

TOPICAL REVIEW

Global perspectives of contemporary epidemiological trends of cutaneous malignant melanoma

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Summary

During the past several decades, there has been a substantial increase in the incidence of cutaneous melanoma among all caucasian populations. The number of deaths due to cutaneous malignant melanoma has also increased in most fair-skinned populations throughout the world in the past few decades. Trends in melanoma incidence worldwide are examined. The most recent data on the mortality from cutaneous melanoma are reported. The role of different environmental, genetic and host factors in the aetiology of melanoma is discussed.

Key words: aetiology, incidence, melanoma, mortality

The incidence of cutaneous malignant melanoma (CMM) has substantially increased among all caucasian populations in the last few decades.¹ Due to the increase in incidence and the consequent mortality, CMM represents a significant and growing public health burden.

Incidence of cutaneous malignant melanoma

The number of melanoma cases worldwide is increasing faster than any other cancer. The annual increase in incidence rate varies between populations, but in general has been in the order of 3–7% per year for fair-skinned Caucasian populations.¹ The estimates suggested a doubling of melanoma incidence every 10–20 years.² Table 1 shows incidence rates of CMM for 23 selected countries reported in *GLOBOCAN 2000*.³

In Australia, CMM is the fourth most common cancer among males (after prostate cancer, bowel cancer and lung cancer) and the third most common cancer among females (after breast cancer and bowel cancer).⁴ Until recently, Queensland, Australia, has had the highest melanoma incidence rate in caucasians. In the period between 1980 and 1987 the reported annual incidence of invasive melanoma in

Queensland was 55.8 per 100 000 inhabitants for men and 42.9 per 100 000 inhabitants for women.⁵ The incidence of melanoma in men almost doubled during this period, reaching epidemic proportions, particularly in individuals over age 50 years. Similar incidence rates were documented in New South Wales, Australia, where between 1986 and 1988 the annual incidence of invasive melanoma was 52.5 per 100 000 in men and 42.9 per 100 000 in women.⁶

Melanoma incidence data for Australia for 1983–1999 are presented in Figure 1. Recently reported statistical data suggest that the lifetime risk for development of melanoma in Australia is now 1 in 25 for men and 1 in 34 for women.⁷ The incidence of melanoma has been decreasing in young women since the mid 1980s, but has continued to rise in older age groups.⁸

Analysis of the data from New Zealand suggested that in 1999 the caucasian population in the region of Auckland, New Zealand, has the highest documented incidence of melanoma in the world, with the crude annual incidence for invasive CMM of 77.7 per 100 000 and the age-standardized annual rate of 56.2 per 100 000, with no statistically significant differences in the rates for males and females. The cumulative risk of developing melanoma over a lifetime in New Zealand has been reported to be 5.7% overall (5.9% for males and 5.4% for females).⁹

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Table 1. Incidence of cutaneous malignant melanoma (per 100 000) for 23 selected countries³

Country	Male		Female	
	Crude	ASR	Crude	ASR
Australia	51.6	40.5	40.7	31.8
New Zealand	45.2	36.7	44.4	34.9
Sweden	19.8	12.6	19.9	13.3
U.S.A.	16.4	13.3	12.9	9.4
Denmark	14.8	10.6	17.6	13.0
Switzerland	12.5	9.3	15.0	11.1
The Netherlands	12.2	9.4	16.7	12.9
Austria	11.5	8.8	15.4	10.4
Canada	10.6	8.2	10.6	8.0
Hungary	10.3	7.6	10.3	6.8
Israel	9.7	9.4	11.0	9.8
Germany	9.3	6.5	11.4	7.1
France	8.6	6.8	11.1	7.9
U.K.	8.3	6.1	11.3	7.7
Poland	6.6	5.6	8.6	6.7
Italy	6.5	4.6	8.2	5.5
Russian Federation	6.3	5.4	6.4	4.7
Spain	4.0	2.8	6.8	4.5
South Africa	3.8	6.4	3.6	4.8
Brazil	2.9	3.5	2.0	2.2
Greece	2.5	1.9	3.2	2.0
Japan	0.63	0.40	0.49	0.29
China	0.21	0.22	0.17	0.17

ASR, Age-standardized incidence rate.

