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Epidemiology of invasive cutaneous melanoma

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Data are presented on the current incidence of melanoma with recent and predicted future trends illustrating a likely continuing increase in incidence. Risk factors for developing melanoma are discussed, including current known melanoma susceptibility genes. Phenotypic markers of high-risk subjects include high counts of benign melanocytic naevi. Other risk factors considered include exposure to natural and artificial ultraviolet radiation, the effect of female sex hormones, socioeconomic status, occupation, exposure to pesticides and ingestion of therapeutic drugs including immunosuppressives and non-steroidal anti-inflammatory drugs. Aids to earlier diagnosis are considered, including public education, screening and use of equipment such as the dermatoscope. Finally, the current pattern of survival and mortality is described.

Key words: cutaneous melanoma, incidence, mortality, risk factors, survival

introduction

At the present time, the epidemiology of cutaneous melanoma is of interest to all those who care for melanoma patients including surgeons, dermatologists, oncologists and primary care physicians. This review will highlight current aspects including the increasing incidence of the disease worldwide, current recognised risk factors for melanoma and the role that any of these may play in increasing incidence. The review will also point out a contrast between small changes in mortality and much larger changes in incidence. Aids to earlier diagnosis will be considered, as will the results of recent campaigns aimed at either primary prevention of melanoma or earlier diagnosis.

current incidence trends

sources of information

The major sources of information on incidence for all cancers including melanoma are national cancer registries. These have the advantage of being reasonably comprehensive, but data tend to be published several years in arrears because of the workload involved, and data presented tend to be minimal. Coding systems for national registries separate lentigo maligna melanoma and lentigo maligna from nodular and superficial spreading varieties, and there is variation in the recording of *in situ* lesions between registries. There is no consistent policy over recording tumour thickness, exact body site is generally not recorded and there is inconsistency over registering second and subsequent primary tumours of the same pathological type.

Specialist melanoma registries record more detail. They may either concentrate on material referred to one major institution, or attempt to capture all melanomas in a given geographic area. Material gathered in such registries is particularly useful for case–control studies, and also for recording changes over time in tumour thickness, a possible surrogate for improving prognosis.

The regular publication of Cancer Incidence in Five Continents by the International Agency for Research on Cancer gives a comparative overview of melanoma incidence worldwide. These volumes aim to record current cancer incidence figures adjusted for age to a world-standardised rate, using material from all cancer registries worldwide that meet appropriate standards of quality control. The recently published volume IX covers the period 1998–2002 [1] and shows that, as in the past, the highest recorded incidence of invasive cutaneous melanoma worldwide is in Queensland, Australia, at a figure of $55.8/10^5$/annum for males and $41.1/10^5$/annum for females (Table 1). Even within Australia there is a clear latitude gradient with incidence figures per annum in New South Wales that are $38.5/10^5$ for males and $26.5/10^5$ for females, and in Victoria as low as $27.3/10^5$ for males and $23.4/10^5$ for females. Incidence figures are also high for New Zealand at $34.8/10^5$ and $31.4/10^5$ per annum for males and females, respectively. Large numbers of registries from North America have contributed, and the most useful figures for the USA are the SEER results from 14 registries, which show an incidence of $19.4/10^5$ and $14.4/10^5$ per annum for males and females in non-Hispanic whites.

Reported incidence rates vary for Europe, and are highest in Switzerland and the Scandinavian countries of Norway, Sweden and Denmark. All European countries report a higher incidence in females than males, in contrast to Australasia and North America, where males have a higher incidence. Incidence rates in Europe are higher in the more affluent countries, as compared with data from the Baltic states of Latvia, Lithuania

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Table 1. Comparative melanoma incidence figures for selected states and countries worldwide for the time period 1998–2002[a]

Country	Incidence (per 10^5 subjects)	
	Male	Female
Queensland Australia	55.8	41.1
New South Wales Australia	38.5	26.5
Victoria Australia	27.3	23.4
New Zealand	34.8	31.4
US SEER 14 registries non-Hispanic whites	19.4	14.4
Switzerland, Vaud	16.6	19.6
Norway	14.2	14.6
Sweden	11.9	12.1
Denmark	11.9	14.1
Latvia	3.2	4.2
Lithuania	3.7	5.2
Estonia	5.3	6.6
Belarus	2.7	3.5
Serbia	3.8	4.8

