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Cutaneous Malignant Melanoma – Epidemiology, risk factors and prevention

Diploma thesis

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Written Declaration

I declare that I completed the submitted work individually and only used the mentioned sources and literature. Concurrently, I give my permission for this diploma/bachelor thesis to be used for study purposes.

Contents

Abbreviations

WHO – World Health Organization

CMM – Cutaneous malignant melanoma

UV – Ultraviolet

UVR – Ultraviolet radiation

UVA – Ultraviolet-A rays

UVB – Ultraviolet-B rays

BCC – Basal cell carcinoma

SCC – Squamous cell carcinoma

ASR – Age standarized rate

SEER – Surveillance Epidemiology and End Results

AMS – Atypical mole syndrome

FAMM – Familial atypical multiple mole syndrome

FDA – Food and Drug Administration

AAD – American Academy of Dermatology

Summary

Worldwide, 160 177 people were diagnosed with cutaneous malignant melanoma (CMM) in 2002. According to WHO, the incidence of CMM is increasing faster than any other cancer. Recent epidemiological studies show that this pattern is fading out in some regions, and that the incidence is even falling in some countries. Norway together with the rest of Scandinavia and Northern America are countries where this change is most evident. Still, in Norway, CMM is one of the most frequent cancers in young people. Exposure to ultraviolet (UV) radiation is the main environmental risk factor for developing CMM, but genetic susceptibility also plays an important role. The effect of sunscreens and the risk of sun bed use are debated. More research on these topics are needed. Early recognition of melanoma is of prime importance for improving the survival rate. It is documented, that public education, as a preventive measure, in respect of sun exposure habits and recognition of changing nevi can decrease the incidence of CMM.

Introduction

This review article will be focused on epidemiology, risk factors and prevention of cutaneous malignant melanoma. The epidemiological part will be an overview of the global situation and consider Norway in greater detail. Data are obtained from The Cancer Registry of Norway, WHO and various scientific papers.

Cutaneous malignant melanoma (CMM) arises in the pigment cells of the skin, the melanocytes which are localized mainly in the lower part of the epidermis. In 30-50 % cases, CMM arises through a malignant change in a pre-existing nevus. In 50-70 % malignant melanoma arises in healthy skin (de novo), rarely on mucus membranes, lymph nodes and in the eye. CMM is a serious disease and has recieved a great amount of publicity, first and foremost because of the high mortality rate connected with advanced disease. On a global basis, the incidence is higher in countries with caucasian populations living close to the equator. It is, therefore, interesting that Norway is among the countries with the highest incidence in the world (1,2). Norway has a relatively homogenous population and stretches over a long north – south distance, with about a 50 % larger annual UVB dose in the south than in the north. This makes the country extra suitable for studying the epidemiology of CMM. The incidence is higher in the Western Europe compared to the Eastern Europe.

Fair skin with freckles, red hair, blue eyes and frequent sunburns are well recognized risk factors for development of CMM (3,4). The use of sunbeds and its role as a risk factor is a bit more diffuse, still, most experts advice on modesty in this matter. Newer research shows that the benefit from sun-exposure (mainly via vitamin D photosynthesis), might be even greater than earlier believed, making the controversy even bigger. The greatest part of this benefit is now thought to be due to the ability of UV-radiation to induce vitamin D synthesis in the skin (5). Possibly, strengthening effects on the immune system may play a role.

Primary prevention of all skin cancers consists of avoidance of sun and use of sunscreens. There is no direct evidence that sunscreen use protects against CMM, as it does for basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of

the skin. However, the incidence of CMM in Norway has not increased significantly since 1990, and even decreased in some age groups. Could this be due to the „anti-sun-propaganda“ of the 1980s or to increasing use of sunscreens?

Epidemiology

In 2002, 79 043 men and 81 134 women developed CMM worldwide. For comparison, lung cancer has the highest incidence of all cancers with 965 241 (men) new cases in 2002 worldwide (6).

The incidence of CMM, however, varies dramatically between different populations.

Eastern Africa	1.2
Middle Africa	2.2
Northern Africa	0.7
Southern Africa	5.4
Western Africa	1.1
Caribbean	1.0
Central America	1.3
South America	2.4
Northern America	16.4
Eastern Asia	0.3
South-Eastern Asia	0.5
South-Central Asia	0.5
Western Asia	1.6
Central and Eastern Europe	3.3
Northern Europe	8.4
Southern Europe	6.0
Western Europe	7.3
Australia/New Zealand	37.8
Melanesia	4.8
Micronesia	1.2
Polynesia	5.1

Table 1. Age-standarized rates Incidence, Men, 2002, GLOBOCAN 2002, IARC.

