Melanoma

Julia A Newton Bishop

Cutaneous melanoma is becoming more common. Although still rarer than some cancers it is important, particularly as it afflicts young adults relatively frequently. Furthermore early detection with resultant better prognosis should be achievable if the public was to become more aware, and if health-care professionals were more familiar with melanoma and the behaviour of normal moles.

Melanoma is a tumour arising from melanocytes. Up to 40% develop in melanocytic naevi, but a significant percentage arise de novo from normal skin (Mackie, 1988).

EPIDEMIOLOGY

Melanoma is a tumour of adult life. Cases have been reported in children but very rarely prepubertal children. It differs, however, from most common cancers in having a relatively flat age distribution curve, so that it is relatively more common in young adults and accounts for a significant proportion of cancer deaths of young adults.

Melanoma is a tumour largely of white peoples, the incidence is very low in black and asian peoples and the greatest incidence is in white people living at low latitudes such as Queensland, Australia. *Figure 1* shows the differences in incidence of melanoma at different ages in the USA, Australia and in Europe.

This observation lead to the suggestion that sun exposure is important in the pathogenesis of the tumour. The incidence of melanoma in Europe, North America and Australia has roughly doubled every 10 years in the last 40 years and this increase has been attributed to changing patterns of behaviour in the sun. Coco Chanel invented the 'suntan' and since the 1920s the pattern of behaviour in the sun has completely changed. Never before has human skin been exposed to the sun as it is now every summer on beaches around the world. Armstrong and Kricker (1993) estimated that around 70% of cases of melanoma may be attributed to sun exposure. It seems likely that other environmental exposures may be identified as risk factors for melanoma but sun exposure is likely to remain the principal one.

GENETICS

Familial melanoma occurs rarely: in the UK around 5% of cases give some sort of family history. In 1% or so, that history is strong, with several cases within the family. These families carry high penetrance susceptibility genes and these genes are associated with a very significantly increased risk of melanoma. Two predisposing genes have been identified. The commonest, CDKN2A, lies on chromosome 9 and codes for a cell cycle protein p16 (Kamb et al, 1994). Thus, the normal protein acts as a brake to the cell cycle, and loss of the protein in vitro leads to hyperproliferative cells with delayed senescence (Hara et al, 1996; Uhrbom et al, 1997). The second susceptibility gene is very rare, there are only three families described worldwide with germline mutations in this gene, CDK4 (Zuo et al, 1996). These mutations code for the p16 binding site of CDK4 and therefore have the same net effect on function as do CDKN2A

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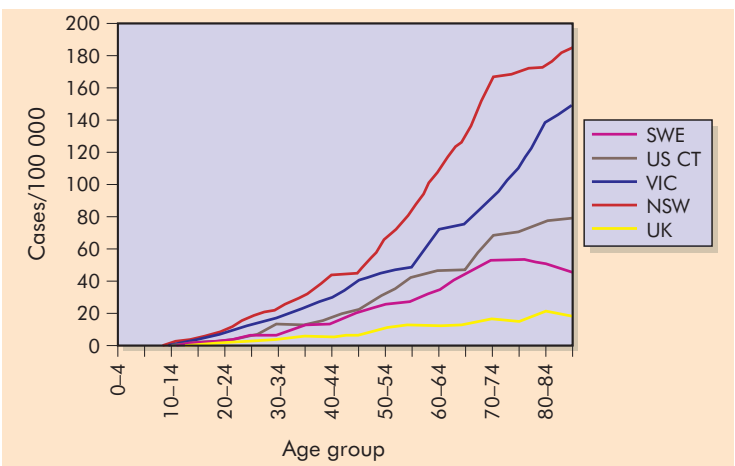

Figure 1. The melanoma incidence at different latitudes for men, in the UK, New South Wales Australia (NSW), Victoria Australia, Connecticut USA (US CT) and Sweden.

