Malignant melanoma of the skin

B. K. ARMSTRONG & C. D. J. HOLMAN

Ultra-violet radiation (UVR) in sunlight is thought to be the main cause of malignant melanoma in lightly-pigmented populations. Individuals with fair skin, fair hair, blue eyes and/or a tendency to burn rather than tan when exposed to the sun are at particularly high risk of melanoma and should be given special attention in primary prevention programmes. Intermittent exposure to the sun, as in recreational exposure, may be a more potent cause of melanoma than more continuous exposure. Primary prevention offers the best prospects for a substantial reduction in mortality from malignant melanoma. However, there is little evidence available to judge the effectiveness of primary prevention of melanoma through reduction of exposure to the sun. Education for reducing exposure to the sun is common in high-risk populations but has never been evaluated adequately. Mortality from melanoma could also possibly be reduced by earlier diagnosis through education or screening of high-risk groups. Regular screening of patients with the familial dysplastic naevus syndrome should reduce their mortality from melanoma.

ETIOLOGY

Constitutional factors

Race. Racial differences in skin pigmentation and the skin's response to sunlight are known to be the predominant factor affecting the incidence rate of melanoma. On average, melanoma is some 3–4 times more common in lightly-pigmented than heavily-pigmented races (1). These differences in pigmentation are due to variation in melanogenesis and the skin content of melanin, and not to the density of melanocytes (2). Melanin exerts a photoprotective effect in skin by acting as a neutral density filter, attenuating radiation by scattering, and absorbing the ultraviolet radiation (UVR) energy. In addition, it can undergo immediate oxidation and, as a stable free radical, can act as a biological exchange polymer (3). These latter effects, while not influencing UVR penetration into the skin, may block chemical reactions leading to carcinogenesis.

Among heavily-pigmented races there is appreciable variation in the incidence of melanoma. Thus, for example, the rates are twice as high in black Africans as in U.S. Blacks; the latter, in turn, have rates three times higher than those in most Asian populations (1). Since Asians are less heavily pigmented than black Africans, factors other than skin pigmentation, which are correlated with race, must influence the risk at this lower end of the incidence distribution. It may be relevant to note that melanoma of the foot (mainly sole) comprises about 30% of all melanomas in the Japanese, but 40–75% of melanomas in U.S. Blacks or black Africans (4).

Individual pigmentary characteristics. Within predominantly lightly-pigmented populations, the incidence of melanoma is influenced by individual pigmentary characteristics. Several studies have shown that incidence is least in those with black hair, olive or dark skin and brown eyes, and highest in those with red hair, fair or light skin and blue eyes (4). In addition, those who tend to burn or freckle in response to sunlight are at greater risk than those who tend to tan (5). These relationships are supported by direct measurement of the sensitivity of skin to sunlight (6).

Specific genetic predisposition. Increased risk of melanoma in some families is well recognized (4). Independently of pigmentary characteristics and number of naevi, a family history of melanoma has been found to be associated with a 2.4 times increased risk of melanoma (5). The dysplastic naevus syndrome (7) is now recognized as associated with familial melanoma in a high proportion of cases. The familial dysplastic naevus syndrome may be present in from 6% to 10% of all melanoma patients (8).

The incidence of melanoma and other skin cancers.
is increased greatly in patients with xeroderma pigmentosum, an autosomal recessive condition characterized, in most cases, by a defect in the capacity to repair UVR-induced DNA damage (9), and in albino subjects who lack normal skin pigmentation.

Benign naevi. The number of benign melanocytic naevi that a person has on the skin is a very strong predictor of subsequent risk of melanoma (5, 10). Number of naevi is arguably a constitutional factor; whether benign naevi are predominantly genetically determined or are due to an environmental agent is uncertain.

Environmental factors

Sunlight. Short-wave UVR in sunlight is thought to be the main environmental factor responsible for melanoma and other skin cancers (4). In this context, short-wave means wavelengths of from about 290 nm (the shortest which reaches the earth's surface) to 315 or 320 nm (so called ultraviolet B radiation). The same wavelength band is mainly responsible for sunburn.

