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Current Perspective

Cutaneous malignant melanoma in Europe

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Abstract

Cutaneous malignant melanoma is on the rise in fair skinned societies. Both its incidence and mortality rates have been incresing in Europe over the past decades, the latter seem to stabilise in Scandinavia. The main cause of melanoma is intermittent exposure to ultraviolet radiation, especially in combination with endogenous factors like skin type and genetic predisposition. Evidence on an association between sunbed use and melanoma is inconclusive, but seems to point to a slightly increased risk associated with sunbed use. Within Europe, considerably variation in patterns of melanoma incidence and mortality existed. In this paper, we discuss the possible explanations for the observed trends and options for primary and secondary prevention. Early detection seems the most promising way to combat the relatively poor survival rates in Southern and Eastern Europe.

Keywords: Melanoma; Incidence; Mortality; Trends; Ultraviolet radiation; Prevention

1. Introduction

Descriptive epidemiology: Cutaneous malignant melanoma (melanoma) (CMM) is less common than the familiar basal and squamous cell tumours of the skin, but is much more fatal. It is mainly a disease of white people, but people with a more pigmented skin can also develop melanomas. It develops by the malignant transformation of melanocytes. In Europe, it is the 17th most commonly diagnosed cancer in males and eighth most common in females [1]. In 2000, approximately 26 100 males and 33 300 females were diagnosed with melanomas in Europe, and around 8300 males and 7600 females died of their disease [1]. In the Netherlands, a country with a relatively high incidence compared with European standards, the cumulative incidence rate before the age of 75 years in 2000 was 1% in males and 1.25% in females. Melanoma is one of the most important cancers in terms of 'years of potential life lost per death' (Fig. 1), as it is diagnosed in relatively young people [2–4]. In the US, a person dying of melanoma would die approximately 17 years before the age of 65 years [2], in Denmark 14–15 years and in Belgium 6–8 years [3,4].

2. Ultraviolet radiation

In white populations, exposure to ultraviolet radiation (UVR) is the main cause of all common skin cancers, including melanomas [5]. It can induce skin cancers by three mechanisms: it directly damages DNA leading to mutations; it produces activated oxygen molecules that in turn damage DNA and other cellular structures; and it leads to a localised immuno-suppression, thus blocking the body's natural anti-cancer defences [6,7].

3. Risk factors for melanoma

Intermittent exposure to UVR is the major environmental risk factor for melanoma, especially in combination with endogenous factors (skin types I and II, immune-deficient status, genetic predisposition) [5]. Patients with genetic abnormalities like *Xeroderma Pigmentosum* are at a 1000-fold increased risk [8]. If

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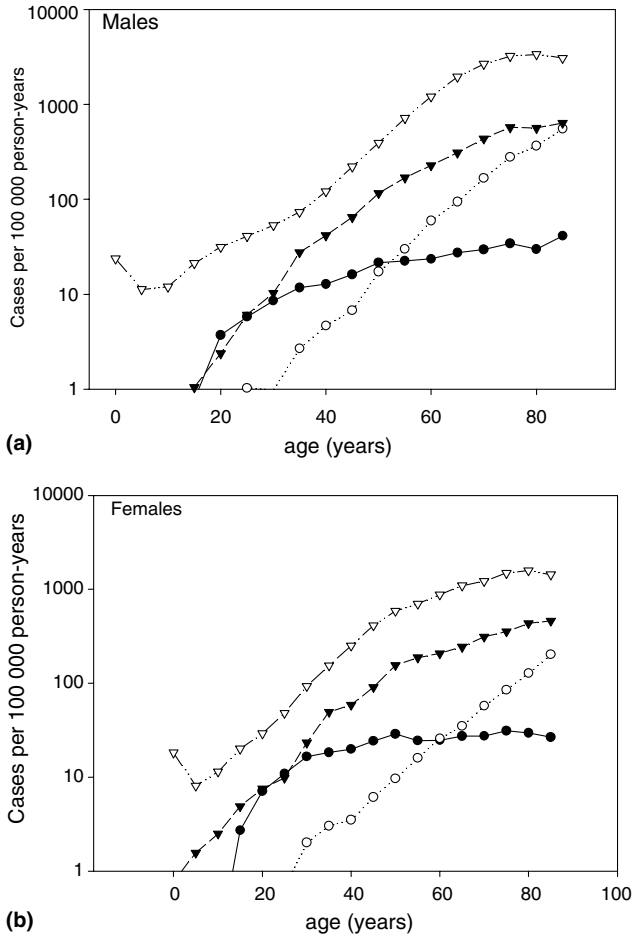

Fig. 1. Age-specific incidence of skin cancer. All data are based on the Netherlands data for 1996–1998, except for basal cell carcinomas (BCC), which are based on the Eindhoven Cancer Registry Area data for 1996–1998. (filled circles: melanomas; open circles: squamous cell carcinomas (SCC); filled triangle: BCC 1996–1998; open triangles: all tumours except skin).

melanoma runs in the family, the relative risk of developing another skin cancer is 2–3 [9] and familiary forms of melanoma (familial atypical multiple mole syndrome) have been discovered [8].