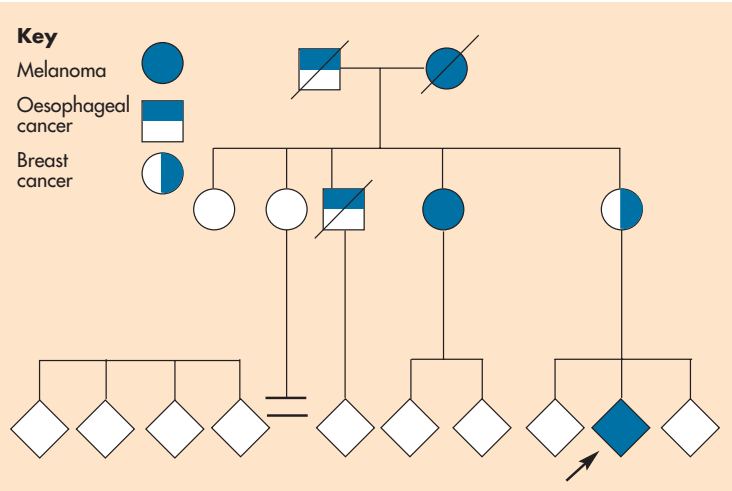

Figure 2. A pedigree showing the inheritance of melanoma in a family with a germline mutation in a susceptibility gene. Circles represent females, squares males. Diamonds indicate individuals in whom gender is obscured for confidentiality purposes. The arrow indicates the proband.

mutations. *Figure 2* shows the pedigree of an English family carrying a CDKN2A mutation.

The genes act as autosomal dominant genes with incomplete penetrance. Our studies suggest that the gene penetrance is around 35% by the age of 65 years and the likelihood is that in less selected families we will find the penetrance to be considerably lower (Newton Bishop et al, 1999).

In families with 2 cases of melanoma only around 5% in our studies are found to have mutations in CDKN2A (Newton Bishop et al, 2000). It could be that these families, or a proportion of them, also have susceptibility genes but with lower penetrance.

THE ATYPICAL MOLE SYNDROME

The most potent phenotypic risk factor for melanoma yet identified is the presence of an abnormal naevus phenotype often referred to as the atypical mole syndrome (AMS) phenotype (otherwise called the dysplastic naevus phenotype or the FAMMM syndrome). Patients affected with AMS have large numbers of moles, moles which are atypical (*Figure 3*) and moles in increased numbers in unusual sites such as on the dorsum of the foot or on the buttocks.

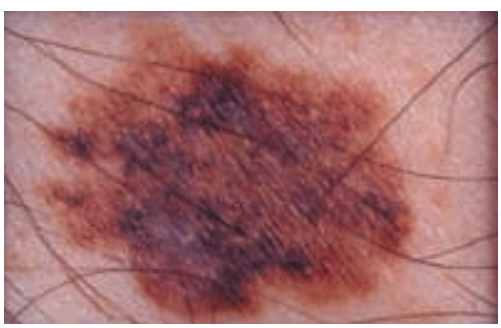

Figure 3. An atypical mole bordering on an in situ melanoma. The mole is much larger than most, with variable shape and colour.

The relationship between this naevus phenotype and the pathogenesis of melanoma is unclear but one hypothesis is that the presence of AMS implies the presence of melanoma susceptibility genes. In the absence of a family history of melanoma this might imply low penetrance genes but this remains unproven. That patients with AMS are at increased risk of melanoma is clear. In England we have established that the relative risk is around 10 compared with the risk for patients with few moles (Newton et al, 1993) (*Table 1*). This gives a lifetime risk in the order of around 1 in 20.

MELANOCYTIC NAEVI (MOLES)

Acquired moles are normal. They start to develop at the age of around 6 months. They increase in numbers until the age of 40 years or so then they involute so that the very old have few moles. Pigment is only produced by melanocytes at the dermo-epidermal junction.

As the mole matures the melanocytes dermalize: they drop down into the dermis and come to resemble neural cells histologically. As this process happens the melanocytes lose their capacity to develop into a melanoma. Such naevi, however, often come to the notice of the patient at that time because they become palpable (*Figure 4*). Patients often present to their GP with these raised dome-shaped skin coloured moles: the message is that these naevi are fine and should be left alone. The naevi which retain junctional activity are the ones to watch (*Figure 3*). Change in such moles is the vital sign:

TABLE 1.
Who is at increased risk of melanoma?

