=5441

Diffey BL. Is daily use of sunscreens of benefit in the U.K.? Br J Dermatol 2002; 146:659–62.

Downing A, Newton-Bishop JA, Forman D. Recent trends in cutaneous malignant melanoma in the Yorkshire region of England; incidence, mortality and survival in relation to stage of disease, 1993–2003. Br J Cancer 2006; 95:91–5.

Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P *et al*. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer 2005; 41:45–60.

Gloster HM, Neal K. Skin cancer in skin of color. J Am Acad Dermatol 2006; 55:741–60.

Hemminki K, Zhang H, Czene K. Familial and attributable risks in cutaneous melanoma: effects of proband and age. J Invest Dermatol 2003; 120:217–23.

International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer. The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: a systematic review. Int J Cancer 2007; 120:1116–22.

Newton-Bishop A, Harland M, Randerson-Moor J, Bishop DT. The management of familial melanoma. Lancet Oncology 2006; in press.