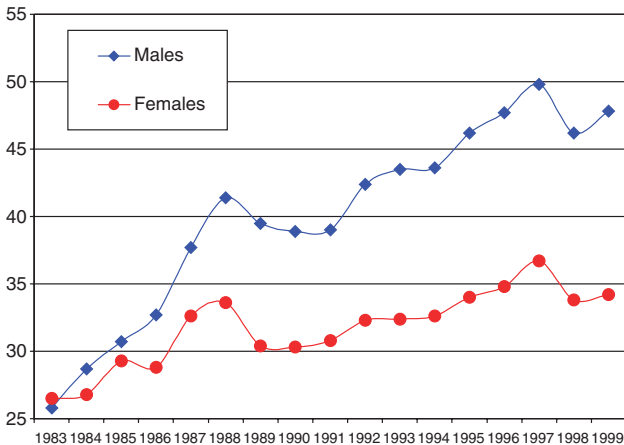


Figure 1. Age-adjusted melanoma incidence (per 100 000) in Australia, 1983–1999 (data from the National Cancer Statistics Clearing House at the Australian Institute of Health and Welfare).

The data from the U.S. Surveillance, Epidemiology, and End Results (SEER) registry (covering approximately 14% of the U.S. population) showed that malignant melanoma was the most rapidly increasing malignancy in both sexes in the U.S.A. during 1973–1997. In that period the age-adjusted melanoma incidence rates (expressed as the number of cases per

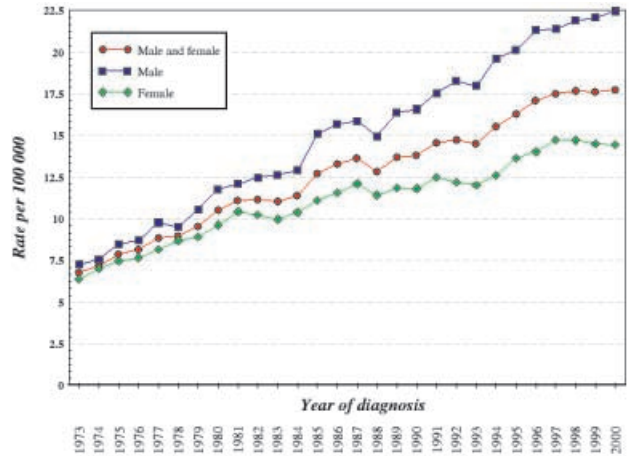


Figure 2. Age-adjusted (2000 U.S. standard population) melanoma incidence (per 100 000), nine registries, 1973–2000 (data from the SEER Program of the National Cancer Institute).

100 000 person-years of observation) almost tripled among males, from 6.7 in 1973 to 19.3 in 1997, and more than doubled among females, from 5.9 to 13.8.¹⁰ The age-adjusted incidence (per 100 000 population) of all melanomas among SEER Registries in the U.S.A. in the period from 1973 to 2000 is presented in Figure 2. The SEER age-adjusted incidence rate for melanoma diagnosed in the period from 1996 to 2000 was 21.8 among males and 14.5 among females.¹¹ The incidence of malignant melanoma has increased steadily in the U.S.A.: in 1935 the lifetime risk of an American developing melanoma was 1 in 1500 individuals, while in 2002 the risk was 1 in 68 individuals.¹² Figure 3 shows the lifetime risk of developing melanoma in the U.S.A. A statistical calculation estimated that in 2003 CMM will be the fifth most common cancer among males and the seventh most common cancer among females in the U.S.A.¹³ In 2003, it is estimated that 54 200 Americans will be diagnosed as having melanoma, and 7600 will die of the disease.