Factor	Relative risk
Patients with large numbers of naevi or moles	10
Patients with 3 or more cases of melanoma in the family	85
Red hair	3

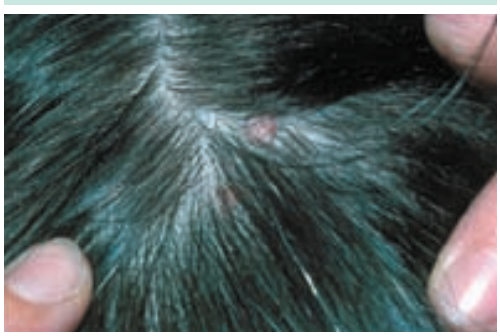

Figure 4. A normal dermal cellular naevus on the scalp.

change in shape, size (surface area) and colour. Melanomas are irregularly coloured and often have blacks, browns and reds within (*Figure 5*).

Some moles carry an increased risk of melanoma. Large congenital naevi certainly carry a significant risk, although the absolute risk is unclear. It is likely to be at most 14% lifetime risk (*Figure 6*). The naevi with the greatest risk, the giant ones, are unfortunately the most difficult both to spot a melanoma early and to reduce the risk by surgery because of the bulk of the melanocyte mass. The risk associated with small naevi remains controversial but in the UK at least the risk is thought to be so moderate that prophylactic excision is not recommended. The authors' personal approach is to leave such naevi in place but to advise the family about what to look for in such naevi. A polaroid picture of the moles and some colour photographs of melanomas will help. If the naevus is in a site where it is difficult to keep under review (such as on the scalp) then prophylactic excision should be considered.

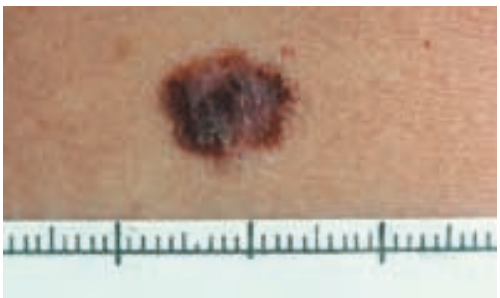

Figure 5. A superficial spreading melanoma with a Breslow thickness of 0.8 mm.

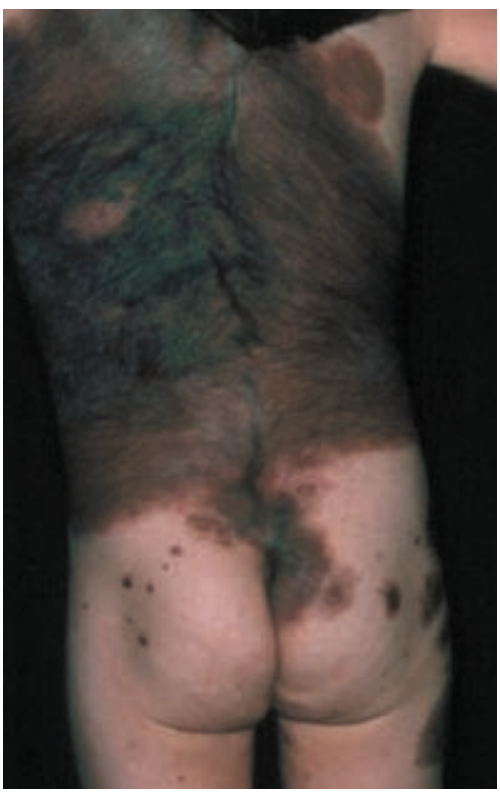

Figure 6. A giant congenital pigmented hairy naevus: such naevi are associated with a significantly increased risk of melanoma.

MELANOMA: CLINICAL TYPES

Clinically there are four types of melanoma. The commonest is the superficial spreading melanoma (*Figure 5, Table 2*) which accounts for the majority of tumours, around 70% overall. It is a relatively slowly developing tumour which develops probably over months, even years. The commonest site is on the legs in women and on the back in men. These tumours are most easily detected by the general public and because they grow over many months are amenable to early detection campaigns via the media.

The second most common is the nodular melanoma (*Figure 7*) which appears to enter a rapid growth phase very much more quickly and is therefore less easy to detect early for excision.

Lentigo maligna melanoma arises in a pre-malignant lentigo, usually on the face which is otherwise known as lentigo maligna or Hutchinson's freckle. The lentigo maligna may remain 'in situ' for many years before an invasive melanoma supervenes (*Figure 8*). Indeed many elderly patients will die of other causes long before a melanoma develops. Once such a melanoma develops, however, the prognosis is the same as for any other type of tumour.