The main effects of UVR are to produce pyrimidine dimers (particularly thymine dimers), cross-linkages between DNA bases and nucleoproteins, and breakages in polynucleotide chains (11). UVR alone can induce sarcomas and squamous cell carcinomas of the skin in mice (12) but not melanoma. It may also promote melanoma development in strains of mice prone to spontaneous melanoma (13).

The associations between the incidence of melanoma and racially determined skin pigmentation, individual pigmentary characteristics, and skin reaction to sunlight in lightly-pigmented races provide strong circumstantial evidence of an etiological role of sunlight in this disease. Evidence is also provided by the increased incidence of melanoma and other skin cancers in patients with xeroderma pigmentosum (see above).

More direct evidence comes from the association between incidence of melanoma in light-skinned populations and proximity to the equator both within and among countries (14). There are, however, exceptions to this pattern. For example, in Australia the incidence of melanoma varies inversely with the latitude between States but within Queensland and Western Australia, both of which have a high incidence, the latitude gradient is reversed. In Europe the latitude gradient is also reversed, with high rates in Nordic countries and the lowest rates in the south. This inconsistency may be explained, at least in part, by greater degrees of constitutional skin pigmentation in southern European populations. Other inconsistencies could be due to supervening climatic factors, as latitude is not the only determinant of UVR flux. A positive association can be shown, in some situations, between melanoma incidence and the mean number of hours of sunshine daily, but this is generally weaker than the association with latitude (15).

The incidence of melanoma also varies with the seasons, with a summer-time peak, and between years apparently in association with sunspot activity (which may influence the atmospheric ozone content, a major absorber of short-wave UVR) (4) or the extent of summer sunshine (16). The latter effects have a lag period of 2 to 5 years, thus suggesting an action of UVR with short latency, more consistent with cancer promotion than cancer initiation.

Attention has been drawn to aspects of the epidemiology of melanoma which are inconsistent with the solar hypothesis (17). For example, the distribution of melanoma on the body surface favours relatively unexposed sites—the trunk is the commonest site in males and the legs in females. This distribution contrasts with the distribution of non-melanocytic skin cancers which favours the face and upper limbs (18). Melanoma also differs from other skin cancers, for which the evidence of a solar etiology is more clear cut (18), in its higher incidence in females than males and the early rise and middle-age peak in its incidence. Non-melanocytic skin cancers are substantially commoner in males (who are more likely to work outdoors) than females, and their incidence rises more or less exponentially with age (as would be expected from continuing accumulation of exposure to the sun). Also against the solar hypothesis for the etiology of melanoma is evidence that the incidence is greater in indoor than outdoor workers and, at least sometimes, in urban than rural populations (4). The opposite is true, in each case, for non-melanocytic skin cancer (18).

Several hypotheses have been advanced to explain these inconsistencies, the most recent being the intermittent exposure hypothesis (19). It suggests that the risk of non-melanocytic skin cancers and possibly also melanoma of the Hutchinson’s melanotic freckle type (which appears to be epidemiologically similar to non-melanocytic skin cancers) varies with the total accumulated dose of UVR, however received, whereas other melanomas are more likely to arise if sun exposure is received in intermittent, intense bursts (as in the recreational exposure of body sites not usually exposed to the sun). If true, this theory could explain most if not all the inconsistencies referred to above.

A number of recent studies of individuals provide evidence for the effects of both cumulative and intermittent exposure to the sun on the incidence of melanoma. In a study in Western Australia, the incidence of melanoma was lower in immigrants (who
generally came from areas of low sun exposure) than in native-born Australians, had a direct correlation with the annual hours of bright sunlight averaged over all places of residence in the native-born, and was positively associated with an objective measure of sun damage in the skin (20). These observations suggest that the total accumulated sun exposure has a bearing on melanoma etiology. The same study failed to find convincing effects from intermittent exposure to the sun as measured by the proportion of all outdoor exposure that was recreational (21). Incidence of melanoma, however, did increase with frequency of participation in waterside recreations, particularly boating and fishing, and melanoma of the trunk was increased substantially in incidence in women who usually wore a two-piece bathing suit at the beach in summer or bathed nude (21). In a similar study from western Canada, positive associations were observed between melanoma and the number of hours of beach activities in summer and the number of sunny vacations per decade (22).