As can be seen from this table, Australia and New Zealand has by far the greatest incidence, illustrating the connection between white populations near the equator and CMM. The number of CMM cases worldwide is increasing faster than that of any other cancer. Every year the increase in incidence rate is typically 3-7 % for fair-skinned Caucasian populations (7). It is important to point out that this is the general trend, great variations exist. This suggests a doubling of melanoma incidence every 10-20 years (8).

	Male		Female	
Country	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

Table 2. Incidence of CMM (per 100 000) for 23 selected countries (9).

We will first consider Australia, where CMM is the fourth most common cancer in males (10). In Queensland, Australia, between 1980 and 1987, incidence of CMM has been 55,8 in men and 42,9 in women. This makes Queensland second only to Auckland, New Zealand. Looking at Figure 1, which illustrates age-adjusted incidence of CMM in Australia in the period 1983-1999, we can see a steady increase in incidence, with peaks in mid 1980s and 1997. With respect to age, however, incidence rates have increased in older age groups and decreased in young women (11).

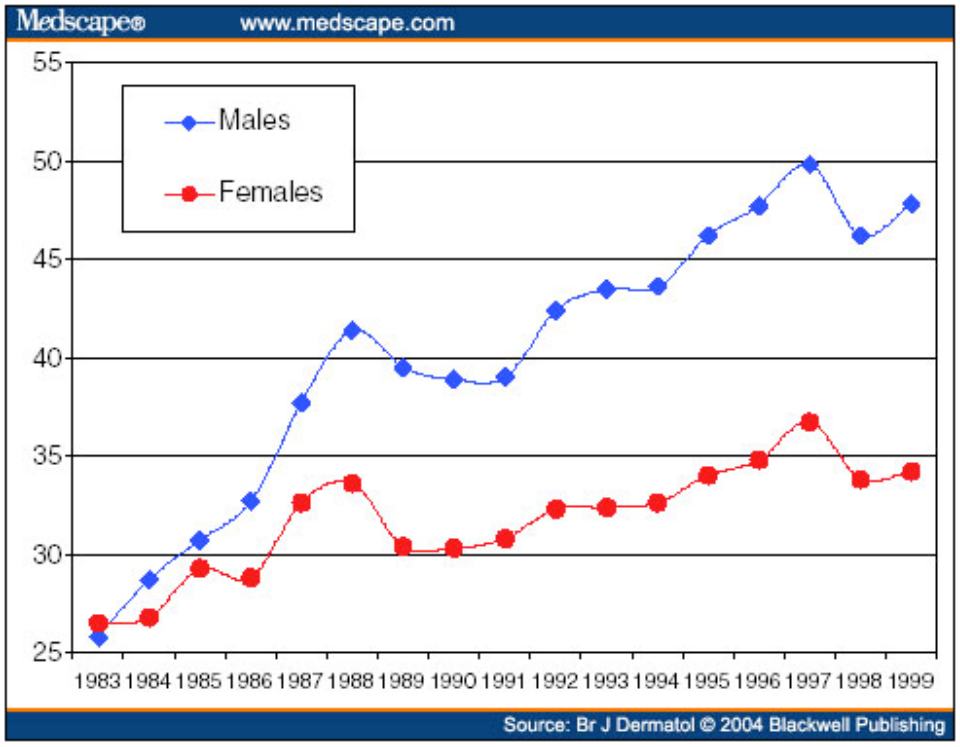

Figure 1. Age-adjusted melanoma incidence (per 100 000) in Australia, 1983-1999 (data from the National Cancer Statistics Clearing House at the Australian Institute of Health and Welfare).

Burton et al (12) reports in 2000 that lifetime risk for developing CMM is 1 in 25 for men and 1 in 34 for women in Australia.

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) (13).
In USA, there has also one of the many countries where the incidence has been on a steady rise untill late 1990s. Figure 2 illustrates this. 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 (14).