TABLE 2.
Changes indicative of superficial spreading melanoma

Change in shape: a naevus becoming irregular in shape
Change in size: a pigmented lesion growing in surface area
Change in colour: varying shades of brown, black and red

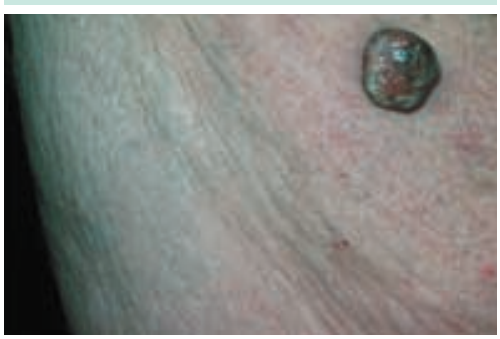

Figure 7. A nodular melanoma.

The last type is the rarest, the acral lentiginous melanoma. This is probably not related aetiologically to sun exposure as it occurs at the same low incidence in all ethnic groups. Such melanomas arise on the sole or palm or under the nail (*Figure 9*). Difficulties in diagnosis, particularly in this last site, mean that these tumours often present late.

- Beware pigmented streaks under or around the nail, it could be melanoma

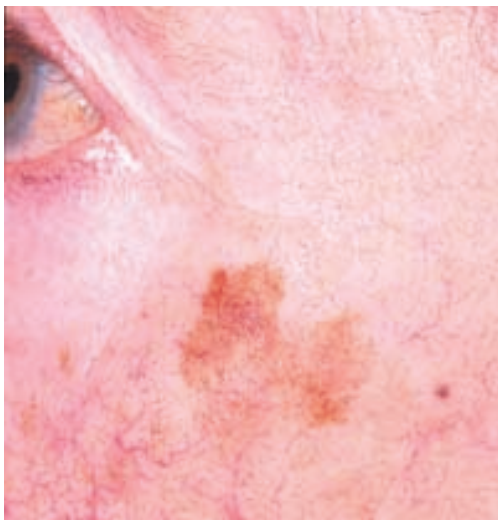

Figure 8. A lentigo maligna.

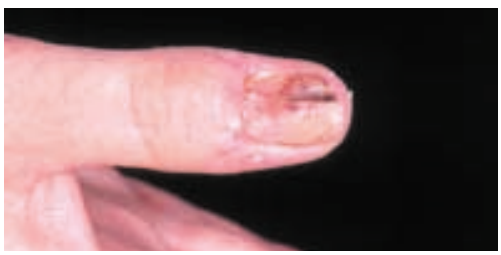

Figure 9. A subungual melanoma after a diagnostic biopsy. Subungual tumours are easily misdiagnosed as fungal infections, pyogenic granulomas or traumatic. A new single band of pigment, any pigment around a nail or friable tissue around the nail should raise the possibility of such a tumour.

TABLE 3.
Disease staging in melanoma patients

Stage	Primary tumour thickness (T)	Lymph node (N)	Distant metastases (M)
IA	Melanoma <0.75 mm	No nodes	None
IB	Melanoma 0.76–1.5 mm	No nodes	None
IIA	Melanoma 1.51–4.0 mm	No nodes	None
IIB	Melanoma >4.0 mm and/or satellites within 2 cm of primary	No nodes	None
IIIA	Any thickness	Lymph nodes but no node >3 cm	None
IIIB	Any thickness	Node >3 cm/ in transit metastases	None
IV	Any thickness	Any nodes	Any metastases

- Always biopsy granulation tissue around nails when cauterizing, it could be melanoma (*Figure 10*).

PROGNOSIS

The prognosis for all melanomas is detemined by the histological measure: the Breslow thickness. This is the distance in millimetres measured from the granular layer of the skin down to the deepest part of the tumour. It is proportional to the volume of the tumour. Fortunately the majority of tumours now present with a Breslow thickness of less than 1.5 mm, giving a disease-free survival of 92% at 5 years. Tumours thicker than 3.5 mm only have a 36% disease-free survival at 5 years (Balch et al, 1985).

Early diagnosis is the key to secondary prevention for melanoma.

INVESTIGATION

Staging of disease in melanoma patients is usually carried out according to the Union Internationale Contre le Cancer/American Joint Committee on Cancer staging (UICC/AJCC) system (*Table 3*) (Buzaid et al, 1997).