The association between UVR and melanoma is ambiguous, with differences in risks associated with the dose, the way it is delivered (intermittent vs chronic exposures) and critical time periods (Table 1).

UVR can be subdivided into UV-A, UV-B and UV-C. Their effects are summarised in Table 2. UVR is absorbed by the skin, but does not penetrate it. The majority of mainly UV-B and UV-C is absorbed in the epidermis by various molecules such as the keratins and DNA, in which UVR can suppress immune reactions, induce tolerance to antigens, upregulate gene expression and induce mutations [6]. Without repair of the damage, mutations in the DNA can eventually result in the formation of tumours [7]. These changes in the molecules are often harmful, but the damaged molecules can usually be replaced by normal molecules.

Various mechanisms exist to repair DNA that was damaged by UVR, for example, the nucleotide excision repair mechanisms (NER). Damage in stem cells or extracellular structures can accumulate and have negative effects, such as elastosis, premature ageing of the skin, wrinkling, cataracts and skin cancer [7].

Intermittent exposure to UVR in white people, especially during childhood, has been postulated to be the main risk factor for the development of melanomas.

UVR increases the risks of developing skin cancer, mainly in susceptible people (skin types 1–2 and tendency to freckle, with many naevi). For all skin cancers, skin phototype is an important determinant of risk; people who easily get sunburned have a higher risk of developing skin cancer compared with those who tan easily and do not burn (Table 3) [13,14].

4. Melanoma in non-caucasians

Melanoma is uncommon in negroid people (Table 4), Asians and Middle- and South-American populations, probably due to a better protection of the skin by a larger amount of pigment in the skin and possibly different ('wiser') sun-exposure patterns. In many African and Asian societies, it is considered beautiful to have a light skin and people try to avoid sun-exposure.

Table 1
Associations between exposure patterns and melanoma features

Host and tumour feature		Size of relative risk of CMM related to	
		Intermittent exposure	Chronic exposure
Age at diagnosis	Young	+++	+
	Old	+	+++
Histology	Superficial spreading	+++	+
	Nodular	++	+
	Lentigo maligna	+	+++
Subsite	Head and neck	+	+++
	Trunk	+++	+
	Extremities	+++	+

CMM, cutaneous maligant melanoma.

Table 2
Features of different types of UV-radiation

Wavelength (nm)	UV-A	UV-B	UV-C
	315–400	280–315	100–280
Penetrates to earth surface	++++	++	±
Induces sunburn	++	+++	+++
Induces pigmentation	++	+++	–
Induces thickening of epidermis	–	+++	–
Skin aging (elastosis, keratosis)	++	+++	–
Stimulates vitamin D_3 synthesis	+++	+++	–
Carcinogenic	++ [10–12]	+++	+

+ weak effect, ++ moderate effect, +++ strong effect, UV, ultra violet.

Table 3
Crude and adjusted relative risks of developing melanoma for selected risk factors [13]

Risk factor		RR Males (95% CI)		RR Females (95% CI)	
		Crude	Adjusted[a]	Crude	Adjusted[a]
Skin type	3–4	1		1.0	
	2	1.2 (0.6–2.5)	4.9 (0.7–36)	1.2 (0.8–1.8)	1.5 (0.7–3.3)
	1	1.4 (0.8–2.5)	7.3 (1.1, 48)	1.1 (0.7–1.7)	1.3 (0.6–2.9)
Severe sunburn	0	1		1	
	1–2	3.0 (1.8–5.0)	2.8 (1.3–5.6)	1.9 (1.3–2.8)	1.5 (1.0–2.4)
	3+	9.2 (3.4–25)	7.6 (1.8–32)	3.6 (1.7–7.7)	2.3 (0.9–5.6)
Total naevi	<20	1		1	
	⩾ 20	10 (3.6–28)	13.9 (2.7–71)	6.6 (3.4–13)	6.7 (2.9–15)
Freckling tendency	None	1		1	
	some	3.8 (1.9–7.6)	4.4 (1.5–13)	2.9 (1.8–4.6)	3.1 (1.7–5.6)

CI, confidence interval; RR, relative risk.
[a] Adjusted for total naevi, atypical naevi, freckling tendency, severe sunburn, tropical residence, ultraviolet use, skin type [13].

Table 4
Age-standardised incidence rates (ASR) per 100 000 person-years in the SEER registry (USA) [18]

SEER REGISTRY (from CI-5)	ASR (world) males	ASR (world) females
Blacks	1.00	0.5
Whites	15.4	11.6

SEER, surveillance, epidemiology and end-results.

UVR is considered a less important risk factor for skin cancer in coloured people. In non-whites, melanomas appear more often on the non-pigmented areas of the skin [15], are often of the acral lentiginous melanoma type and appear on the palms of hands, soles of the feet and under the nails [16,17]. A common problem in non-Caucasian populations is that pigmented lesions in the skin are often more difficult to notice and therefore melanomas are often detected at late stages, hence the high case-fatality rates [16,17].