Other factors. A variety of other environmental factors have been suggested as increasing the risk of melanoma. They include female sex hormones (both endogenous and exogenous), diet, alcohol drinking, use of certain medications, use of hair dyes, exposure to fluorescent light, occupational exposure to petroleum products and other hydrocarbons, trauma and X-irradiation. The evidence for most of them is limited at present (4, 23). It is doubtful whether any could explain more than a small proportion of melanomas in any general population.

THERAPY AND OUTCOME

Therapy

Surgical excision of the primary lesion is the treatment of choice for all but advanced malignant melanoma. Traditionally, wide local excision of the primary lesion has been recommended but there is little evidence that wide excision is especially beneficial (24). Recent recommendations for stage I disease require an excision margin of no more than 1.5 cm for a lesion with a good prognosis and a 3.0 cm margin for all other lesions (25). Therapeutic block dissection of draining lymph nodes is beneficial when, on clinical evidence, the nodes are the site of metastases. Prophylactic block dissection in stage I disease probably does not confer a survival advantage (26).

Outcome

The prognosis of melanoma depends mainly on sex, clinical stage, and the site and thickness of the primary lesion. Females have a better prognosis than males; stage I lesions (local disease only) do better than stage II (nodes involved) and stage III lesions (distant metastases); lesions of the extremities tend to have a better prognosis than lesions of the trunk; and thin lesions have a better prognosis than thick lesions (25, 27). Preinvasive melanomas (Clark's level I) and invasive melanomas less than 0.76 mm in thickness show 100% disease-free survival at 5 years (28).

The prognosis of melanoma has improved substantially over the past 20 to 30 years. Thus, for example, in the U.S. National Cancer Institute's End Results Surveys the relative 5-year survival increased from 41% in melanomas diagnosed in 1940-49 to 67% in melanomas diagnosed in 1965-69 (29) and to 76% in 1973-79 in the US SEER (Staging, Epidemiology and End Results) Registries (30). In some populations a parallel trend towards diagnosis of less advanced lesions has been documented. For example, in Queensland (Australia) in 1966 some 70% of melanomas were diagnosed at level III or higher, whereas in 1977 this proportion had fallen to 50% (31).

The improving prognosis of melanoma has paralleled increasing incidence rates (see below). To illustrate again from the experience in Queensland, the estimated crude incidence of invasive melanoma (level 2 or deeper) rose from 11.4 per 100 000 in males and 14.1 per 100 000 in females in 1963-69 to 24.9 per 100 000 in males and 25.4 per 100 000 in females in 1977 (31, 32). The estimated crude incidence of preinvasive (level 1) melanoma rose proportionately more from 1.3 per 100 000 in males and 1.5 per 100 000 in females to 8.4 per 100 000 and 8.7 per 100 000, respectively. Over the same period mortality from melanoma in Queensland was almost constant (32), thus implying an improving prognosis.

In addition to a temporal association there is a geographical association between incidence and prognosis of melanoma (28). Australia has the highest incidence of melanoma and the best prognosis; patients with invasive melanoma diagnosed in Western Australia in 1975 and 1976 had relative 5-year survival rates of 85% in males and 89% in females. By way of comparison the 5-year survival rates from melanomas diagnosed in Iowa (USA) (which has one sixth the incidence rate of Western Australia) in 1970-74 were 58% in males and 71% in females (28). Differences in distributions of tumour thickness probably underlie this geographical variation in prognosis (33).