TREATMENT

The treatment of melanoma is essentially surgical both for the primary tumour and for metastases.

Surgery for the primary tumour

In situ tumours should be removed with histological evidence of clearance. Tumours less than 2.0 mm in Breslow thickness should be removed with a 1 cm margin of normal skin. The optimal margins of excision for thicker tumours are not known but margins between 1 and 3 cm are thought to be acceptable.

Surgery for metastases

The commonest site of first metastasis is in regional lymph nodes. If the disease is limited to a single lymph node bed the treatment is radical lymph node dissection. The prognosis is better if only one node is replaced by tumour and there-

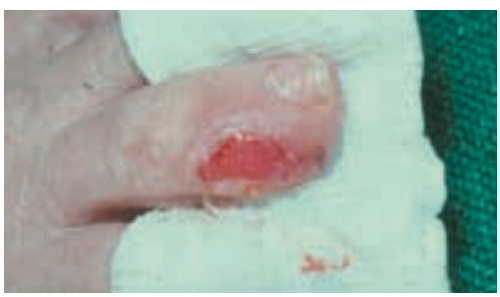

Figure 10. An amelanotic melanoma around the nail: easily mis-diagnosed as granulation tissue.

fore it is supposed that early detection of such metastases will impart a better prognosis. The aim of follow-up in clinic is to detect such malignant nodes early. An experimental technique, sentinel node biopsy (Morton et al, 1992), is currently being evaluated in an attempt to discover tumour in nodes early, but the role of this remains to be established.

Local skin metastases are a common problem in advanced disease and surgery is helpful. Occasionally recurrent disease in a limb may continue for years in the absence of widespread disease elsewhere. Surgery is the treatment of choice for such patients (*Figure 11*), although isolated limb perfusion with melphalan and/or tumour necrosis factor is of considerable palliative value in expert hands.

Radiotherapy has only an occasional palliative role except for cerebral disease (see below).

Chemotherapy with dacarbazine is well tolerated and gives extremely valuable palliation but is not curative. Trials of high dose multiple chemotherapies, often including biological therapies such as interleukin 2 (IL-2) continue. The data suggest that such approaches are associated with the possibility of cure for a very small proportion of patients (less than 10%) at the costs of considerable toxicity (Newton Bishop, 1996). These more aggressive treatments should probably be reserved for the fit patient with widespread but smaller volume disease, but the choice is obviously that of the patient after careful counselling from the multidisciplinary melanoma team.

Brain metastasis is common in advanced disease. Excision of single metastases with postoperative radiotherapy is recommended and radiotherapy is of palliative value for multiple lesions.

ADJUVANT THERAPIES

There is no adjuvant therapy of proven value for melanoma but clinical trials are taking place to evaluate the use of alpha interferon and a variety of vaccines (monovalent and polyvalent) (Hersey, 1994; Bystryn et al, 1996). HM

Conflict of interest: Dr Newton Bishop's research is funded by the Imperial Cancer Research Fund.

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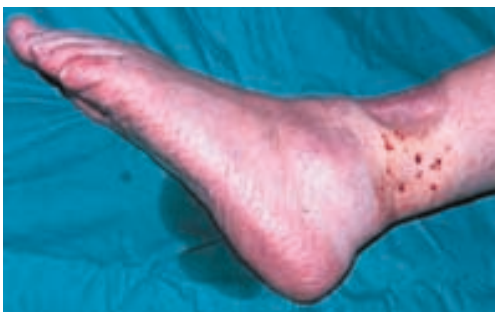

Figure 11. Local skin metastases treated by multiple small excisions: punch biopsy is a useful means of removing such lesions.

KEY POINTS

- The increasing incidence of melanoma is attributed to excessive sun exposure.
- Early detection is the key to controlling the disease.
- Patients with large numbers of moles, particularly unusual moles are at increased risk of melanoma.
- Rare families are at increased risk of melanoma and a proportion of these have identifiable mutations in the CDKN2A gene.
- Pigmented lesions which change in shape, size or colour should be referred to an expert.
- Beware granulation tissue or pyogenic granulomas around nails: biopsy as amelanotic melanoma may mimic these benign lesions.
- Chemotherapy is not curative for melanoma but it has a valuable palliative role.
- The role of interferon and vaccines as adjuvants for poor prognosis primary disease is being evaluated.
- Melanoma should be managed in cancer units or cancer centres.