[a]Data taken from ref. [1].

and Estonia, and also eastern European countries such as Belarus and Serbia (Table 1), although recent data show a rise in incidence in many east European countries [2]. Within Italy there appears to be a latitude gradient, with a higher incidence in both sexes in northern Italy around Milan compared with that in the Naples area. Table 1 also shows that, for the time period studied, the incidence of melanoma in Queensland is more than three times that of any European country. This will be discussed further below and should be kept in mind when considering public education in prevention and early detection campaigns appropriate for the target population.

incidence figures from individual cancer registries and specialist melanoma registries

As stated above, incidence figures from these sources may not be strictly comparable between registries because of differing methods of case ascertainment, geographic area covered and pathological criteria required for inclusion.

A study from Tauranga, New Zealand, records an extremely high incidence of invasive melanoma of $79/10^5$ in the non-Maori population for 2003. Possible explanations include a very fair-skinned population, a climate conducive to year-round outdoor activities, and possibly also the effects of ozone depletion [3]. A cohort effect has been well explored in New South Wales, covering the time period 1983–1996. This report records a continuing increase in incidence in older males (≥75 at diagnosis), but a stabilisation in younger males and an average annual percentage fall of 3.3% in females aged 15–34 [4].

In Europe, national cancer registries show a rising incidence of melanoma overall during the past two decades. In France, the incidence increased between 1980 and 2000 in males from $2.4/10^5$ to $7.6/10^5$ and in females from $3.9/10^5$ to $9.5/10^5$ per annum. Tumour thickness is only recorded in one department, but in that, the proportion of thin melanomas increased [5]. Following incidence in Sweden between 1990 and 1999, the Swedish Melanoma Group reported 12 533 melanoma patients diagnosed from 1990 to 1999 with no significant incidence change in this population over the time period [6].

A second Swedish study, which was investigating site-specific incidence changes between 1960 and 2004, reported 46 337 melanomas diagnosed during this time period [7]. The greatest incidence increase in both sexes was on the upper limb, followed by the trunk and then the lower limb, with trunk melanomas forming an increasing proportion of all melanomas in both sexes. Head and neck melanomas increased less rapidly and more commonly involved those aged ≥70. These data are presented as evidence of the relative importance of intermittent recreational sun exposure as an aetiological agent as compared with continuous sun exposure, as is found on the head and neck.

The Eurocare working group has studied melanoma incidence rates and changes in eastern and western Europe before 1992 [8]. Between 1978 and 1992 incidence rates were lower in eastern than in western Europe, but melanomas were thicker. The group also reports the paradox of higher incidence rates in southern countries of eastern Europe and the converse in western Europe with higher rates in northern countries, and it predicts a swing in eastern Europe toward a pattern similar to that seen in western Europe.

The Scottish Melanoma Group has studied 12 450 cases of invasive cutaneous melanoma diagnosed from 1979 to 2003, and it reports a trebling of incidence in males of all ages and a 2.3-fold increase in females. The steepest rates of increase are seen in males aged ≥60 at diagnosis, and although the rate of increasing incidence fell in the period 1990–1999 compared with the period 1980–1989, there is as yet no evidence of stabilisation of incidence rate in any age group or either sex [9].

Data on melanoma from the majority of countries thus show a continuing incidence increase overall, with a slowing of the rate of increase in the period 1990–2000 compared with the previous decade in many countries. Differing patterns are emerging in relation to subjects' sex and age in that a static or even falling incidence is observed in younger females in some countries. In contrast, however, the incidence increase continues in older males in most countries [9].

The main reason proposed for the general increasing melanoma incidence over the last 40 years is greater exposure of pale Caucasian skin to natural ultraviolet (UV) radiation. Inexpensive flights from high-latitude countries, such as Scandinavia, to Mediterranean or warmer climates have become available at all times of the year. Short, intermittent burning episodes of sun exposure have been identified by Elwood et al. [10] as a major melanoma risk factor, so some of the increase could be attributed to greater opportunities for burning of pale, non-acclimatised Caucasian skin.

