CHAPTER

UV RADIATION AND CUTANEOUS MALIGNANT MELANOMA

Johan Emilian Moan,*[,1,2] Zivile Baturaite,[1] Arne Dahlback[2] and Alina Carmen Porojnicu[1]

[1]*Department of Radiation Biology, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway;* [2]*Institute of Physics, University of Oslo, Oslo, Norway.*
**Corresponding Author: Johan Emilian Moan—Email: j.e.moan@fys.uio.no*

Abstract: Essential features of the epidemiology and photobiology of cutaneous malignant melanoma (CMM) in Norway were studied in comparison with data from countries at lower latitudes. Arguments for and against a relationship between UV radiation (UV) from sun and artificial light and CMM are discussed. Our data indicate that UV is a carcinogen for CMM and that intermittent exposures are notably melanomagenic. This hypothesis was supported both by latitude gradients, by time trends and by changing patterns of tumor density on different body localizations. However, even though UV radiation generates CMM, it may also have a protective action and/or an action that improves prognosis.

There appears to be no, or even an inverse latitude gradient for CMM arising on non-UV exposed body localizations (uveal melanoma, CMMs arising in the vulva, perianal/anorectal regions, etc.). Furthermore, CMM prognosis was gradually improved over all years of increasing incidence (up to 1990), but during the past 20 y, incidence rates stabilized and prognosis was not improved significantly.

Comparisons of skin cancer data from Norway, Australia and New Zealand indicate that squamous cell carcinoma and basal cell carcinoma are mainly related to annual solar UVB fluences, while UVA fluences play a larger role of CMM.

INTRODUCTION

UV radiation (UV) is believed to be the main risk factor for the major forms of skin cancer: squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and cutaneous malignant melanoma (CMM).[1,2] The former two are classified as non-melanoma skin

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cancers and have lower death risks per case of incidence than CMM: less than one percent vs. 20–30 percent in most countries.[1,2] CMM, SCC and BCC have different etiologies.[3,4] The action spectra for erythema[5] and SCC[6] are likely to be strongly UVB weighted, and there seems to be a relationship with the total UV exposure, particularly in the case of SCC.[6] For CMM the relationship has been debated for decades,[1,2,7-13] although most investigators tend to conclude that UV is CMM-generating in humans. Some authors argue that UV plays no major role.[14] The exposure pattern (continuous, occupational exposure vs. episodes of intense exposure, often classified as "intermittent exposure") appears to be of importance for CMM.[15-17]

While BCC and SCC, like most other cancers, are diseases of old people, with risks increasing sharply with age almost in an exponential manner, CMM is most frequent among middle aged people.[1,3] The localization pattern on the body is also different for the three skin cancer forms, and this pattern is changing with time.

Scandinavia is located at high latitudes (> 54° North). Therefore, the annual UVB (280–320 nm) exposures are limited and are of the order of 25% of the Equatorial UVB exposures.[18] In spite of this, CMM is a significant health problem in Scandinavia, in fact more important than one might expect in view of the high latitudes, with Denmark, Norway and Sweden presenting high incidence rates comparing with other countries (Fig. 1).