5. Ultraviolet radiation from sunbed use (risks and behaviour)

The increased use of sunbeds, emitting significant amounts of UV-A and/or UV-B radiation, is of concern, especially since a substantial proportion of young people use sunbeds [19]. Although the risks of melanoma associated with sunbed use have not been unequivocally established, it is likely that the effects on the skin are equal for all sources of UVR. Studies on the risk of sunlamp use for the development of skin cancer, have suffered from various methodological and practical problems (Table 5).

Table 5
Problems in interpretation of the association between sunbed use and melanoma risk

Strong confounding of sunbed use with sun exposure
Lack of objective measures for sun exposure to adjust for confounding
Recall bias in recalling lifetime sun- and sunbed exposure in cases and controls [12,20–24]
Type of sunbed use
Reliable information on frequency and duration of sunbed use

Table 6
European studies on the association between melanoma risk and sunbed use published since 1990, only studies that adjusted at least for an indicator of sun exposure and phototype and give an estimate of the adjusted risk are included

Authors [Ref.]	Country, year	Cases	Controls	Adjusted RR/OR
Garbe [25]	Germany, 1993	856	705	RR: 1.5 (0.9–2.4)
Autier [20]	Germany, France, Belgium, 1994	420	447	OR: 2.1 (0.84–5.4)
Westerdahl [23]	Sweden, 1994	400	640	OR: 1.3 (0.9–1.8)
Westerdahl [24]	Sweden, 2000	567	913	OR: 1.8 (1.2–2.7)
Bataille [21]	United Kingdom, 2004	413	416	OR: 1.2 (0.84–1.7)

OR, odd ratio.

However, all studies on this topic since 1990 point to an increased risk associated with sunbed use, although most studies did not find significant effects. Moreover, sunbed use has become widespread only relatively recently and it might take a longer time to see the effects of sunbed use on the skin cancer risk (Table 6).

6. Prognostic indicators

Melanoma thickness, body site, histological type of the melanoma, gender of the patient and ulceration are important indicators of patient prognosis (Table 7). By far the most important prognostic indicator of melanoma survival is thickness. Generally, older patients do less well than younger patients with the same tumour thickness, even after correcting for age, and females do better than males. Superficial spreading melanomas generally have a better prognosis compared with other histological subtypes, because they usually have a thin Breslow thickness [26].

Table 7
Prognostic indicators for melanoma

Prognostic factor	Most favourable when
Breslow thickness	Thin (<1.51 mm)
Histology	Superficial spreading melanoma
Age	Young
Gender	Female
Ulceration	Absent
Mitotic activity index	Low

7. Geographical variation in melanoma incidence and mortality in Europe

Melanoma has shown a rapid rate of secular increase in incidence for white populations, whereas in pigmented people its incidence has remained rather stable. Generally, melanoma incidence rates in white populations increase with proximity to the Equator [27] but in Western Europe, the inverse pattern is observed, with the highest incidence rates noted in the North [28], (Figs. 2 and 3). Exceptions are the mountainous countries of Switzerland and Austria, which exhibit high incidence rates compared with the countries surrounding them [18,29,30]. Within the Nordic countries, the melanoma incidence displays a North–South gradient, as would be expected (Fig. 2) [31,32].

However, in Eastern Europe the highest incidence rates were observed in the South [33]. Age-standardised incidence rates per 100 000 person-years varied from around three in Spain, Belarus and Poland to around 14 in Norway and parts of Switzerland [18]. The higher incidence rates in Northern Europe were usually attributed to the lighter skin type of the Northern European populations compared with the Mediterranean populations and their relative affluence, enabling them

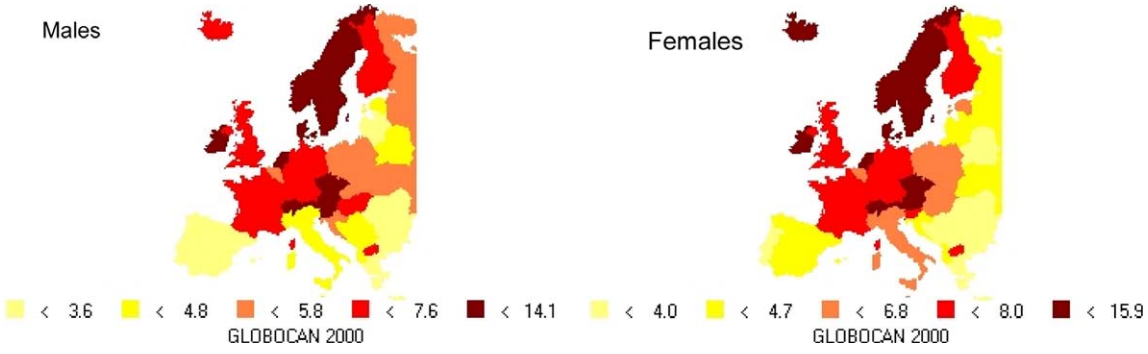

Fig. 2. Incidence of melanoma in Europe (Source: Globocan).