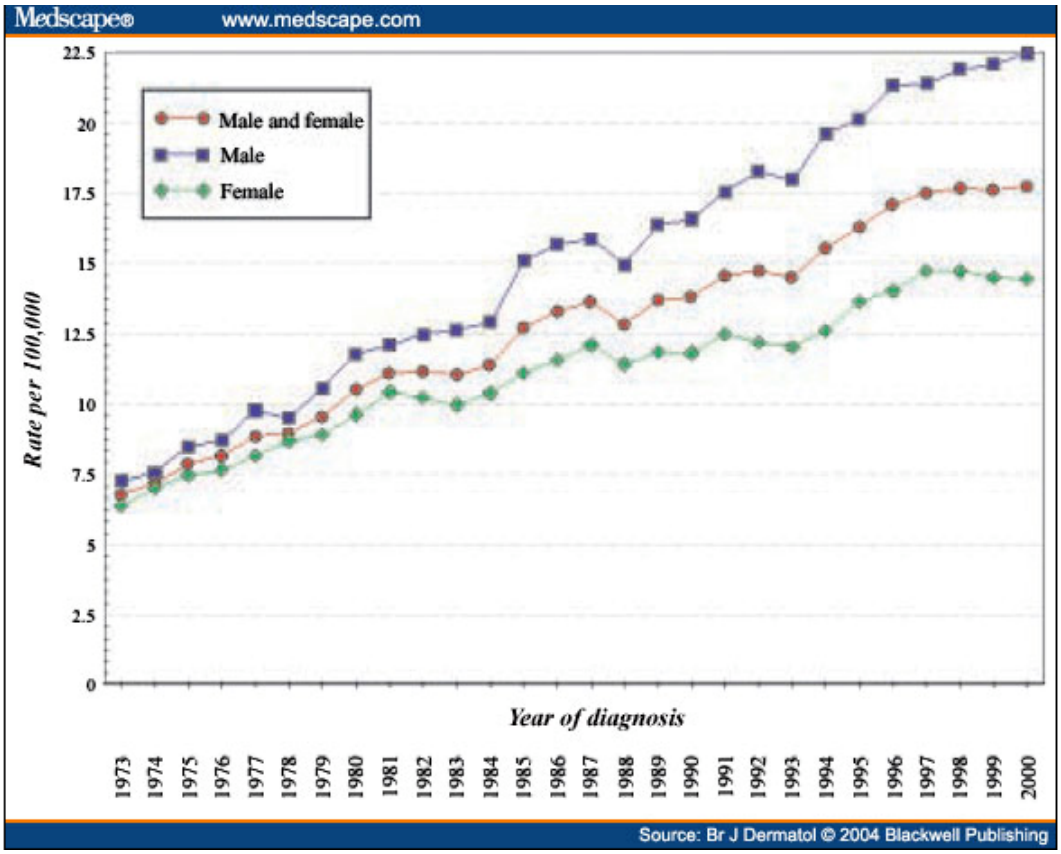

Figure 2. Age-adjusted (2000 U.S. standard population) melanoma incidence (per 100 000), nine registries, 1973-2000 (data from the SEER Program of the National Cancer Institute).

The highest incidence in Europe is found in Scandinavia. Here the incidence is roughly 15 per 100 000, significantly higher than in the Mediterranean countries, where incidence is about 5-7 per 100 000 (lowest in Europe) (15). When comparing different regions, it is important to remember that populations have

different skin types. Scandinavian countries have typically type 1 and 2 skin, while i.e Mediteranean regions have predominance of skin type 3 and 4.

In Norway, CMM has until 1990 been among the cancers with the highest rate of increase in incidence since the Norwegian Cancer Registry was founded. In 1955, there was 2 cases of CMM per 100 000, while in 2003 there was 16 per 100 000. Historically, CMM has been more frequent among women, but this pattern is slowly fading out. In 2008 The Norwegian Cancer Registry concluded with 1285 new cases of CMM in Norway and the age adjusted rate was 17,6 for men and 16,4 for women. CMM is one of the most common cancers of young adults. In the age group 15-54 years this is the second most common cancer when both sexes are combined. In the age group 15-29 years it is the most common form of cancer in women and makes 24 % of all new cases of cancer. In men, CMM is the most common form of cancer in the age group 30-54 years and makes 11 % of all new cases of cancer (18). CMM is extremely rare in children under 15 years, but makes 4 % of all cancers in ages above 55 years. The median age at diagnosis is 53 years.

CMM is more than twice as common in the southern as the northern counties (16). According to numbers from the Cancer Registry, the incidence rate in the most northern county is less than 5, while in the most southern above 20.