A major problem in linking putative risk factors to diagnosis of melanoma is the lack of current knowledge on the latent period between initiating factors such as UV exposure and clinical appearance of a melanoma. This is thought to be measured in decades, and therefore Diffey in the UK [11] and de Vries in the Netherlands [12] predict that melanoma incidence will continue to increase for at least the next 10 years. While there is no sound current data on ozone layer changes

affecting melanoma incidence, it is quite possible that such data will become available.

risk factors for melanoma

Risk factors for any malignancy can be subdivided into genetic and environmental with interaction between the two. Table 2 gives a list of both established and also postulated risk factors for cutaneous melanoma.

Approximately 5% of all invasive cutaneous melanomas occur in a familial setting with two or more close relatives affected. This observation indicates that, in a small minority of melanoma patients, low prevalence/high penetrance genes are involved. In addition, the typical phenotype of the melanoma patient, with pale Caucasian skin, red or blond hair and blue eyes indicates that high prevalence/low penetrance genes such as MC1R may interact with environmental factors, particularly with sun exposure.

melanoma susceptibility genes

The work of two international melanoma genetics collaborative groups, Genomel and Gem, has shown that around one-third of patients in melanoma families worldwide have an identifiable germline mutation in CDKN2A, a gene important in controlling entry into the cell cycle. A wide range of mutations has been reported in these families, with concentration of specific mutations in certain geographic areas, such as the Mediterranean, Sweden and Scotland, indicating the likely source of the founder mutation (for review see ref. [13]). Functional studies on some of these mutations have indicated that they are likely to be a significant causative factor in melanoma development. A second melanoma susceptibility gene, CDK4, has been identified in five families to date worldwide [14], but in >50% of all families with pathologically confirmed invasive cutaneous melanomas no putative responsible gene has yet been identified. A number of research groups are currently actively investigating these families for new melanoma susceptibility genes.

The gene MC1R encodes a protein involved in the production of eumelanin, which is responsible for dark colouring, and phaeomelanin, which is responsible for red hair and freckles. Subjects with red hair have a higher proportion of three MC1R variants, currently known as red-hair variants, and it has been a matter of discussion whether these variants are also more common in non-red-haired patients with sporadic melanoma [15]. A study from New South Wales in Australia indicates that in familial melanoma, there is an interaction between mutated CDKN2A and MC1R [16]. High prevalence/low penetrance genes such as MC1R are important in that they may be relevant to a much larger proportion of the melanoma population compared with the small number of familial cases with CDKN2A mutations.

Two recent publications also add to the list of possible high prevalence/low penetrance genetic variations affecting melanoma risk. The first study analysed pooled DNA from two distinct Australian populations and reported that, in these populations, common sequence variants on chromosome 20q11.22 confer melanoma susceptibility [17]. These results require confirmation in a non-Australian population, as well as identification of the likely genes. The second study examined DNA samples from 2121 European melanoma patients and 40 000 controls and reported pigmentation gene variants ASIP and TYR associated with melanoma [18]. The ASIP locus encodes the agouti signalling protein and TYR codes for tyrosinase, so this report brings a molecular genetic explanation of the clinical observation of the association between melanoma, fair skin and fair or red hair.

Table 2. Established and postulated risk factors for cutaneous melanoma

Invasive cutaneous melanoma in one or more first-degree relatives.
Previous personal primary invasive melanoma.
Multiple banal melanocytic naevi (>100).
Three or more clinically atypical (dysplastic) naevi.
High solar exposure in early childhood (before age 10).
Pale Caucasian skin (skin type 1 or 2).
Red or blond hair.
Past history of one or more severe blistering sunburns.
Higher socioeconomic group.
Past sunbed use, especially before age 30.
Occupation (airline crew).
Past pesticide exposure.

phenotypic risk factors for melanoma

The likely melanoma patient is a pale-skinned Caucasian. Studies from Australasia [19], North America [20] and Europe [21] have all shown that a high count of banal melanocytic naevi is a major risk factor for sporadic melanoma. Naevus counts vary according to country; high counts are associated with UV exposure and may be used as a surrogate marker for UV-induced cutaneous damage. The presence of large, atypical naevi, termed dysplastic naevi in pathology, is also an independent risk factor adding to melanoma risk.