Trends in melanoma incidence by anatomical site were examined in Canada, where ascertainment of cancer has been of a high standard. The analysis of 41 239 patients with malignant melanomas registered in Canada between 1969 and 1993 showed that the estimated annual increase in incidence was 4.8% for males and 3.1% for females.¹⁴ The largest relative increases occurred for the upper limbs (5.7% annual change for males and 4.3% for females), followed by the trunk (5.6% annual change for males and 3.6% for females).

In Europe the highest incidence rates have been reported in Scandinavia (about 15 cases per 100 000

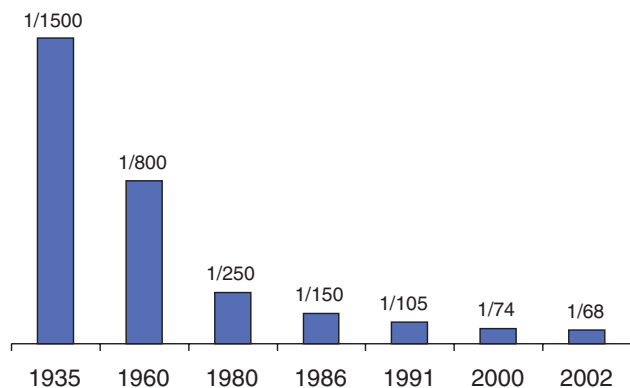


Figure 3. Lifetime risk of developing malignant melanoma in the U.S.A.

inhabitants per year) and the lowest in the Mediterranean countries (about five to seven cases per 100 000 inhabitants per year).¹⁵

In Sweden, age-adjusted incidence rates (per 100 000 population) were 11.6 for males and 10.9 for females in 1981, while the rates in 1991 were 18.0 and 15.6, respectively. The increase was less prominent in the period between 1991 and 2000, with incidence rates of 19.6 for males and 17.4 for females in 2000.¹⁶ A study evaluating incidence trends of CMM *in situ* in Sweden in 1968–1992 demonstrated that among men, age-standardized rates increased from 0.1 per 100 000 in 1968 to 2.9 per 100 000 in 1992 (mean annual increase of 15.0%), while among women rates increased from 0.3 to 3.7 per 100 000 (mean annual increase of 12.8%).¹⁷ Analysis of the trend in incidence of CMM in the Swedish population in the period 1976–1994 showed an upward incidence trend not only for *in situ* melanoma but also for invasive melanoma, although the estimated mean annual increase was about twice as large for *in situ* melanoma (9–10%) as for invasive melanoma (4–5%).¹⁸

Examination of the incidence of primary invasive melanoma in Northern Italy in the period 1986–1997 gave the age-standardized incidence of CMM of 7.57 per 100 000 in males and 11 per 100 000 in females. Between 1986–1991 and 1992–1997, the incidence of melanoma rose from 5.0 to 10.0 cases per 100 000 person-years in males and from 8.9 to 13.1 cases per 100 000 person-years in females.¹⁹

In the U.K. in 1996, CMM was the eleventh most common cancer in women and the twelfth most common cancer in men. Among people under 35 years, it is the third most common cancer in women and the fifth most common cancer in men. In

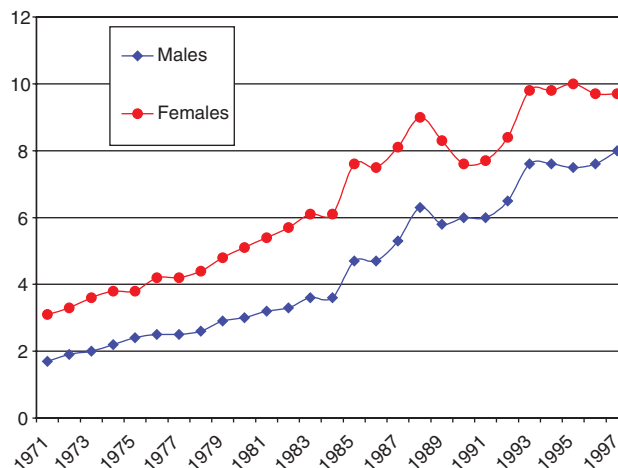


Figure 4. Incidence of cutaneous malignant melanoma in the U.K., age-standardized to the European standard population (rates per 100 000 population).