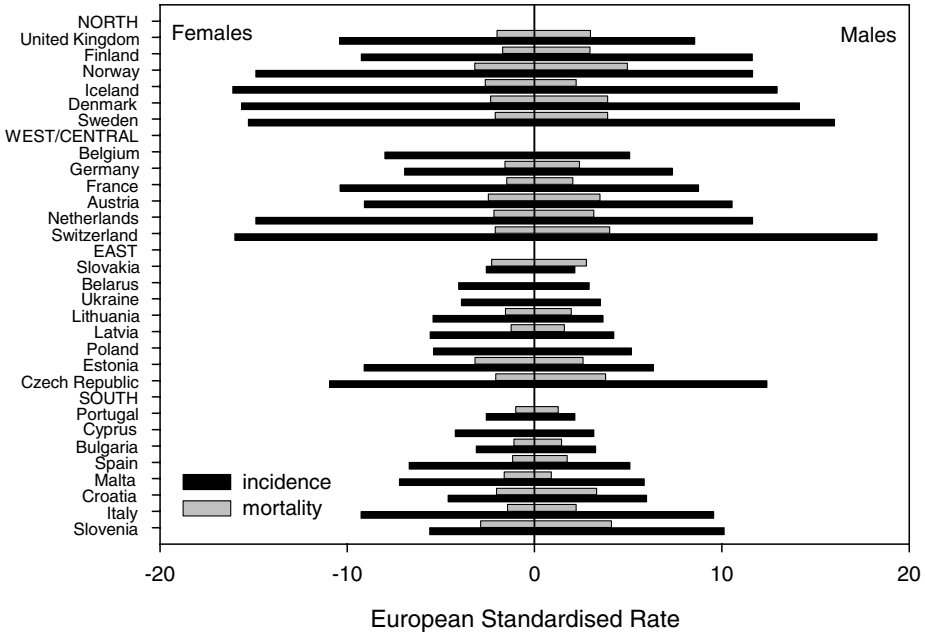

Fig. 3. Incidence and mortality of melanoma in Europe. Rates are given for 1996–1998, except for Austria, Belarus, Latvia, Lithuania, Norway, Portugal, Slovakia (1995–1997) and Cyprus (1998–1999). Source: EUROCIM.

to go on holidays to Southern Europe during the summer where they may expose themselves intensively and intermittently to amounts of sun that their skin is not used to [27].

8. Trends in incidence and mortality

Since the 1970s, there have been reports of 'alarming' increases, initially in melanoma mortality [34], closely followed by reports on melanoma incidence [31]. These reports observed a doubling in the rates of melanoma every 10 to 20 years (annual increments of between 3% and 7%) in populations of European origin for both genders [4]. Generally, the incidence rates increased markedly for the intermittently exposed body sites (trunk, legs, etc.), whereas increases on the face and neck were moderate. In males, the largest increases were found on the trunk and in females on the legs and arms [35–43].

In Northern Europe, where incidence rates became very high during the 1980s, the rates seem to be levelling off since the mid-1990s, especially in younger age groups [28,41,42,44–47]. In contrast, in Southern and Eastern Europe, rates are now increasing steeply in all age categories [28,45,47].

Over the last decades, increases in incidence have mainly been observed for thin melanomas, whereas the rate of thick melanomas seems to be relatively stable [48,49]. The increase in the number of thin melanomas is mainly observed in countries with high incidence rates, where increases in rates are mainly seen in the superficial spreading type [41,50–54]. In countries with lower incidence rates, increases are generally more evenly spread across the different thickness categories.