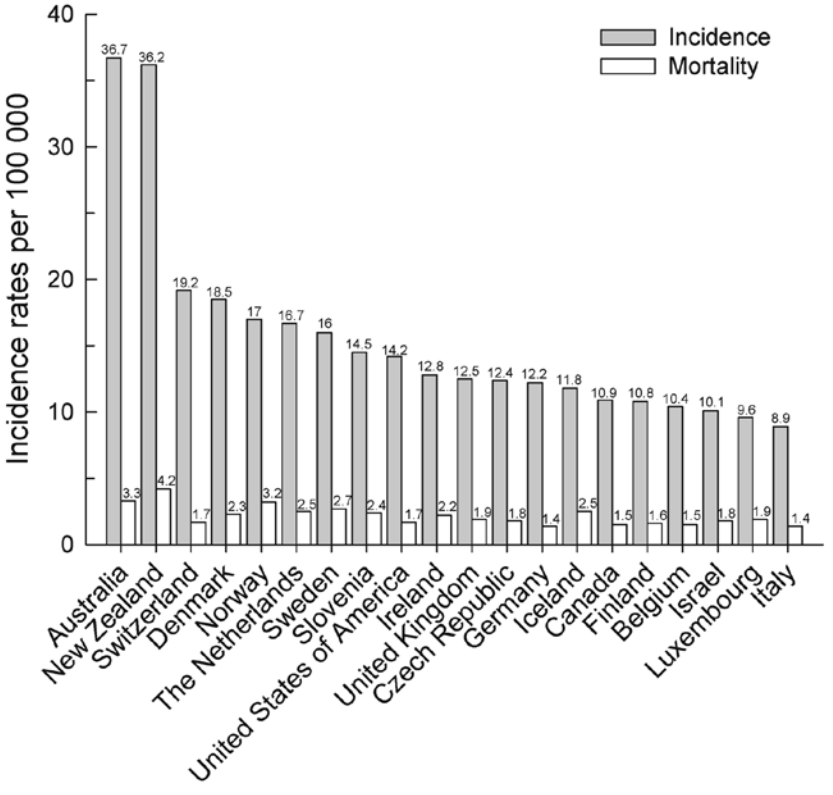

Figure 1. Cutaneous malignant melanoma age standardized incidence and mortality rates (according to the world population) in 2008.[66]

The discussion of whether UV can generate CMM is of interest from the viewpoints of photobiology and physics. The main argument for and against a relationship between UV and CMM incidence will be discussed in this chapter.

The fact that the incidence rates of CMM, BCC and SCC have increased over many decades has been a serious concern for health authorities. Therefore, large campaigns against sun- and sunbed exposure and for sunscreen use have been launched. An emerging, complicating factor associated with such campaigns is that the health benefits of vitamin D have become evident during the last decade. Not only solar radiation, but also radiation from sunbeds produces vitamin D,[19,20] while sunscreens, applied as recommended, eliminate the production.[21]

In this chapter we will summarize the epidemiology of CMM in Norway, compare it with data from other countries. We will start with a list of the arguments against and for melanoma-generating effect of solar radiation.

DOES UV INDUCE CMM?

Main Arguments *against* a Relationship between UV and CMM

1. CMM is more frequent among people with occupations giving low accumulated UV exposures, so called white-collar workers, than among people with large accumulated UV exposures (farmers, fishermen, etc).[15-17]
2. The localization pattern of CMM on the body is different from that of SCC, which is clearly UV related.[1]
3. CMM appears to be uncommon among albino Africans; opposite to what is found for BCC and SCC.[22]
4. The incidence rate of CMM in sunny Australia (15–35° South) is only two times higher than in the high-latitude country Norway (> 59° North), while the incidence rates of BCC and SCC are 20 to 40 times higher in Australia.[23] In some US populations there are a large north-south gradients of BCC and SCC, but no gradient of CMM.[24]
5. In Europe, which is populated mainly by Caucasians, CMM is more frequent in the north than in the south.[23,25]
6. Sun and artificial sources of UVB are efficient generators of vitamin D which seems to reduce carcinogenesis and tumor progression. It has been demonstrated that higher 25-hydroxyvitamin D3 levels, at CMM diagnosis, were associated with both thinner tumors and better survival from melanoma, independent of Breslow thickness.[26-29]
7. CMM may be a disease related to affluence, since the incidence rates appear to increase with increasing gross domestic product (GDP).[10]
8. A number of chemicals seem to be causing CMM. There is a possible relationship between polycyclic aromatic hydrocarbons (PAH), benzene, and/or polychlorinated biphenyls (PCB) exposure of workers in the petroleum and automobile industry and an increased risk for CMM.[30]
9. UVA induces CMM neither in *Monodelphis domestica* nor in transgenic mice.[31,32]
10. Recently, the original *Xiphophorus* experiments of Setlow et al. were attempted to reproduce, but no CMM generating effect of UVA was found.[33,34]