While behavioural factors leading to earlier diagnosis in high-incidence populations are generally thought to be responsible for these temporal and geographical associations between incidence and survival, the possibility that a high incidence of melanoma is associated with a less aggressive form of
the disease cannot be excluded. Alternatively, or as well, the association of a high incidence of melanoma with increased public and professional awareness of the disease may lead to increased diagnosis of lesions which, if left, would not lead to death. It should be noted, however, that in Queensland at least, as described above, the incidence of preinvasive, as well as invasive, melanoma increased while mortality was constant.

A near 100% cure rate could be achieved for melanoma if all patients were diagnosed in the preinvasive stage, or with lesions less than 0.76 mm in thickness, and treated surgically (28). Currently some 30% of melanomas diagnosed in Western Australia are preinvasive and 48% of invasive melanomas are less than 0.76 mm thick. As indicated above, this comparatively favourable distribution could be due as much to the nature of the underlying disease as to awareness of the need for early diagnosis. It cannot be assumed, therefore, that similar or better distributions could be obtained elsewhere by education for early diagnosis or screening.

**SIZE OF THE WORLDWIDE PROBLEM**

**Geographical variation in incidence**

Melanoma varies some 300-fold in incidence between different populations. The highest incidence rates, 39.6 per 100 000 person-years in males and 31.3 per 100 000 person-years in females (standardized to the age distribution of the "world" population), were reported from Queensland (Australia) in 1979–80 (34). The lowest recent rates, 0.2 per 100 000 in both sexes, came from Osaka (Japan) in 1973–75 (35). In Australia the disease is essentially confined to the white population, in whom it is the fourth most common cancer in incidence (after lung, breast and colon) and the fourth most common cause of loss of life before the age of 70 years (36).

Between the extremes of Australia and Asia lie the populations of New Zealand, North America and Scandinavia towards the top end of the range, although with rates one half or less than those in Australia (4 to 18 per 100 000); other northern European populations (2 to 4 per 100 000); black Africans, whether resident in Africa or not (0.5 to 2 per 100 000); populations in Spain and of Mediterranean origin in South America (0.3 to 2 per 100 000); and, finally, other Asian populations (0.2 to 1 per 100 000) (35). This distribution, which is highly skewed to the right, is determined almost certainly by a combination of constitutional susceptibility and environmental exposure to, mainly, UVR. Differences in the availability of health services and diagnostic evaluation of preinvasive melanomas may also contribute to variation between populations in the recorded incidence rates. The median incidence of melanoma in a survey of 53 populations was 1.2 per 100 000 in males and 1.5 per 100 000 in females (35).

Like melanoma, non-melanocytic skin cancer varies very widely in incidence. In the same survey of 53 populations the highest incidence was in Manitoba, Canada (97 per 100 000 in males and 67 per 100 000 in females) and the lowest in Osaka, Japan (1.4 per 100 000 in males and 0.6 per 100 000 in females) (35). The crude incidence in the white population of Queensland, Australia has been reported at 265 per 100 000 in males and 156 per 100 000 in females (37). There is a rough positive correlation between the incidence of non-melanocytic skin cancer and melanoma, with the former usually substantially higher (10-fold or more in males and 5-fold or more in females) than the latter. Like melanoma also, non-melanocytic skin cancer is rare in most Asian populations for which incidence data are available (35), and uncommon in heavily pigmented populations in comparison with lightly pigmented populations living in the same area. In heavily-pigmented populations non-melanocytic skin cancer has a predilection for the lower limbs where it commonly occurs in burn scars or at the site of chronic infection or ulceration (18). In most populations mortality from melanoma is higher than that from non-melanocytic skin cancer; in a few, in which mortality from both is low, the opposite is true (39).

**Trends in incidence with time**

Almost all white populations have experienced an increase in incidence of melanomas, averaging from 1.5% to 20% per year (40), since at least 1950 (4). No similar increase has been seen in black populations. Where it has been studied, a birth-cohort effect has usually been evident in the increases with a peak incidence and/or mortality in those born between about 1920 and 1930 (40). This suggests that the increase will level off and then end shortly after the year 2000 in the absence of introduction of any new causal or protective agent.