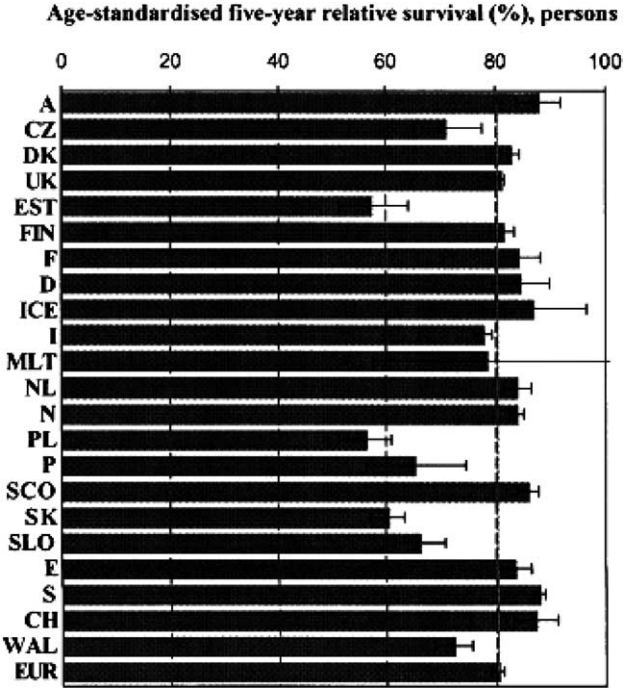

Fig. 4. Age-standardised five-year relative survival of melanoma of skin in European adults diagnosed between 1990 and 1994. Figure taken from [57]. (A = Austria, CZ = Czech Republic, DK = Denmark, UK = United Kingdom, EST = Estonia, FIN = Finland, F = France, D = Germany, ICE = Iceland, I = Italy, MLT = Malta, NL = The Netherlands, N = Norway, PL = Poland, P = Portugal, SCO = Scotland, SK = Slovakia, SLO = Slovenia, E = Spain, S = Sweden, CH = Switzerland, WAL = Wales, EUR = Total for Europe).

Table 8
Schematic presentation of possible determinants of the changes in trends and the associated expected and actual observations

Cause of 'increase'	Hypothetical observations	Actual observations
Completeness of registration improved or not by increasing involvement of pathology laboratories	More out-patient diagnoses	• Increases also observed in near-complete registries with link to pathology
Increased awareness/early detection	Temporary increase	• Often not observed
	Improved stage at diagnosis	• Often observed
	Decreasing mortality	• Small increases and some decreases
Changes in diagnostic criteria	Changing practises	• Not observed
	Period effects for changes	• Birth cohort effects
Increased intermittent sun exposure in the past		
• In behaviour, fashions	Generation(birth cohort) effects	• Birth cohort effects were observed in mortality rates
• In environment (e.g. ozone)	Period effects	• Period effects were observed
• Charter flights		

Survival is related to the stage distribution of the melanomas at diagnosis. This is generally good in countries with high incidence rates, whereas survival rates are rather poor in the lower incidence countries (Fig. 4) [33,41,42,55].

Although incidence rates of melanoma vary greatly within Europe, mortality rates show less variation. Currently, mortality rates are levelling off in many populations with high melanoma incidence rates, such as Australia, the United States of America (USA), and countries in North-Western Europe (Scandinavian countries, United Kingdom (UK), the Netherlands, Germany, Switzerland) [28–30,46,47,56]. In some countries, a levelling off of the incidence rates is also now being observed, starting in the young age groups [28]. Awareness usually starts in the younger age groups.

8.1. Age-period-cohort analysis

Evidence is accumulating that in several populations (USA, Australia, New Zealand, Sweden, the Netherlands, Germany) the increasing mortality rates have started to level off, starting with the birth cohorts from the 1930s/1940s [44,56,58–63]. In other countries, generally those with lower incidence rates (Italy, Spain, Southern Europe), there was no sign of a downwards trend, at least up until the 1990s [45,64,65].

9. Explanation of the trends – are the increases real or partly due to an artefact?

The strong increases in melanoma incidence and mortality over recent decades also indicates the growing problem of the burden of skin cancer prevalence on the health-care system, even though many patients are truly cured. To assess the causes of these trends, whether they are real or artificial and if rising incidence rates can be prevented, is therefore important [49] (Table 8).

9.1. Completeness of registration

In many registries, the completeness of melanoma registration will have improved over time. However, there are still indications that melanoma is underreported in several cancer registries [66–68]. Underreporting is more likely for out-patients and in cases where the pathological laboratories do not report cases to the cancer registry. This concerns mainly the thin, early stage melanomas [67]. However, the marked increases in melanoma incidence have also been observed in countries which are known to have a nearly complete pathology-based registration of melanoma cases, such as in the Netherlands, Scotland, Finland and Sweden [41,53,67]. Therefore, improvements in the completeness of registration are unlikely to explain the marked increases observed in recent decades.

9.2. Increased awareness/early detection

Increased awareness among the population in general and the medical profession seems a more plausible reason for the increases, observed in melanoma incidence. Increased awareness of the population and/or early detection campaigns have urged more people to see a doctor when they have a skin lesion, thereby improving the detection of (mainly thin) melanomas. This would result in an increase in the incidence of thin melanomas, and, after a while, a decrease in the number of thick melanomas, as melanomas would be detected in early stages, before they developed to advanced disease [49]. This increase in melanoma incidence should, however, be temporary, as the time of diagnosis is only brought forward, without any real increase in incidence; without the early detection the melanomas would be detected at later stages (lead-time bias). However, there has been no such temporary increase: in some countries, melanoma incidence rates increased in all age groups since the 1960s until at least the end of the 1980s and in some cases, into the 21st century [28]. In the case of mela-

noma, the effect of increased awareness could take a long time, starting mainly in the young and higher socio-economic classes, slowly spreading to the middle-aged, elderly and lower socio-economic groups.