1997 melanoma contributed 2% to the total cancer burden in the U.K.²⁰ Incidence rates in the U.K. have increased from around 1.7 in 1971 to 8.0 per 100 000 population in 1997 for males, and from 3.1 to 9.7 per 100 000 population for females, a fourfold and a threefold rise, respectively. The incidence of CMM in the U.K. is presented in Figure 4.

The analysis by the Scottish Melanoma Group of 8830 patients diagnosed as having invasive CMM (Clark level 2 or deeper) in Scotland, U.K., during the period 1979–1998, showed a steady and continuing rise in the incidence of invasive melanoma in both genders. Incidence rate (age-standardized) rose from 3.5 in 1979 to 10.6 per 100 000 population in 1998 among men, and from 7.0 to 13.1 among women.²¹

In the area of South Wales, U.K., analysis of the melanoma incidence trends in the period 1986–1998 showed a rise in incidence of 74% in the last 10 years. The age-standardized rate of 9.6 per 100 000 for males, and 14.5 for females, is one of the highest recorded in Europe.²² Most of the increased incidence is ascribed to increased numbers of superficial spreading melanoma.²³

This review has shown considerable variation in the incidence rates of melanoma worldwide. Reported data suggested more favourable incidence trends in some countries while in others the incidence of melanoma is still rising. Recent evidence suggests that the current trend of increased melanoma incidence is due to improved surveillance techniques with early diagnosis, together with changes in lifestyle in terms of excessive recreational exposure to sunlight.^{24,25} The overall

increases in melanoma incidence have begun to slow in the later years in Western Europe and North America. One of the explanations for the slowing in the melanoma incidence rates in these countries is the decrease in sun exposure of the type likely to cause melanoma (improved sun exposure behaviour), particularly to parts of the body normally covered by clothes. With effective skin cancer prevention campaigns and public education, further declines in incidence can be expected over the coming years.

Mortality from cutaneous malignant melanoma

The number of deaths due to CMM has also increased in most fair-skinned populations throughout the world in the past few decades.¹ The death rate from melanoma continues to increase faster than the death rate for most cancers, with the exception of nonHodgkin's lymphoma, lung cancer in women, and testicular cancer. However, melanoma mortality rates have been rising at a rate of increase lower than that for melanoma incidence.

Between 1955 and 1984, mortality from CMM had been rising both in young adults (20–44 years) and in middle-aged populations (45–64 years) in most European countries, North America, Australia and New Zealand, with a rate of increase of 2–4% annually.²⁶ Analysis of the data from the World Health Organization (WHO) Cancer Mortality Data Bank suggested that populations are currently at different places on the melanoma mortality epidemic curve.²⁷ In some countries (U.S.A., Australia, Nordic European countries, U.K., Canada) a moderation or stabilization of the rising trends in mortality has been reported in more recent birth cohorts, while in other countries a steep increase with no major changes in this trend was observed (central and southern European countries).

Analysis of mortality datasets of 18 countries revealed that in the period 1985–1995, CMM mortality rates were still rising in several countries for middle-aged men, although to a lesser extent, they were more favourable in middle-aged women and declined in young adults in most countries, particularly in northern Europe.²⁶ Scottish data showed a rise in melanoma mortality among men younger than 65 years (from 1.2 in 1979 to 1.35 per 100 000 in 1998), while the mortality fell among women younger than 65 years (1.3 to 1.15 per 100 000).²¹ A difference in mortality trends from CMM between the genders is explained by the fact that middle-aged men have a