natural UV radiation exposure and melanoma risk

As already stated, short, intense episodes of burning sun exposure appear to be a significant risk factor for melanoma [10], but cumulative UV exposure over the years may also contribute to the risk. Studies of place of birth and residence during the first decade of life from Australia [22], Israel [23] and the USA [24] all record that birth and early life spent in a high-UV environment increases melanoma risk for the lifetime of the individual in question. There also appears to be an interaction between chronic UV exposure and the type of melanoma that may subsequently develop. The lentigo maligna variety of melanoma, found most commonly on constantly exposed body sites such as the face, is associated more with possible chronic occupational UV exposure than intermittent burning UV exposure episodes. Whiteman et al. [25] have taken this observation further and postulated two distinct, partly UV-induced pathways to melanoma that give rise to slightly different clinical outcomes. The first pathway involves intense intermittent exposure on the trunk of individuals who have large numbers of banal naevi and have melanoma

diagnosed at a relatively young age. The second pathway, probably more related to chronic UV exposure, is found in older individuals who may have a past history of non-melanoma skin cancer. These melanomas develop on sun-damaged, constantly exposed sites. This dual-pathway concept has been strengthened by the observation of Thomas et al. [26] that *BRAF* gene mutations are more likely in melanoma of younger subjects with large numbers of naevi (type A) than in lesions on sun-exposed skin of older patients (type B).

artificial UV radiation exposure and melanoma risk

Over the past two decades, artificial UV sources in the form of sunbeds have become widely available for both salon use and home purchase. A number of case–control studies have investigated the potential melanoma risk associated with sunbed use. The results are inconsistent, and interpretation is complex. Subjects who use sunbeds also tend to expose their skin to higher quantities of UV from natural sunlight, and separating the contribution of natural and artificial UV exposure to melanoma risk may be impossible. In addition, recall bias has to be considered as a possible confounding factor. Most melanoma patients are aware that UV exposure is a risk factor for melanoma, and are therefore likely to recall after diagnosis even small numbers of sunbed exposures. This type of recall is much less likely in the control group. A recent meta-analysis of sunbed use and melanoma has concluded that overall sunbed exposure does add to melanoma risk [27].

female sex hormones and melanoma risk

Differing melanoma incidence between males and females, and the tendency for females to develop excess melanin pigmentation during periods of hormonal stimulation such as pregnancy, has led to a number of studies investigating the role of pregnancy, oral contraceptives and hormone replacement therapy both as risk factors for melanoma and also as events that may affect prognosis. Cumulative data from publications on these topics provide no evidence that prior pregnancy is a risk factor for melanoma [28]. Similarly, there is no evidence to indicate that oral contraceptive [29] or hormone replacement [30] use contributes to melanoma risk, nor that either factor alters the prognosis for those in whom melanoma has already been diagnosed.

socioeconomic status

A number of studies have reported that, in contrast to squamous cell cancer of the skin, melanomas are more prevalent in the wealthier strata of society. Studies from the USA and UK [31, 32] show that the incidence of melanoma in age-matched sections of the population is higher in those with a larger income and other measures of affluence. This may be due to the greater opportunity of the more affluent for recreational sun exposure and sunny holidays in the winter months.

occupation and melanoma risk

Airline crews, particularly pilots, have been recorded in a number of studies as having a higher-than-expected incidence of melanoma [33, 34]. It is suggested that this may be due to greater opportunities for recreational sun exposure during regulation breaks between flights in areas of the world with a high solar exposure.

pesticide exposure

A case–control study comparing melanoma on the palms and soles in both the UK and Australia observed that melanoma patients reported greater exposure to pesticides than that reported by controls [33], and recently, an Italian case–control study has confirmed higher use of pesticides in a residential setting in melanoma patients compared with that in controls [34]. Interpretation of these data is complex, as over the past decade there have been many regulatory changes in Europe regarding the range of pesticides available for domestic use. However, data from these studies indicate that questions regarding the type and frequency of pesticide use should be added to future case–control studies.

therapeutic use of non-steroidal anti-inflammatory agents and statins

A recent case–control study of oral non-steroidal anti-inflammatory use in melanoma patients and age-matched controls indicates that regular use of this class of drugs is associated with reduced melanoma risk [35]. Further studies are needed to confirm this finding. A number of studies have investigated the possibility of an association between the oral use of statins and melanoma risk. The most recent study from the Netherlands indicates no association with melanoma risk, but does report that melanoma patients using statins have thinner tumours [36].