Moreover, inspecting the relative survival curves, the early detection of melanomas would be expected to translate into decreasing mortality rates after around 5–7 years. However, melanoma mortality rates have also been increasing, albeit more slowly than the incidence rates. While the proportion and number of thin melanomas has increased, the number of thick melanomas has remained stable or slightly increased, instead of decreasing [48,49]. However, this might be age-dependent. In the Eindhoven cancer registry, large increases in the rates of thin melanomas (<1.5 mm) were observed in the young, with decreasing rates of thick melanomas, whereas in the elderly (aged 60 years and older), there were no major changes in the thickness distribution [69].

There is no other explanation for the relatively low mortality rates in countries with high melanoma incidence rates than a higher awareness of melanoma in these populations. This means that most melanomas are diagnosed in early, treatable stages.

9.3. Changes in diagnostic criteria

Increased concerns about the melanoma problem in the medical field should urge medical doctors to more carefully inspect suspected lesions. Some lesions that were previously regarded as benign might, due to a more careful inspection, be regarded as melanoma. This theory has been tested by several groups, but there seems to be little evidence for changes in histological criteria as the cause for the rises in melanoma incidence [70,71]. Furthermore, the observation of birth cohort effects [44,56,58–63] makes it unlikely that a systematic improvement in death certification would have accounted for the rises in melanoma mortality rates, as this would translate into period effects.

The proportion of thin melanomas has increased over recent decades [41,48,49,54]. Assessment of malignancy of pigmented lesions is based on microscopically-observed characteristics. This malignancy criterion is used for all melanomas, both thick and thin, and is used to predict the biological behaviour of the disease. In other words, an untreated malignant lesion would eventually kill the patient. For the thick melanomas, this prediction of malignant behaviour seems to hold true: in Scotland, 5-year survival was 47% and 55% for men and women with tumours thicker than 3.5 mm, whereas this was 93% and 97% for those with tumours thinner than 1.5 mm [41]. The assumption of malignancy has been debated for thin melanomas; it was hypothesised that a non-metastasising form of melanoma might explain recent observations of increasing trends of thin melanomas with a better survival in South-Australia [72], and the stable numbers of thick melanomas despite a growing number of thin melanomas [49]. However, the increased awareness of melanoma risk in the population could also lead to the overdiagnosis of thin lesions, with similar clinical and histological characteristics as malignant melanoma, but with a benign biology.

Changes in melanoma biology have also been proposed to explain the trends: if UVR acts as a promotor in melanoma, then a decrease in UV-exposure could lead to a slower progression of the lesions [73]. Thin melanomas more recently diagnosed in New South Wales seem to progress at a slower rate than expected based on past trends [72].

Considering the above, the increasing incidence rates may partly be caused by early detection and the diagnosis of clinically insignificant melanomas [49]; however, the largest part of the increases in melanoma incidence and mortality rates is assumed to be real.

10. Causes of the real increases in melanoma rates

The 'real' increases in melanoma rates are most commonly attributed to changes in lifestyle with increasing intermittent exposure to UV radiation, due to the popularity of sunbathing and tanning since the late 19th century. Before the Industrial Revolution, wealthy people had a pale skin: they worked or stayed indoors, lower classes were mainly outdoors. During the industrialisation of society (1750–1800), machines appeared, and the working classes started working indoors in the factories. Only the rich had the time and money to afford recreational outdoor life, such as going to the beach, sports, walking in the mountains, skiing and sailing, and having a tan became the symbol of having money and being healthy. By the early 1920s, daily exposure to sunlight was also advised as a cure for many diseases (acne, rickets, tuberculosis), especially for children. By the 1930s, a suntan had become a symbol for wealth and health. Swimwear changed, with shoulder straps, which could be lowered to keep an even tan. During the 1960s, the bikini, and later monokini, appeared, allowing women's bodies close to total exposure.

Since the 1950s, holidays to sunny destinations and charter flights (first to Mediterranean regions, from the 1980s also to the (sub)tropical countries) became popular, and could be afforded by an increasing number of people.

In the 1940s, suntan lotion was introduced, originally designed to help in getting a tan, not to protect against the sun. In the 1950s, the first suspicions that sunlight could cause melanoma arose [74]. In the 1960s, indoor tanning, mainly in the winter, became possible through the use of sunlamps. Throughout the 1970s and 1980s, reports of the increasing incidence and mortality rates of melanoma were reported [75–77], while the fashion press suggested that suntans make you look and feel healthier

Table 9
The excess number of skin cancers under the Vienna protocol: scenario's of ozone depletion in the years 2050 and 2100 in a population of 160 million in North-Western Europe (including Belgium, the Netherlands, Luxembourg, Denmark, Germany and Great Britain) [85]

Ozone depletion Scenario	Extra cases of skin cancer per year in 2050	Extra cases of skin cancer per year in 2100
No restrictions	55 680 (+35%)	550 000 (+315%)
Montreal protocol	36 960 (+21%)	170 000 (+95%)
Copenhagen amendments	14 240 (+7.5%)	4000 (+2%)

and younger. The use of sunbeds became increasingly popular during the 1980s. Tanning saloons boomed and sunbeds became available for use at home. Moreover, in Germany in the 1970s, the 'Körpercultur' and nudism became popular, exposing the whole body to the sun. Tanning became increasingly popular, despite a growing body of scientific evidence that tanning not only leads to early aging of the skin, but also causes skin cancer [31,74]. Awareness of the link between UV-exposure and skin cancer grew slowly – especially when people started to worry about damage to the ozone layer in the early 1980s.