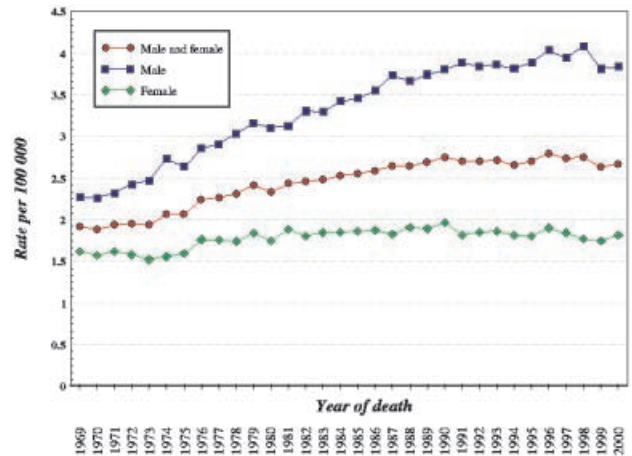


Figure 5. Age-adjusted (2000 U.S. standard population) melanoma mortality rates (per 100 000), total U.S.A., 1969–2000 (data from the SEER Program of the National Cancer Institute).

higher mortality rate due to less knowledge about appropriate primary and secondary preventive measures and later diagnosis of the primary tumour.²⁸

Analysis of all deaths from melanoma registered in Australia between 1931 and 1994 showed that melanoma mortality for Australia increased steeply from 1945 to 1959 (average annual increase of 11.5% in men and 8.9% in women) and more slowly from 1960 to 1989 (average annual increase of 6.3% in men and 2.9% in women). Mortalities for both sexes seem to have plateaued from June 1985 onwards. In 1985–1999 the mean age-standardized rates were 4.8 and 2.5 per 100 000 in men and women, respectively. In 1990–1994 the rate rose by 3.7% in men to 5.0 per 100 000 and in women it fell by 5.2% to 2.4 per 100 000.²⁹ Recent statistics cohort analysis of mortality rates reveals that age-adjusted mortality rates are dropping in the younger cohorts.³⁰

In the U.S.A. from 1969 to 1985, the increase in the mortality rate was significantly higher in males (51.9%, 2.3 to 3.5 per 100 000) than in females (14.8%, 1.6 to 1.9 per 100 000). In the period 1992–1998, the melanoma death rates increased more slowly for white males (1.0% annually) and were stable for white females.³¹ SEER age-adjusted mortality rates for the period 1969–2000 are presented in Figure 5.

In the U.K. in 1971–1991 the mortality rate increased by 130.0% (from 1.0 to 2.3 per 100 000) for males and 28.6% for females (from 1.4 to 1.8 per 100 000).¹⁸ Changes were much lower during 1991–2001: increases were 13.0% for males (from 2.3 to 2.6 per 100 000) and 11.1% for females (from 1.8 to

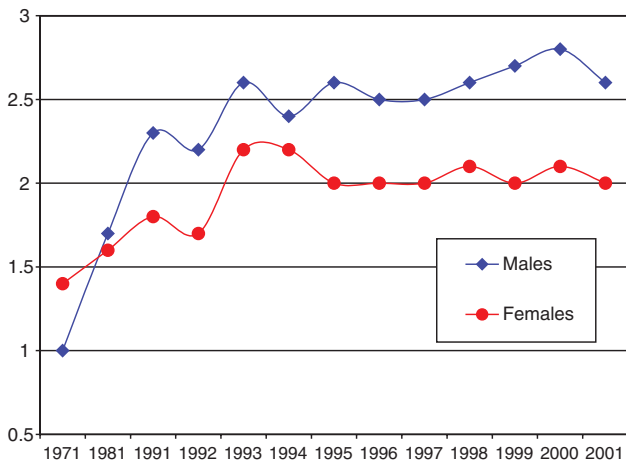


Figure 6. Age-standardized melanoma mortality rates in the U.K., 1971–2001, age-standardized to the European standard population (rates per 100 000 population).

2.0 per 100 000). Age-standardized mortality rates for 1971–2001 are presented in Figure 6.