Arguments *for* a Relationship between UV and CMM

1. In populations with similar skin type there is a clear latitudinal gradient, which is larger for BCC and SCC than for CMM. The UVB gradient is also larger than the UVA gradient. The incidence rate of CMM in sunny Australia is only two times higher than in the high-latitude country Norway, while the incidence rates of BCC and SCC are 20 to 40 times higher.[25]
2. CMM risk decreases with increasing pigmentation.[35]
3. Albino Africans lacking melanin have very high rates of BCC and SCC but low rates of CMM. This seems to suggest that melanin, which absorbs UVA, is a chromophore for CMM.[22]
4. Migration to more sunny countries increases the CMM risk.[36,37]
5. CMMs often arise in the borders of pigmented nevi.[38,39]
6. Sunburn episodes are risk factors for CMM and CMMs used to occur mainly on sun exposed skin.[10,37,39-41]
7. CMM patients often have low DNA repair capacity and low minimum erythema doses (MEDs).[11,42-45]
8. *Lentigo maligna melanoma* is clearly related to UV exposure.[46]
9. Patients with *Xeroderma Pigmentosum* (abnormal DNA repair) have at least 1000 times increased CMM risks.[11,44,47]
10. Some CMMs contain mutations pointing toward UV damage.[9,12,48-50]
11. CMM-resembling tumors can be induced in some animals by UV (examples: Angora goats, Sinclair swine, *Monodelphis domestica* (an opossum), white horses and *Xiphophorus* (a small swordfish).[32]
12. Patients with CMM have increased risk of BCC and SCC.[51]
13. Some reports indicate increased CMM risk for persons frequently using sunbeds. Most sunbeds emit relatively more UVA than the sun does.[52-57]
14. There seems to be little CMM protective effect of only UVB absorbing sunscreens. However, a broad-spectrum (UVB-UVA) sunscreen reduces risk of CMM.[58-61]
15. Around CMM lesions solar elastosis is found. Solar elastosis is related to accumulated UV exposure.[26,62,63]
16. Per unit skin area CMMs occurred more frequently on heavily exposed (face, scalp) than on rarely exposed (female breast) skin regions, although this is not always true for younger generations.[8] The topless fashion was introduced in the early 1970-ies,[64] and, before that time, very few cases of CMM on the breasts of women were registered.

MATERIALS AND METHODS

We have analyzed epidemiological data from the Cancer Registries of Norway for overall CMMs in different counties. The age-standardized incidence for CMM by age (0–49 and older than 50 y of age) and mortality rates per 100 000 persons (according to the world standard population) in Norway are retrieved from the online database of International Agency for Research on Cancer (IARC).[65,66] Data from other sources are also used for CMM incidence rates in different countries in the world and referred to in the text. The two largest cities, Oslo and Bergen, are excluded from the study, to reduce the errors that may arise from different sun-exposure habits of urban and rural populations.

Relevant UVA doses are determined under the assumption that the action spectrum of CMM is similar to the action spectrum for melanoma in the *Xiphophorus* fish.[33] UVB doses are represented by the CIE action spectrum for erythema.[5] Calculations are based on daily satellite measurements (Total Ozone Mapping Spectrometer (TOMS) on Nimbus-7 satellite). The calculations include daily cloud cover and total ozone. The annual doses are averages over a ten-year period (1980–1989). A cylinder representation of the human skin surface was used as described and argued for earlier.[67] The conclusions arrived in the present work would be essentially the same if a planar, horizontal surface were used, although the north–south gradients would be different.

Age-standartised incidence rates were used to compare time trends between CMM at different age groups (0–49 and older than 50 y of age) for the north and south-east regions of Norway. Assignment of the Norwegian counties into two regions was based on ambient annual UV doses, calculated and measured as earlier described.[68,69] The South-East region of Norway (mean latitude 60° North) has a high annual ambient UV exposure (37×10^4 J m^{-2}) and the North region (mean latitude 70° North) has a low annual ambient UV exposure (26×10^4 J m^{-2}).[68,69]

The data were analyzed using SigmaPlot 11.0 software from Systat Software, Inc. (Richmond, CA, USA). Significant *P*-value was considered < 0.05.