melanoma risk after renal transplantation

A number of publications show conflicting results concerning the risk of melanoma developing after renal transplantation and the necessary immunosuppression. Studies from Sweden and the Netherlands show no increase in melanoma incidence over that expected in these countries [37, 38], while studies from the USA and UK show a significantly increased risk, 3.6- and 8-fold higher for US [39] and UK patients [40], respectively. While some of these differences may relate to time frames of studies and changes in immunosuppressive regimes over time, further large long-term contemporary studies are required to determine the degree of increased cutaneous surveillance required for transplant patients.

approaches aimed at achieving earlier diagnosis

public education, screening and visual aids to earlier melanoma recognition

Over the past two decades, a number of public education exercises have been carried out aimed at increasing general knowledge about melanoma and, in particular, at helping the general public recognise early melanoma and seek medical advice. The objective is to have melanomas removed at an earlier growth stage when they are thinner and, therefore, have a better prognosis. This approach was pioneered by the

Queensland Melanoma Project and has been reproduced in both Europe and the USA. Data from Europe indicate that before such activities, there was poor knowledge of melanoma and, therefore, long delays between noting a new or changing pigmented lesion on the skin and seeking medical advice [41]. After such campaigns this type of patient delay reduced significantly, and the proportion of patients with thinner melanomas and thus better prognoses increased [42]. Earlier public recognition of melanoma concentrates on simple guidelines aimed mainly at superficial spreading lesions, which are the bulk of primary tumours. These guides include the US-based ABCDEs of melanoma recognition and the Glasgow 7-point checklist (Table 3). Other useful, simple aids to earlier diagnosis include the so called 'ugly duckling' sign [43], signifying a pigmented lesion that is clearly distinct from other pigmented lesions on the same body site.

Screening exercises have concentrated on the offer of a free skin examination and advice to consult the participants' regular medical attendants if a suspicious pigmented lesion is identified. The offer of a free skin check, often labelled 'melanoma Monday', has been popular in both the USA [44] and countries in Europe [45], where it has been adopted with large numbers of the public attending. This has been excellent publicity and a good opportunity for education on recognising melanoma, among other skin lesions, but the number of pathologically proven melanomas calculated per attendee is low in relation to the screened population. In the USA, a comprehensive review of the results of the AAD annual free skin check reported a yield of one melanoma per 667 participants [44], while in Belgium, the reported yield was one melanoma per 110 participants [45]. A report from the UK [46] gives a yield of one melanoma per 277 participants and concludes that rapid access to pigmented lesion clinics is a more cost-effective approach in its healthcare system.

Population-based screening has also been considered in Australia. A randomised trial of population screening was carried out in small Queensland towns, where some residents were selected for the screening, and compared with control towns, where mass screening was not offered [47, 48]. Results indicated a greater public interest in screening and self-examination, but the original plan to extend the work to a larger national trial has been abandoned because of cost. If the cost of such an exercise is prohibitive in the country with the highest incidence of melanoma worldwide, it is unlikely to be practical in countries with lower incidence.

Table 3. ABCDE(s) of melanoma and Glasgow 7-point checklist to assist accurate preoperative diagnosis of cutaneous malignant melanoma

ABCDE	Glasgow 7-point checklist	
A – asymmetry	Three major points	Four minor points
B – border irregularity	Change in size	Diameter ≥6 mm
C – colour variation	Change in shape	Oozing or crusting
D – diameter ≥6 mm	Change in colour	Inflammation
E – elevation or enlargement or exudation		Itch

visual aids to earlier diagnosis

A number of attempts have been made to increase the ease with which professionals, either dermatologists or general practitioners, can recognise melanoma at an early growth stage. The simplest of these is the hand-held dermatoscope, which enables the observer to examine and photograph cutaneous lesions at 5- to 25-fold magnifications. With this level of magnification, a number of surface features, such as pattern of melanin pigment spread around the lesion and erythema due to inflammation, can be visualised. Although these machines are now common in many European countries, there is little published data on their efficacy compared with naked eye examination. Available data indicate that training in dermatoscope use improves both sensitivity and specificity of clinical diagnosis by non-expert clinicians, but without training, preoperative diagnostic accuracy is reduced [49, 50]. More sophisticated equipment with the same aim involves computerised image analysis using machines such as the SIAscope and MoleMate. These machines are still under evaluation, and trials are required to establish whether they improve sensitivity or specificity of melanoma diagnosis in the hands of both well-trained dermatologists and less-experienced general physicians. A recent trial of the SIAscope in the setting of a pigmented lesion specialist clinic in northern England showed no diagnostic benefit compared with the clinical judgement of trained dermatologists [51]. A further trial assessing the value of the same machine in a general practice setting is currently in progress.

mortality, survival and factors influencing survival

Mortality figures over the past two decades show trends that differ from those for incidence, with a much lower rate of mortality increase than that recorded for incidence. This is well illustrated in Figure 1, which charts UK figures for incidence and mortality together for the 30-year period between 1975 and 2005, covering a population of 55 million.