Most of the increase in melanoma incidence has been on the trunk in males and legs in females. There has been little change in melanoma of the head and neck (40). The increase has been attributed to increasing recreational exposure to the sun.

**Prospects for reduction in incidence**

On present evidence it would be reasonable to suggest that the difference in melanoma incidence
between the white population of Australia and the populations in their countries of origin (predominantly the United Kingdom and Ireland) is attributable largely to their difference in exposure to sunlight. The potential exists, therefore, by control of such exposure, to reduce the incidence rates in Australia from between 10 and 40 per 100 000 (depending mainly on latitude of residence) to the levels of 2 to 4 per 100 000 as in the United Kingdom, or even lower. Reduction to these levels should also be possible in other high-incidence white populations (e.g., in New Zealand, USA and Scandinavia).

A reduction in incidence does not promise the same relative reduction in mortality. Mortality from melanoma varies only 20- to 30-fold, from about 2 to 3 per 100 000 in Australia and New Zealand to 0.1 per 100 000 in Japan. Median levels of mortality in a survey of 26 populations were 0.8 per 100 000 in males and 0.9 per 100 000 in females (41). The distribution of mortality from melanoma is therefore much less skewed than that of incidence, the difference probably being due to the association between incidence and survival (see above, p. 247). By use of the reasoning applied to incidence rates (see above), mortality from melanoma in Australia and New Zealand could be reduced from 2-3 to 0.7-0.8 per 100 000 by control of sun exposure.

PREVENTION

Primary prevention

On present evidence, only control of exposure to sunlight warrants serious attention as a measure for the primary prevention of melanoma. Attention in controlling such exposure can be directed towards readily identifiable high-risk groups—generally lightly-pigmented populations living in areas where average UV flux is high, and specifically fair-skinned people whose predominant reaction on exposure to the sun is to burn rather than tan.

The process of prevention has so far been through education towards the following behaviour:

(i) reducing the total time spent out of doors, particularly in summer;
(ii) limiting outdoor activities, again particularly in summer, to before 10h00 and after 14h00 solar time; about 66% of UV energy from the sun in any 24-hour period is received during these four hours (42);
(iii) wearing a wide-brimmed hat whenever in the sun;
(iv) covering the skin as much as possible in the sun; different clothing materials may allow passage of as little as none to as much as 50% of the UVR that would otherwise reach unclothed skin (42);
(v) making maximum use of available shade out of doors; in seeking shade, consideration must be given to skylight, light scattered from clouds, dust and moisture, and reflected light as well as direct sunlight; as much as 50% of UVR may be received as skylight and appreciable amounts of UVR are reflected from fresh snow and, to a lesser extent, dry, white sand (42);
(vi) using highly protective sunscreen lotions or creams correctly on all skin not protected in any of the above ways.

Educational programmes based on the above principles are conducted regularly in Australia (43) and have been implemented elsewhere. There has been little research into their likely effects (knowledge, attitudes, acceptability, etc.) and no evaluation of their ultimate effectiveness has been reported. There are limited indications that such programmes might work. Experimentally, para-aminobenzoic acid (an effective sunscreen) applied topically one hour before exposure to UVR can block the production of squamous cell carcinoma of the skin in hairless mice first given dimethylbenzantracene (44). In patients with xeroderma pigmentosum, a programme of protection against UVR, similar to that described above, has slowed or halted the development of solar keratoses and other skin cancers, including melanoma (45).

Secondary prevention

Theoretically early detection, as well as incidence reduction, has the potential to reduce mortality from malignant melanoma although, as stated above (see above, page 247), there is no certainty that recent improvements in prognosis of melanoma have been due to earlier recognition of suspicious lesions. Efforts at early detection have been based on education of the public and the medical profession regarding features of a pigmented lesion that should excite suspicion (46).

The effectiveness of education for early diagnosis has not been evaluated. In Queensland, however, following the Queensland Melanoma Project, which was accompanied by a substantial amount of public education (43), mortality from melanoma has remained comparatively steady although the incidence has risen, while mortality has continued to rise in the other States of Australia (32). This is suggestive of an effect of early diagnosis on incidence and mortality.