RESULTS AND DISCUSSION

Latitude Gradients

When CMM rates in white populations worldwide are listed no evident latitudinal gradient is revealed (Fig. 1). In homogeneous populations skin cancer incidence rates increase with decreasing latitude.[8] Thus, in Norway the rates are a factor of two to three larger in the South than in the North at 10° higher latitude,[70] where the annual sun exposure is 33% smaller. "Latitude gradients" are meaningful quantities only within populations with homogeneous skin type and sun-exposure behavior. Such a gradient can be described by the biological amplification factor, A_b, which is defined by the equation $A_b = (dR/R)/(dD/D)$, where R is the age adjusted incidence rate and D is the annual exposure to carcinogenic solar radiation. D is often calculated by using the CIE reference spectrum for erythema,[71] as we have done in the present chapter. Using a planar, horizontal surface in the calculations, D increases by 50% per 10° latitude decrease in Norway.[18] Norwegian skin cancer rates are well described by the equation $\ln R = A_b \ln D + \text{const}$,[18,25,72] corresponding to the equation of definition for A_b above.

For SCC and BCC values of A_b between 1.5 and 2.5 were found, slightly smaller than those for CMM.[18,25,72] For BCC and SCC the Norwegian and Australian data agree quite well, and A_b values of 2.3–2.5 are obtained when the two data sets are combined.[72] A_b values of 1.5 and 2 correspond to 75% and 100%, respectively, increase in skin cancer incidence rates per 10° decrease in latitude. Thus, the risks of SCC and BCC are roughly twice as large in South Norway (60° N) as in North Norway (70° N).

In our analysis Norway is divided in 20 counties (Fig. 2). Earlier we have found biological amplification factors of about 3 for CMM in Norway.[72] There were no significant differences between urban and rural areas, neither between different body localizations.[72] Furthermore, the factor remained constant over the time period from 1966 to 1986.[72] As shown in Figure 3 (A and B panels), the relationship between age adjusted incidence

Figure 2. Counties of Norway (given the numbers used in this chapter).

rates of CMM (averaged for the period 1970 to 2009) and CIE weighted exposure is also well described by the same equation as given above for BCC and SCC, and as earlier found for CMM,[72] but the biological amplification factor is slightly smaller, about 2.4 for both men and women (Fig. 3). The mortality rates follow a similar equation, but with slightly smaller A_b values for women. This is demonstrated by the ratios of death rates to incidence rates, DR/R, in the lower part of Figure 3. Thus, for women the prognosis is slightly improving with increasing annual UV exposure, but the trend is not significant. The Norwegian data for the latitudinal dependency of DR/R agree with the combined data from Scandinavia, New Zealand and Australia (see Table 1 in ref. 73). The death to incidence ratios for CMM are, according to 2002 estimates, about 0.09 (women) and 0.14 (men) for New Zealand and Australia. The corresponding ratios for Northern Europe are significantly larger: 0.16 and 0.26, respectively. The incidence rates are much higher in Australia and New Zealand than in Northern Europe: 36.7 (Australia),[65] 36.2 (New Zealand)[65] vs. 15.39 (Nordic countries).[66] These data are in agreement with our data. No difference in CMM diagnosis, or in therapy, is expected to be found in the different regions of Norway, and it seems that the prognosis of CMM improves with increasing sun exposure, in agreement with the work of Berwick et al.[26] and with the immunological