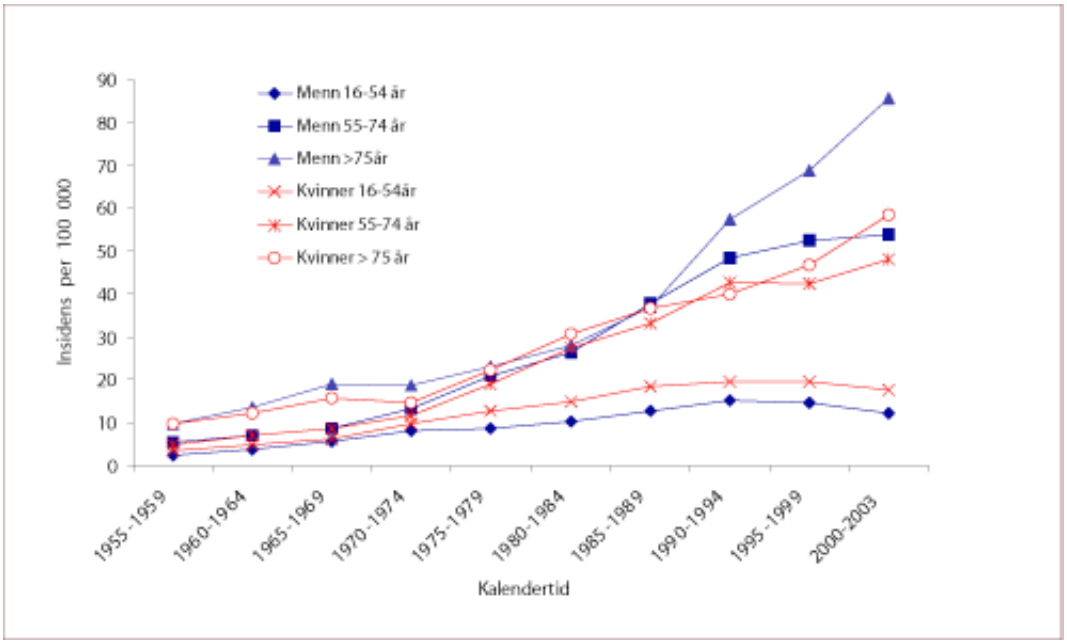

Figure 3. Source: Norwegian Melanoma Group. (Menn=men, Kvinner=women)

The incidence of CMM in Norway is among the highest, both in Europe and worldwide (17). Still, it looks as the incidence rate is now decreasing for the younger part of the population. Similar trends are found in a number other countries, indicating that the public campains for awareness of carcinogenic effect of sun exposure have been successfull. The incidence is, however, still slightly increasing in the older age groups, especially among men.

As a cause of the steep increase in incidence seen during the last 30 years, a british study claims that increased biopsy-taking is perphaps just as important as the other suggestions as increased sun exposure and weakened ozone layer (18).

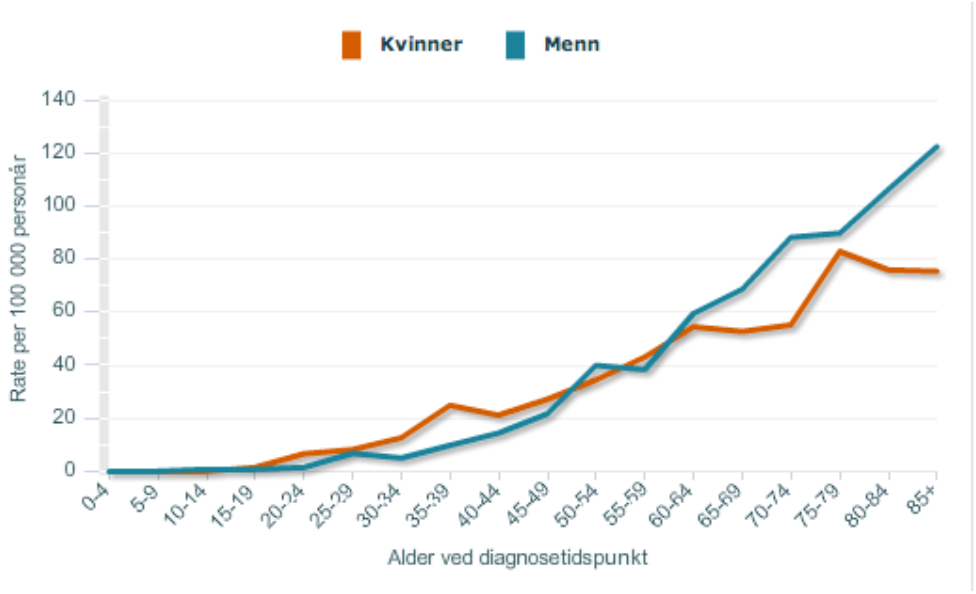

Figure 4. Age-specific incidence of CMM from 2004-2008. (Kvinner=women, menn=men)Source: Cancer Registry

Figure 4 shows the age-specific incidence of CMM from 2004-2008 in Norway. Clearly, CMM is a disease increasing with age, and age-standarization is of great importance in comparing data from different populations.
It is estimated that liftime risk for developing CMM in Norway is 1 %.