Although today we know the risks of sun-exposure, a tanned skin remains desirable, beaches are crowded, sales figures of self-tanning lotions and sunbeds are high and cheap flights to sunny destinations in (sub)tropical areas are widely available and consumed.

Given an induction time of some 20–40 years between exposure and melanoma occurrence, the increasing popularity of sunbathing and getting a tan in the past is in accordance with the currently continuing increases of melanoma incidence, mainly on the trunk in males and on the legs in women [39,78–83].

Another explanation for the increases is the depletion of the ozone layer, which protects the earth's surface against UV-radiation by filtering out a large part of the UVR from the sunlight before it reaches the earths' surface. Chemical substances released in the earth's atmosphere are slowly breaking down the ozone layer, increasing the amount of UVR that reaches the earth's surface and likely increasing the risk of skin cancer. Estimates indicate that skin cancer incidence rates could increase dramatically by the end of this century compared with the situation around 2000 [84] (Table 9).

Vaccination during childhood against tuberculosis with the Bacille Calmette–Guérin (BCG) vaccine or against smallpox with the vaccinia vaccine, or having experienced one or more infectious diseases may decrease the risk of developing melanomas (odds ratios between 0.29 and 0.44) [86–88]. Part of the increases in melanoma incidence could be due to the abolishment of this type of vaccination in Europe.

11. Stabilisations

Recent stabilisations in melanoma mortality rates (in some cases followed by incidence rates) are reported in high-incidence countries, such as Australia, USA, Sweden, Norway and Germany [4,28,37,42,47]. Only the mortality rates levelled off initially, starting in the late 1970s, with increasing incidence rates. This was most likely because of an improved patient survival [41,42,55] due to earlier detection, as there were no major improvements in systemic melanoma treatments. Melanoma incidence rates were also levelling off (Denmark, the Netherlands, Switzerland and the United Kingdom) or even decreasing (Finland, Norway, Sweden) in the young age groups, starting in the 1980s [28]. Furthermore, the mean and median stage or thickness at diagnosis is decreasing [41,48,49,54,55] with an increasing registration of thin, superficial spreading melanomas.

Changes in the biology of the melanoma with less aggressive lesions could also be consistent with a continuing increase in melanoma incidence, with a moderation or stabilisation in the mortality rates.

12. Primary and secondary prevention

The fashion of tanning has contributed substantially to the increases in skin cancer incidence. However, undoubtedly incidence rates may have increased due to the greater awareness of people about the risks of sunbathing and their growing knowledge about the need to inspect the skin for suspected lesions. In the late 1970s and the 1980s, projects were initiated to increase awareness (starting in Australia, followed by Scotland, Scandinavia, and other European countries) which increased the detection of skin cancers, often in more favourable stages than they used to be [89–92]. These campaigns seemed to be most effective in young females, whereas males were more difficult to reach [93].

12.1. Primary prevention

If melanomas and other skin tumours develop mainly due to excessive intermittent exposure to UVR in susceptible people then limiting exposure to UVR should prevent skin cancer. The question is whether a high-risk approach is sufficient (only preventing skin cancer in the high-risk groups) or whether a mass-campaign should be organised. Moreover, since UVR also exerts positive effects on human health [94–98], one cannot advise plain avoidance of exposure, espe-

cially in moderate climates like North-Western Europe.

However, if having a tan would no longer be considered healthy and beautiful, people could change their patterns of sun exposure, possibly resulting in decreasing skin cancer incidence rates. In the prevention of melanoma, it seems particularly meaningful to prevent multiple erythemas during childhood, convincing parents and caretakers not to let children stay too long in the sun. For these purposes, mass media campaigns would be most effective, since the general attitude of the population towards sunbathing and having a tan needs to be adapted before behavioural changes might be induced.

13. Protection against UV radiation

Given the positive and negative effects of UV radiation, balanced messages should inform people about 'safe' ways to be in the sun. There are several ways to protect your skin against the harmful effects of UV-radiation: natural protection; tanning, avoiding the sun, clothes/hats, sunscreens.

13.1. Natural protection

Tanning is a protection mechanism of the skin. Absorbing layers are thickened and pigmented and mechanisms to clear away or repair the damage are stimulated (renewing proteins, repairing DNA, replacing dead or damaged cells). The extra pigment and thickening of the epidermis serve to protect the underlying cells of the skin against UVR, rendering the skin less sensitive to sunburns. This protection disappears after a couple of weeks of limited exposure.

A slow adaptation of the skin to the sun is important in protecting against UV radiation, both in the sun and in sunbeds, allowing the skin to thicken and form pigmentation as protective mechanisms. Sunbed manufacturers have developed schemes for the use of sunbeds.