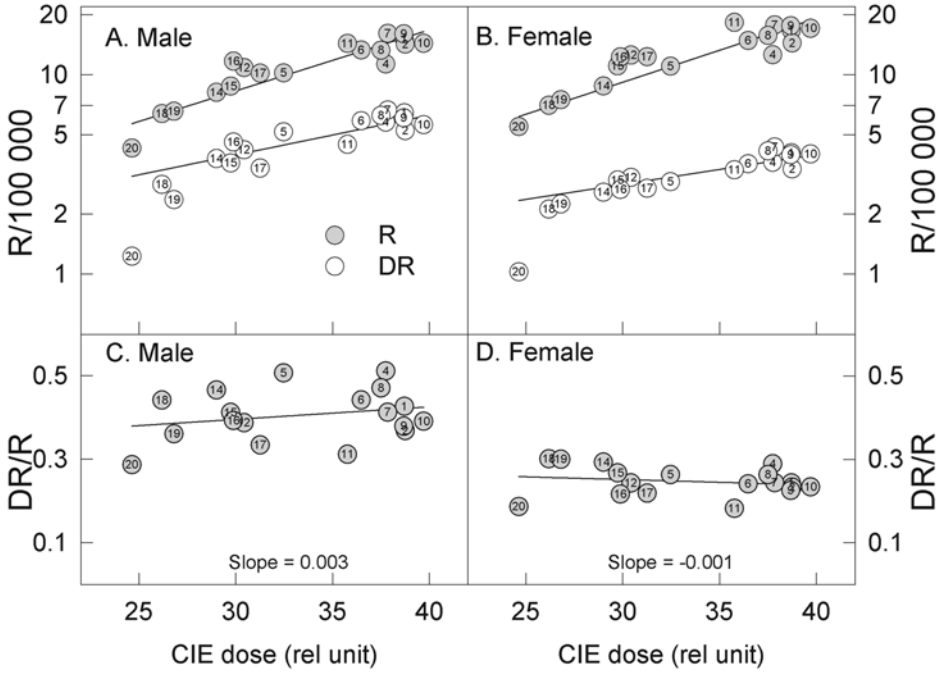

Figure 3. CMM incidence rates (R, filled circles) and death rates (DR, open circles) per 100 000 persons (age-standartised to the world population) as a functions of CIE weighted annual UV doses for CMM in males (A) and females (B) in different counties of Norway from 1970 to 2009. Lower panel represents the ratio of death rates to the incidence rates for males (C) and females (D).

work by Sigmundsdottir et al.[74] Their findings indicate that small UV doses may improve the potency of the immune system of the skin, possibly through generation of vitamin D.

The dependency of ocular melanoma on latitude in USA[75] can be interpreted in a similar way: stimulation of the immune system by UV radiation via vitamin D synthesis may explain why the rate of uveal melanoma decreases with increasing UV exposure, opposite to what is found for CMM.

When the CMM rates in Australia and New Zealand are combined with the Scandinavian rates, the value of A_b becomes smaller, about 1 (data not shown, see Fig. 3 in ref. 8). Using data for SCC and BCC in Australia[76-78] and in Norway[70] we find that SCC and BCC are about factors of 35 and 25, respectively, more frequent in Australia than in Norway per 100 000 persons (see also Table 1 in ref. 8), while CMM is only a factor of about 2 more frequent.[8,70] As earlier suggested,[25] this may have two explanations: (1) Scandinavians may follow a more melanomagenic sun exposure pattern, i.e., a more intermittent pattern than Australians. (2) UVA from the sun may play a larger role for CMM induction than for BCC and SCC induction, in agreement with Setlow's action spectrum for melanoma in Xiphophorus, as earlier discussed[25] and with a recent review of melanomagenesis.[79]

In some investigations the latitude gradients are opposite to those found in the present work.[41,80] Most states grouped in the two highest CMM death rate quartiles in USA are

not located at the lowest latitudes. Furthermore, the North-South incidence gradient has been decreasing since the 1950ies, so that within some years no gradient is expected.[81] Furthermore, in southern Europe the CMM incidence rates are much smaller than in Scandinavia as can be seen in Figure 1. This may have at least two reasons: (1) Southern Europeans generally have darker skin and darker hair than blond or red-haired Scandinavians and Celts. (2) We have shown that CMM incidence rates of different countries seem to increase with GDP/capita.[82] GDP may influence the sun exposure pattern, since one may assume that rich people can afford more vacations and weekend tours to southern latitudes and get excessive, intermittent sun exposures. Several CMM epidemiologists have stated that CMM is a "white collar" rather than a "blue collar" disease.