In Scotland, melanoma mortality in males doubled between 1979 and 2003, a time period during which incidence tripled. In females in Scotland, mortality has remained constant, while incidence doubled [9]. Similar data are reported from other countries, and in Scandinavia in recent years a fall in melanoma-specific mortality has been recorded in younger females. This pattern of divergence between incidence and

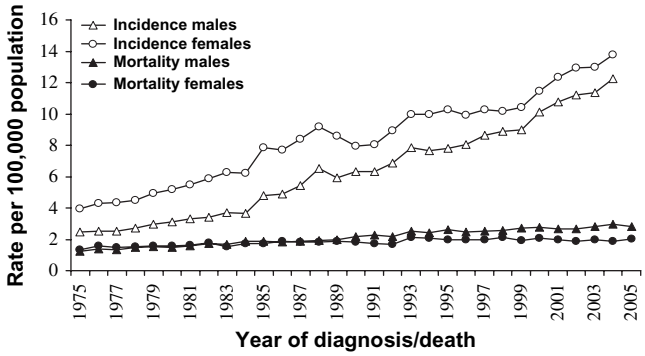

Figure 1. Age-standardised incidence and mortality rates of malignant melanoma in Great Britain between 1975 and 2005.

Table 4. Five-year survival (%) of 8897 patients diagnosed in Scotland from 1979 to 1998 based on the time period and thickness category[a]

Males	<1.0 mm	1–1.99 mm	2–2.99 mm	3–3.99 mm	>4.0 mm
1979–83	73.2	68.4	55.0	40.0	33.9
1984–88	82.7	78.3	56.5	45.1	30.8
1989–93	90.2	80.0	61.4	56.1	36.2
1994–98	93.6	87.9	71.3	65.3	52.4
Females[b]					
1979–83	86.0	84.9	62.9	55.7	37.6
1984–88	93.6	87.8	79.4	64.1	43.0
1989–93	93.5	94.9	77.4	66.2	44.8
1994–98	95.8	94.3	86.6	71.4	48.3

[a]Data taken from ref. [9].
[b]Note the superior female survival in each thickness category and time period.

mortality indicates improved survival, most of which is attributed to earlier detection of thinner tumours. Scottish data show improving 5-year survival in each quinquennium between 1979 and 1998 (Table 4), which also illustrates the better survival for females in each thickness grouping over this time period. This superior female survival in Scotland has been confirmed in Dutch patients and also shown to be independent of tumour thickness, histological type or body site of tumour [52].

Data from France for the period 1969–1997 show a 2.7- and 2.9-fold mortality increase in females and males, respectively [5], and Swedish data show decreased mortality between 1990 and 1999 compared with previous time periods [6]. A report from southern Germany concerning a cohort of 4791 patients and covering the time period 1976–2001 shows significantly improved survival in the time period 1990–2001 compared with 1976–1989 [53]. The authors of this paper speculate that improvements in surgical approaches, a greater use of adjuvant therapy and greater public awareness leading to earlier diagnosis may have contributed to this improvement.

concluding remarks

At the start of the 21st century, melanoma remains a potentially fatal malignancy giving rise to continuing concern for a number of reasons. At a time when the incidence of many tumour types is decreasing, melanoma incidence continues to increase. Much of this increase is seen in relatively young adults, and consequently the number of life years lost per melanoma death is higher than that for most other solid tumours. Although mortality data indicate that extensive public education campaigns have been at least partially effective in encouraging earlier self-referral of thinner melanomas with a better prognosis, few data indicate that primary prevention campaigns have had a substantial effect. These are mainly aimed at encouraging safe and reasonable sun exposure habits according to the latitude of the country in question and the skin type of the individual. More work is needed on the psychological factors leading to inappropriate sun exposure so that future campaigns may be more effective.

conflict of interest disclosures

The authors declare no conflict of interest.

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