Lens and Dawes (21) review paper from 2004 analyses world wide epidemiological data on CMM. They conclude that there is considerable variation in the incidence rates of melanoma worldwide. Reported data suggested more favorable incidence trends in some countries while in others the incidence of melanoma is still rising. Recent evidence suggests that the current trend of increasing melanoma incidence is due to improved surveillance techniques with early diagnosis, together with changes in lifestyle in terms of excessive recreational exposure to sunlight. The overall increases in melanoma incidence have begun to slow in the later years in Western Europe and in 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 behavior), 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.

Around 4 % of all skin cancers are CMMs. Still, it is responsible for more than 74 % of skin cancer deaths. One person dies each hour from metastatic CMM in the U.S. Treatment of melanoma in its early stages provides the best opportunity for cure.

De Vries (2) analyzed time trends in incidence and mortality in Europe from 1953-1997. It was found that mortality has leveled off in Western Europe, just like the incidence. The mortality has continued to increase in the Southern and Eastern Europe. de Vries attributes the declining mortality in Northern Europe to earlier diagnosis, more frequent excision of pigmented lesions and public awareness of dangers of sun exposure. The same is stated in Parkins study (22): Individuals with cutaneous melanoma have higher survival rates in developed countries (91 % in US SEER registries and 81 % in Europe) than in developing countries (approximately 40 %). Increased educational efforts in developed areas result in earlier diagnosis, treatment, and potential cure of thinner lesions.

In Norway, 275 people died from CMM in 2007. The mortality of CMM is low compared to other cancers, still, it has increased since early 1980s. This tells us that the increase in incidence, can probably not be attributed only to better diagnostics and changed diagnostic criteria (17).

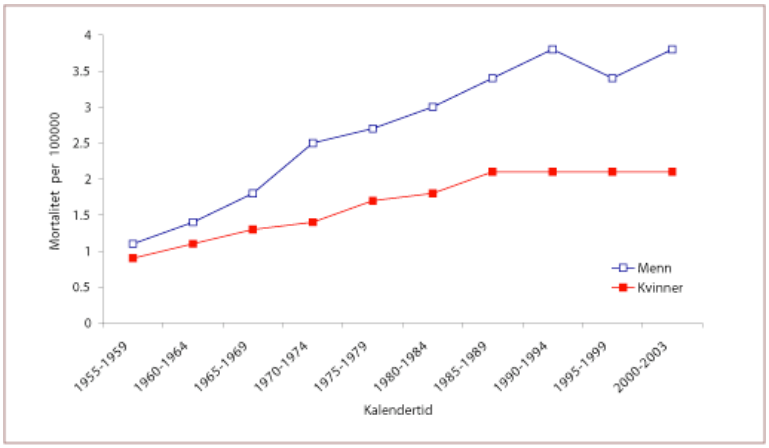

Figure 5. Mortality of CMM in Norway. (Kvinner=women, menn=men.) Source: Norwegian Melanoma Group

The mortality rate is higher for men than for women. This can partly be explained by mens latency in consultation leading to more advanced disease at time of diagnosis. Faye et al (20) has found in a case-control study with 457 Norwegian CMM patients that men are above the mean latency time of 8 weeks before seeking advice from a doctor.

5-year relative survival, CMM diagnosed in the period 1996-2000:

(source: Norwegian Cancer Registry)

Men		Women	
Total	78,1 %	Total	89,4 %
Local	89,4 %	Local	95,2 %
Regional	41,8 %	Regional	61,6 %
Distant metastases	6,8 %	Distant metastases	18,7 %

5-year survival related to depth of primary lesion (Arndt 1996):

- < 0,75 mm – 96 %
- 0,76-1,49 mm – 87 %
- 1,50-2,49 mm – 75 %
- 2,50-3,99 mm – 66 %
- > 4,00 mm – 47 %

Risk factors

Many risk factors have been identified, genetical as well as environmental ones. Based on many publications we will first consider the genetic factors.

Many inherited factors influence the development of CMM, one of the most important being skin pigmentation. There are 6 skin types with respect to pigmentation and UV-sensitivity, type 1 always getting red and never tanned, and type 4 never getting red, easily tanned. Africans black skin is type 6. This reflects the amount of melanin in the skin. Melanin has a protective effect in that it absorbs ultraviolet radiation (UVR), thus shielding the DNA from damage and so all types of skin cancer. The melanin granules, the melanosomes, also have the ability to backscatter UV radiation. Type 1 and 2 skin will have greater risk developing CMM than types 3 and 4. In black Africans and Caucasians living in the same latitude, the incidence rate of CMM is 10-20 times higher in the Caucasian population than among the Africans (24). This is also reflected by the fact that CMM is more common in light skinned Scandinavians compared to Mediteraneans.