Analysis of the data from the Belgian National Institute of Statistics from 1973 to 1992 showed that the risk of dying from CMM increased in both men and women continuously over the whole period with approximately a 20% increase in mortality per 5-year period. The age-adjusted mortality rates for the age group 25–84 years increased from 0.5 in 1954 to 3.0 per 100 000 in 1992 in men, and from 0.8 in 1954 to 2.2 per 100 000 in 1992 in women.³²

Analysis of the data from Spain between 1975 and 1998 demonstrated annual increases of 13% in the risk of mortality from CMM among males and 33% among females.³³ In males there were marked increases in all CMM mortality rates between 1975 and 1994, followed by their decrease during 1995–1998. In contrast, rates rose in females between 1975 and 1998.

Despite rising incidence, there has fortunately been a marked concomitant improvement in the 5-year survival rate, from approximately 40% in the 1940s to over 90% now. The data from the Scottish Melanoma Group showed significant improvement in survival in both sexes.²¹ Five-year survival was 58% for men and 74% for women diagnosed with melanoma in the period 1979–1981, while for those diagnosed in the period 1991–1993 it was 80% and 85%, respectively.

Survival is strongly associated with thickness of tumour at time of diagnosis. Scottish data showed that 5-year survival for patients with melanoma thinner than 1.5 mm was 93% among males and 97% among females. Patients with thicker melanomas (particularly

more than 3.5 mm) had a steep decrease in survival. Five-year survival in patients with melanoma thicker than 3.5 mm was 47% in men and 55% in women.

The improvement in survival can be attributed to the earlier detection of melanoma. Active public education campaigns aimed at encouraging earlier detection of melanoma led to the diagnosis of thinner lesions with a better prognosis.^{21,24} The median tumour thickness appears indeed to have decreased over time. However, the steady number of thick tumours does not seem to be altered by publicity. Progress in melanoma treatment that could have provided patients with a better chance of survival are unlikely to explain this improvement as there have been no major changes in melanoma therapy.

Aetiology of cutaneous malignant melanoma

CMM is a malignancy with multifactorial aetiology. The development of melanoma is the result of the interaction between different environmental, genetic and host factors. Epidemiological studies have shown that the major environmental aetiological factor of CMM is sunlight exposure.²⁵ Epidemiological evidence for the causative role of sunlight is conflicting. The measurement of sun exposure is complex, while the relationship between CMM and sun exposure has not yet been identified.³⁴ The risk of melanoma appears to depend on the interaction between the nature of the sun exposure and the skin type. Most epidemiological studies found that sun exposure in childhood is the major risk factor for the development of melanoma.³⁵ There is less evidence that sun exposure during adulthood contributes to the risk of CMM. However, most of the evidence that the pattern of exposure is important relates to exposure in adulthood. Thus, it is impossible to exclude completely the effect of sun exposure in adult life on the risk of melanoma. Although different patterns of sun exposure are associated with different levels of risk for melanoma among individuals, it seems that intermittent sun exposure is more important for risk than total lifetime exposure.³⁶

The currently recommended sun protection regimen includes wearing protective long-sleeved clothing, avoiding midday sun, and regular use of broad-spectrum high sun protection factor (15 or higher) sunscreen.¹² The association between melanoma and sunscreens is still not clear. The results from the literature are controversial. Some studies showed a protective effect of sunscreens, while others showed increased risk of developing melanoma with sunscreen

use due to the increase in the duration of recreational exposure to the sun.³⁷ However, due to low relative risks, the lack of a dose–response relationship and the numerous biases, currently available data do not support the presence of an association between sun-screen use and melanoma.