13.2. Clothes and seeking shade

Wearing clothes and hats when outside or seeking the shade decreases the amount of exposure to UVR drastically, although not completely. Fabrics let fractions of UVR through, depending on their texture and UVR often gets reflected, for example by sand or snow, making UVR exposure in shadows possible.

13.3. Sunscreen use

Most sunscreens in use consist of a combination of organic substances that absorb both UV-A and UV-B. Sunscreens with zinc oxide or titanium dioxide protect the skin mainly by reflecting UVR.The sun protection factor (SPF) is determined with an artificial light-source and applying 2 mg of product per m^2. In practise, people usually use insufficient amounts of the product to realise the protection they envisage. Reasons for this are ignorance, aesthetic unattractiveness (so much lotion will make you look white), and the high costs of sunscreens. Protection by sunscreens is also lower than the indicated SPF at high altitudes and where there is a lot of wind and transpiration.

A group of experts from the International Agency for Research on Cancer (IARC) has investigated the preventive effects of sunscreen use on the development of skin cancer: the use of protective cream could indeed prevent erythema and squamous cell carcinoma after *non-intensive* sun-exposure. Its protective effect for basal cell carcinoma and melanoma, however, is not yet determined, as it is difficult to study due to the long latency period. There is even evidence that the use of sunscreens may paradoxically increase the risk of CMM development by increasing sunbathing-time. Out of the 15 case-control studies examined by group of experts, only three resulted in a significantly reduced risk of melanoma with relative risks between 0.2 and 0.6, the others observed no significant effect (four studies) or an increased risk (eight studies, RR between 1.7 and 3.5) [99].

More sunscreen is needed in areas closer to the equator or highup in the mountains, in the summer, and during the warmest hours of the day.

13.4. Quick- and self-tanning lotions

There is no connection between skin cancer and the use of quick-tanning substances, except for products containing bergamot oil, which have a carcinogenic effect and is this product currently banned [100]. Self-tanning substances, which give the skin a brown colour without sun exposure colourise the corned layer of the skin, but do not stimulate melanin production. Many of these substances contain β-carotene. Elevated risks from the use of these products have not been demonstrated to date.

14. Secondary prevention

Early detection of skin tumours seems useful, as a relatively simple surgical treatment in early stages dramatically improves the prognosis of patients and an effective treatment for metastases is not yet available. Early detection aims at reducing 'patient delay', limiting mutilation and preventing death. Early stage melanoma is recognised by patients and their partners and by dermatologists, general practitioners and doctors doing physical examinations on their patients.

One can distinguish between screening of persons with an increased risk of melanoma because of a familial vulnerability, with an increased risk of melanoma because of skin type and skin damage, and screening of the general population.

Regular screening of the total population for CMM does not seem useful and is not propagated in any country in the world. The advantages gained are small, because the incidence of melanoma is low, and melanomas are already diagnosed at favourable stages, especially in women and young males. The chance that screening will result in a more positive stage is small. Moreover, every screen interval (in other tumours usually 2–5 years) would be too long for the fast-growing aggressive melanomas.

However, it seems likely that people with a familial risk of developing melanomas (those with familial or sporadic dysplastic naevus syndrome, *Xeroderma Pigmentosum* and large congenital naevi, representing approximately 10% of all melanoma patients) can benefit from regular check-ups. Screening in these populations, and regular checks (every 6–12 months) leads to earlier detection [101].

Heightened alertness is desirable in groups of people with a combination of risk factors, indicating an increased risk of developing melanomas (a sum of having light skin, blond or red hair, freckles, family history of skin cancer, multiple dysplastic naevi, men aged 50 years and older, history of severe sunburns in childhood).

Initiatives for screening, even if only directed at high-risk groups, increases the awareness in the general population. This effect may be more important than the direct effects of screening itself.

15. Future perspectives

In many countries where incidence is high and where awareness and (secondary) prevention campaigns have often been organised, moderations in the increases of melanoma mortality rates are observed within a few years, followed by moderations in melanoma incidence in younger age groups after more than 10 years, corresponding with the observed birth cohort effects in the mortality rates [28,44,46,47,56,58–63]. If these trends persist, and efforts to improve awareness and increase early detection of melanomas are maintained and/or initiated, a decrease in the overall melanoma mortality rates can be expected. However, melanoma incidence rates in the elderly, mainly in males, remains high and survival rates for this group are worse than average.

If the hypothesis that many of the newly-diagnosed thin melanomas are of a benign biology holds true, some of the increases in melanomas might turn out to have been artificial.

If a more prudent attitude towards sun exposure and having a tanned skin can be achieved, incidence rates of melanoma can really be expected to decrease, as in Europe between 54% and 80% of melanomas are assumed to be caused by intermittent sun exposure [5].

Without measures to prevent the ozone layer from further breakdown and more prudent recreational and sunbathing behaviour and clothing styles, skin cancer incidence rates will keep increasing rapidly.

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