Congenital nevi are found in about 1 % of newborns. Most of these are small. Definition of small vs. large nevi varies, but National Institute of Healths defines small < 1,5 cm, medium size 1,5-20 cm and large (giant nevi) > 20 cm. There are discrepancies in studies assessing the risk of developing melanoma in small and medium congenital nevi. No study has been able to document increased risk, most researchers, therefore, assume that the risk is very low in these instances. The case is different with congenital giant nevi (>20 cm). These nevi have increased risk of malignant change. Lifetime risk is estimated to 9 % (25). Large congenital nevi with a dorsal axial localization shoud be investigated with CT/MRI to exclude leptomeningeal affection, which can give rise to neurologic damage. Large congenital nevi should be frequently controlled. All congenital nevi should be biopsied if there is any clinical suspicion of malignant change (26). Pigmented, congenital nevi were in a stystematic study found to undergo malignant transformation in 0,7 % of cases (27).

Dysplastic nevi (atypical moles) have an increased risk of malignant change and thus of changes to CMM. The risk is however significantly increased if dysplastic nevi are frequent within a family. It is estimated that 5-10 % of all CMMs are familiary inherited (26). Individuals with a high number of atypical moles without an inheritance pattern are often referred to as having atypical mole syndrome (AMS) (100 or more nevi, one or more nevi larger than 8 mm in diameter and one or more atypical moles). An individual with the same characteristics as AMS with the addition of a familiary pattern of inheritance (one or more 1. or 2. degree relative with CMM) is defined as having familial atypical multiple mole syndrome (FAMMM) (26,28). These individuals have an extremely high risk of developing CMM. Approximately half of all melanoma-families reveals a link to chromosom 9p21. In 1994, it was found that the affected persons in these families had mutations in CDKN2A, a gene coding for tumor suppressor proteins (26). These mutations have high penetrance, and ca. 30 % of carriers will deveop CMM at 50 years of age, and ca. 70 % will at the age of 80 years. To what extent isolated dysplastic nevi can be counted as precancerous states or if this is indication lesions for a skin type more prone to developing dysplastic nevi and CMM is currently not clear (28).

Convincing proofs for the involvement of genetic factors in combination with UV induced DNA damage are that CMM rates are high among patients with xeroderma pigmentosum and ataxia telangiectazia (inherited deficiencies in DNA repair).

Other genetic factors that are documented as increasing the risk of developing CMM are red hair color, blue eye color and freckles.

We will now take a look at environmental risk factors for development of CMM documented in the literature.

Ultraviolet radiation is divided into 3 wavelength ranges:

UVA rays (320-400 nm) cause cells to age and can cause some damage to cells' DNA. They are linked to long-term skin damage such as wrinkles and solar eczema, but are also thought to play a role in some skin cancers, notably in CMM.

UVA can give sunburns, but needs an exposure, as counted in photons, of 1000 times higher than for UVB radiation. In solar radiation at the earth surface there is 40 to 1000 times higher intensities of UVA than of UVB, the exact number depending on time and place. Compared to UVB, only a small amount of the UVA is spread and absorbed by the atmosphere. Roughly 50 % of UVA comes via one or more scattering events even in a cloudless atmosphere.

UVB rays (280-320 nm) can cause direct damage to the DNA, and are the rays that primarily cause sunburns. They are also thought to cause most skin cancers.

UVC rays cannot penetrate our atmosphere and therefore are not present in sunlight at the earth surface.

While UVA and UVB radiation make up only a very small portion of the sun's spectrum (roughly 6 %), they are the main cause of the damaging effects of the sun on the skin. UV radiation damages the DNA of skin cells, UVB in a direct way, UVA in an indirect way by forming radicals and oxidative species in the skin. Skin cancers begin when this damage affects the DNA of genes that control skin cell growth. Both UVA and UVB rays damage skin and cause skin cancer. UVB rays are, because of their direct absorption in DNA, a more potent cause of at least some skin cancers. The amount of UV exposure, the dose, depends on the intensity of the radiation, length of time the skin was exposed, and whether the skin was protected by clothing and/or sunscreen.

The role of sun exposure in the development of CMM has been debated for years. The arguments speaking for sun exposure as a causative agent in CMM are numerous. Examples include (30): CMM incidence rates increases with decreasing latitude when comparing people with similar skin type. Lighter skin color has more commonly CMM than dark skin color (melanin absorbs UVR). Migration to more sunny countries increases the risk of getting CMM. Episodes of sunburns in childhood appear to increase the CMM risk.