Sun exposure is generally equated with ultraviolet (UV) radiation, although the evidence does not rule out other unmeasured exposures associated with the sun. Use of artificial sources of UV radiation, such as sun beds or sunlamps, has become popular in recent years for cosmetic or recreational purposes, particularly among teenagers and young adults. Many clinical studies have reported that exposure to sunbeds or sunlamps has adverse effects on the skin and that their use might increase the risk of developing CMM. An epidemiological assessment of 19 epidemiological studies evaluating the association between sunbed/sunlamp exposure and CMM found that at this time, the published data are insufficient to determine whether sunbeds/sunlamps cause melanoma.³⁸ As there were many methodological limitations in interpreting the results from the available studies, further well-designed studies are needed. These studies should also elucidate the possible longer lag period (one or two decades) effects of sunbeds/sunlamps and the spectra and intensities of UV radiation from these devices.

Other environmental factors (smoking, diet, hormone therapy, fluorescent lighting and stress) have been examined but no correlation between them and melanoma risk has been found. The most important host risk factor for CMM in fair-skinned people is the presence of both common acquired and atypical (dysplastic) melanocytic naevi.²³ An atypical mole syndrome phenotype was strongly predictive of an increased risk of melanoma outside the familial context. Development of melanocytic naevi in children is related to sun exposure and phenotype.³⁹ UV radiation is a major factor in the development of naevi, although the relationships with intensity and duration of exposure are still not clear.

Effects of the sun seem to be modulated by pigmentation factors of the host. Light pigmentation increases the risk of the development of melanoma. Many epidemiologists are explaining wide geographical variations in melanoma incidence by the variations in host characteristics and differences in the amount of UV radiation by geographical latitude.

Patients with a family history of melanoma are at increased risk. Around 5–12% of patients with melanoma have a family history of CMM in one or more first-degree relatives.⁴⁰ Some of these patients

have inherited a mutation in highly penetrant susceptibility genes which are associated with a significantly increased risk of melanoma. To date, constitutional mutations have been identified in two melanoma susceptibility genes: *CDKN2A* (p16), located on chromosome 9 (9p21) and *CDK4*, located on chromosome 12 (12q13). Overall, approximately 20% of tested melanoma families showed inheritance of mutations in *CDKN2A*, while so far only three families have been found to have mutations in *CDK4*.⁴¹ *CDKN2A* mutations have not been observed in sporadic cutaneous melanoma. Penetrance of *CDKN2A* mutations is influenced by environmental or genetic factors. Penetrance varies with melanoma population incidence rates: it is higher in regions with higher baseline incidence (U.S.A., Australia and Sweden) than in regions with lower incidence (Europe except Sweden). Thus, the estimated penetrance of *CDKN2A* mutations before the age of 50 years was 0.50 in the U.S.A., 0.32 in Australia and 0.13 in Europe.⁴¹

Research screening suggested that the prevalence of *CDKN2A* mutation carriers is less than 1% in high-incidence populations. Thus, no mutations will be identified in the majority of families undergoing genetic testing for melanoma. Given the very low actual likelihood of *CDKN2A* mutations and gaps in the knowledge about the expression of melanoma susceptibility genes in the population, the Melanoma Genetics Consortium recommended that genetic testing for melanoma should currently be carried out only in the context of clinical research.⁴² Other genetic factors and their inheritance pattern remain to be determined.

Conclusions

According to the WHO the number of melanoma cases worldwide is increasing faster than any other cancer. Recent evidence suggests that melanoma incidence may have reached a peak. Incidence trends showed that most of the increased incidence may be ascribed to increased numbers of thinner, less aggressive superficial spreading melanomas. Despite improved survival rates, the death rate from CMM continues to climb as a result of exponential increases in incidence, making it a major public health problem for the foreseeable future. The risk factors for melanoma include a combination of constitutional predisposition and exposure to environmental factors. The epidemiological data confirm that the major environmental risk factor for melanoma is intermittent sunlight exposure. Early recognition of

CMM is extremely important as excision of primary melanomas with a Breslow thickness of <1.5 mm significantly improves survival probabilities, with 10-year disease-free survival rates exceeding 90%. Primary and secondary prevention campaigns are essential for further reduction of the incidence and mortality from CMM in the future.

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