Specific screening of skin for suspicious lesions by a trained observer has been advocated and practised in a desultory fashion but never evaluated as to effectiveness or cost. It is most likely to be justified in patients with the dysplastic naevus syndrome (see
CONCLUSIONS

Ultraviolet radiation (UVR) in sunlight is thought to be the main cause of malignant melanoma in lightly-pigmented populations. Individuals with fair skin, fair hair, blue eyes and/or a tendency to burn rather than tan when exposed to the sun are at particularly high risk of melanoma and should be given special attention in primary prevention programmes. Intermittent exposure to the sun, as in recreational exposure, may be a more potent cause of melanoma than long continued exposure. There is little evidence available to judge the effectiveness of primary prevention of melanoma through reduction of exposure to the sun. Education for reduction in sun exposure is common in high-risk populations but has never been evaluated adequately.

Mortality from melanoma could possibly be reduced by earlier diagnosis through education or screening of high-risk groups. Regular screening of patients with the familial dysplastic naevus syndrome should reduce their mortality from melanoma.

No research aimed directly at evaluating the effectiveness of primary or secondary prevention of melanoma in known to be in progress. However, primary prevention offers the best prospects for a substantial reduction in mortality from malignant melanoma. There is a need for evaluation of the effectiveness of the measures detailed above in reducing the incidence of and mortality from melanoma. This could be done best by a multi-centre, collaborative controlled trial of these or related measures. Effectiveness would be assessed, in the short term, as behaviour change and, in the long term, as change in the incidence rate of melanoma.

RÉSUMÉ

MÉLANOME MALIN

L'incidence du mélanome malin est variable et peut être jusqu'à 300 fois plus élevée d'une population à l'autre. Les taux d'incidence les plus élevés sont signalés dans le Queensland, en Australie, et les plus faibles à Osaka, au Japon.

Dans les populations à faible pigmentation, on estime que les radiations ultraviolettes (UV) de la lumière solaire constituent la principale cause de mélanome malin. Les individus à peau claire, cheveux blonds, yeux bleus ou ayant tendance à attraper des coups de soleil plutôt qu'à bronzer présentent un risque de mélanome malin particulièrement élevé et doivent faire l'objet d'une attention spéciale dans les programmes de prévention primaire. L'exposition intermittente au soleil, dans le cadre des loisirs par exemple, serait une cause plus importante de mélanome malin qu'une exposition plus continue.

La prévention primaire est l'activité qui offre les meilleures perspectives en matière de réduction de la mortalité par mélanome malin. Les programmes éducatifs devront être centrés sur l'incitation aux comportements suivants:

i) diminuer la durée totale passée en extérieur, notamment l'été;

ii) limiter les activités en extérieur, une fois encore surtout l'été, aux tranches horaires situées avant 10 heures et après 14 heures (heure solaire);

iii) porter un chapeau à large bord chaque fois que l'on est au soleil;

iv) au soleil se couvrir le corps autant que possible;

v) en extérieur, se tenir le plus à l'ombre possible;

vi) s'enduire correctement de lotion ou de crème solaire haute protection à tous les endroits non protégés.

Toutefois, il n'y a que peu d'indices qui permettent de juger de l'efficacité de la prévention primaire du mélanome malin par le biais d'une diminution de l'exposition au soleil. Ce type de programme éducatif n'a jamais été évalué de façon satisfaisante.

Un diagnostic plus précoce pourrait également diminuer la mortalité par mélanome malin, qu'on y parvienne l'éducation ou par le dépistage des groupes à haut risque. On obtient un taux de guérison de près de 100% si chez tous les malades le mélanome malin a été diagnostiqué au stade pré-invasif, ou lorsque l'épaisseur des lésions est inférieure à 0,76 mm et qu'elles sont traitées par exérèse chirurgicale. Le dépistage régulier chez les malades présentant un syndrome familial de naevus dysplasique, devrait réduire chez eux la mortalité par mélanome.
REFERENCES