Confusingly, some phenomena speak against this relationship. For example: There is little solar elastosis in the surroundings of CMMs (solar elastosis is related to accumulated UV exposure). Epidemiological case control studies give conflicting results; some show dependency of CMMs on UV exposure, while

some even show protection. Distribution on body sites is widely different from that of SCCs. Farmers and fishermen traditionally have higher accumulated sun exposures than others, but do not have alarmingly high frequencies of CMM.

However, most researchers agree on that UVR is a major environmental risk factor in the genesis of CMMs, especially in the form of intermittent sun exposure with high intensity, and that frequent sunburns is the most important environmental cause of developing CMM (31). The intermittent sun exposure hypothesis is supported by the fact that: CMMs are more frequently found on the trunk of men and legs of women. CMM on the breast area was hardly found prior to 1970s, when topless sunbathing was uncommon. Furthermore, relative risk of developing CMM is higher for office-workers than farmers and fishermen (30). It seems that intermittent sun exposure is more important for risk than total lifetime exposure (32).

A controversial issue the last couple of years has been whether sun beds are causing CMM or not. After many case-control studies and epidemiologic analyses, there is still no conclusive evidence of this. A few studies even show a protective effect against CMM by sun bed use. Although many studies do point to a relationship between sun beds and CMM, an epidemiological assessment has found that the published data are insufficient to determine wether sun beds cause CMM (33). The discrepant results probably reflect methodological difficulties associated with this type of research. Further, well-designed studies are needed. Modern sun beds emit light with wavelengths in the UVB and UVA region. Even sun beds claiming to be “pure UVA sun beds” emit small amounts of UVB (the part of light which is thought to be responsible for causing CMM). Sun bed use has increased rapidly during the last two decades. Artificial tanning is mostly being used for cosmetic or recreational purposes, particularly by the younger population. As mentioned, the incidence of CMM in the younger population has decreased in the same period. This could mean that artificial tanning is not a great concern for the population as a whole. WHO and also The Norwegian Cancer Association advices against recreational use of sun beds based on the consensus that UVR from sun exposure causes CMM, and therefore sun beds might do the

same. Both sun exposure and artificial tanning increases the levels of vitamin D in the blood. Recent studies have revealed that vitamin D could have even greater health benefit than earlier assumed and therefore moderate sun bed use can be positive during the winter (30). Speaking for this assumption is the fact that some cancers decrease in incidence with lower latitudes, the opposite as CMM. Also, the prognosis for CMM in Norway diagnosed in the late summer is better than for those diagnosed during the winter. UVB promotes vitamin D production and hence, the vitamin levels are higher during summer. Also CMM on shielded skin, such vulva, decreases in rate with increasing sun exposure.

A number of studies have revealed associations between chemicals like polyvinylchloride, arsenic, polycyclic hydrocarbons and asbestos and increased risk of CMM (34). Children and youngsters treated with cytotoxic drugs have been shown to have and increased risk of developing CMM of 6-8 % (35).

The previous diagnosis of CMM confers an increased risk of 9-10 % compared to the general population. The risk is highest the first two years after diagnosis (36).

Prevention

PRIMARY PREVENTION

The dramatic increase in CMM over several decades until 1990 has lead to increased awareness among people about the relationship between sun exposure and melanoma. As mentioned, countries like Australia and Norway now report a falling incidence in younger cohorts. This can be the result of mentality changes with decreased sun exposure and use of sun protective measurements.

As discussed in the previous section, there is little doubt that intermittent sun exposure and frequent sunburns are major risk factors for developing CMM. The best way to avoid UVB-radiation is to avoid sun exposure, especially the intense intermittent type and when the sun is at its highest (37). During the summer, this means 1-2 hours before and after 1 PM in Norway. This is also what is recomended by the Norwegian Cancer Association. Reducing UV exposure is the

most important modiviable behavior for melanoma prevention (38). Unfortunately this is also the time of the day yielding most vitamin D synthesis.

Reducing the exposure can also be achieved by protective clothing and wearing broad-brimmed hats. It is important to note, that some textiles filter the UVB rays less efficiantly than others. For example, through wet cotton, 20-30 % of the radiation dose reach the skin (35). Detergents exist that increase the photoprotective ability of one's clothing.

There is no doubt that these measures are effective in reducing UV exposure and thus CMM. The answer is not as obvious when it comes to the use of sunscreen as protection. Sunscreen contains chemical filters that absorb UV rays. Many also contain physical blockers that reflect the rays. This includes particles and micropigments, i.e titanoxide and zincoxide. The physical blockers give the best protection against UVA radiation. Chemical filters offer good protection against UVB but are poor filters for UVA. On the declaration of a sunscreen, usually only the UVB-factor is given. This factor reflects how long skin *with* sunscreen can be exposed to sun before erythema appears compared to skin *without* sunscreen. Sunscreens are broken down in the skin over time during exposure to sun, and hence, the effect is reduced.

Sunscreens are shown to reduce the risk of DNA damage in the skin during UV exposure, reduce UV induced immunosuppression, reduce the development of melanocytic nevi, reduce age changes in the skin, reduce incidence of actinic keratoses and SCC (39). However, it is not proved yet that sunscreens reduce the risk of CMM. Many authors think this is due to methodological problems of case-control studies. Surprisingly, many investigations indicate a higher CMM rate among sunscreen users than among non-users. In most cases, no significant effects are found. Some authors even suggest that certain sunscreens may be risk factors for CMM (40). Some animal experiments indicate that some common sunscreens provide protection against sunburn, but not against CMM (41). The use of sunscreen may give a fake sense of safety and thereby people may allow themselves to stay in the sun for longer periods. This can lead to prolonged exposure to UVA radiation, consequences of which is not entirely clear at present.

Furthermore, as mentioned, applying UVB filter strongly suppress vitamin D production, and may, according to some authors potentially promote progression of cancers. A controversial statement in the literature is that sunscreen use may cause more cancer deaths than it prevents (42). Clearly, more research is needed on this matter. Meanwhile, FDA (Food and Drug Administration), AAD (American Academy of Dermatology) and Norwegian Cancer Association recommend sunscreen use if physical protection is not possible or appropriate, this to reduce the risk of developing CMM.

The role of restricting sunbeds has already been discussed in the previous section.

Education of the population about sun protection and skin self-examination is essential in the prevention of CMM. A good example of the success in such measures is the effort of the Anti-Cancer Council of Victoria in Australia. Their strong organization has been educating the population for over 20 years. The pay off is evident with marked reductions in sun exposure and it has changed the society's approach to the sun (43).

SECONDARY PREVENTION

Secondary prevention of melanoma is accomplished by diagnosis and treatment of early-stage (highly curable) melanoma. People at high risk for development of melanoma should be identified and evaluated. Early diagnosis is the single most important factor for successful treatment. Excision of a primary melanoma with a Breslow thickness of < 1,5 mm significantly improves survival probabilities, with 10-year disease-free survival rates exceeding 90 % (21). In the Norwegian study referred to in previous sections, the median latency from observing change of a nevus till doctor consultation was 8 weeks. Young men had the longest latency. Several international studies show the same result. In one study, 46 percent of patients with melanoma did not seek medical attention until they found ulceration, bleeding or a lump in the pigmented lesion, all late signs of melanoma (50). Educating the population about skin self-examination and the danger signs of a changing nevus (ABCD of melanoma) is essential to shorten the consultation latency (44).

Screening of the general population has not been proven effective (45). Screening of high risk individual, on the other hand, is cost-effective and likely to be associated with an improved survival (46). Individuals with xeroderma pigmentosum, giant congenital nevi, immunosuppression, familial atypical multiple mole and melanoma syndrome, unusual-appearing nevi, numerous (>50) nevi, changing nevi, and a family history of melanoma and men older than 50 years should receive complete baseline and periodic follow-up skin examinations by a physician (38). Melanoma screening includes complete skin examination as part of a general medical examination by primary care physicians, during evaluations for other skin problems by a dermatologist, and community-based screening programs. Both of these methods yield increased rates of melanoma detection (47-49).

Prophylactic excicion of suspicious nevi is recommended. Excision after identifying a suspicious lesion, a properly performed biopsy is essential. In the event that melanoma is diagnosed, the histologic interpretation of the biopsy will determine the prognosis and treatment plan. To date, no studies have evaluated or compared biopsy techniques for pigmented lesions. However, general recommendations include performing an excisional biopsy whenever possible (51).

Tertiary prevention of melanoma involves limiting morbidity and extending survival in patients with advanced disease and is not within the scope of this text.

Conclusions

Worldwide, number of CMM cases is increasing faster than any other cancer, according to WHO. As pointed out in this article, with recent evidence, it is reason to believe that the peak might have been reached. Possibly, the increased incidence can be ascribed to increased numbers of thinner, less aggressive superficial spreading melanomas. Still, the mortality rate from CMM continues to rise because of the exponential increase in incidence. Survival rates have improved. CMM is a major public health problem for the future. The factors leading to increased risk for developing melanoma is a combination of genetic predisposition and exposure to environmental factors. Most studies confirm that intermittent sun exposure is the major environmental risk factor. The extreme importance of early recognition must be clearly planted in the minds of the general population and health-care-professionals. Excising melanomas with Breslow thickness of <1,5 mm significantly gives 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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