The latitudinal dependencies of CMM and ocular melanoma in some states in USA were studied.[75] Latitudinal gradients, similar to those reported in the present work, were found for CMM and for external, ocular melanomas (eyelid and conjunctivae melanomas). For uveal melanomas (internal ocular melanomas) an opposite gradient was found: increasing incidence rates with increasing latitude. In agreement with our suggestions it was concluded that solar radiation has both a protective and a generating effect with respect to melanomas. Obviously, total exposures as well as exposure patterns are important for the balance between the two effects: high, intermittent exposures will mainly act generating, while low, regular exposures will act more protective. Time trends of uveal melanomas seem to be opposite of those of CMM: While the incidence rates of CMM increased in many countries up to around 1990 (see below), those of uveal melanomas tended to decrease.[83-85]

Time Trends

For several decades before 1990 the incidence rates of all three skin cancer forms were increasing in Norway, as in most other Western countries.[72,82] However, during the last two decades the increase of the rates of CMM for the youngest generations has stopped, and even a decreasing trend is seen (Fig. 4). Similar trends have been reported from other countries.[86-91] The prognosis of CMM improved over all the years of increasing incidence, as indicated by the decreasing DR/R ratio (Fig. 4B). However, after 1990, when the rates changed from an increasing to a decreasing trend, the improvement of prognosis appears to have stopped (Fig. 4). Another way to study prognosis is to determine the five-year survival percentage (Fig. 5). From 1970 to about 1995 the percentage of CMM patients surviving five years after diagnosis increased from 55% (men) – 77% (women) to about 80% (men) – 90% (women), while after 1995 no significant change has taken place, neither for men, nor for women (Fig. 5). Again, a relationship with the flattening incidence curves seems possible: as long as the incidence rates increased, i.e., until 1990–1995, the survival improved. The finding that the ratio of the number of old ($\geq$ 50 y) to that of young ($<$ 50 y) patients has been increasing, notably for men in the southern regions of the country, is in agreement with these observations.

Up to 1990 the time trends of CMM incidence rates are similar in all Nordic countries, in all regions of Norway and for all age cohorts above 35 y.[72,87,92]

Body Localization

Relative tumor density (RTD) is here defined as the age adjusted incidence rate of CMM on a given body localization (head and neck, trunk, breast) divided by the fraction

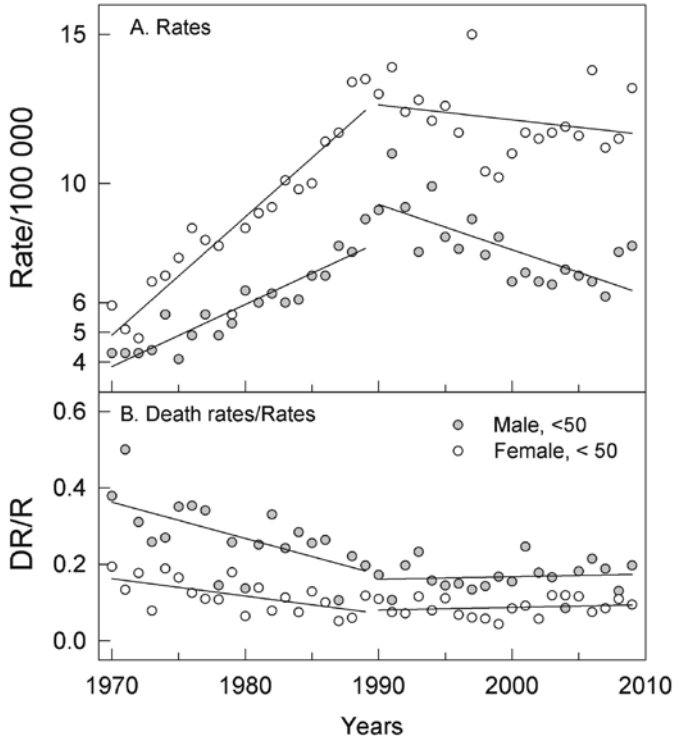

Figure 4. Incidence rates (age-standardized to the word population) of cutaneous malignant melanoma for persons younger than 50 y (A) and death to incidence ratios (B) in Norway.

Figure 5. Incidence rates of cutaneous malignant melanoma and five years survival (%) in Norway from 1970 to 2009.

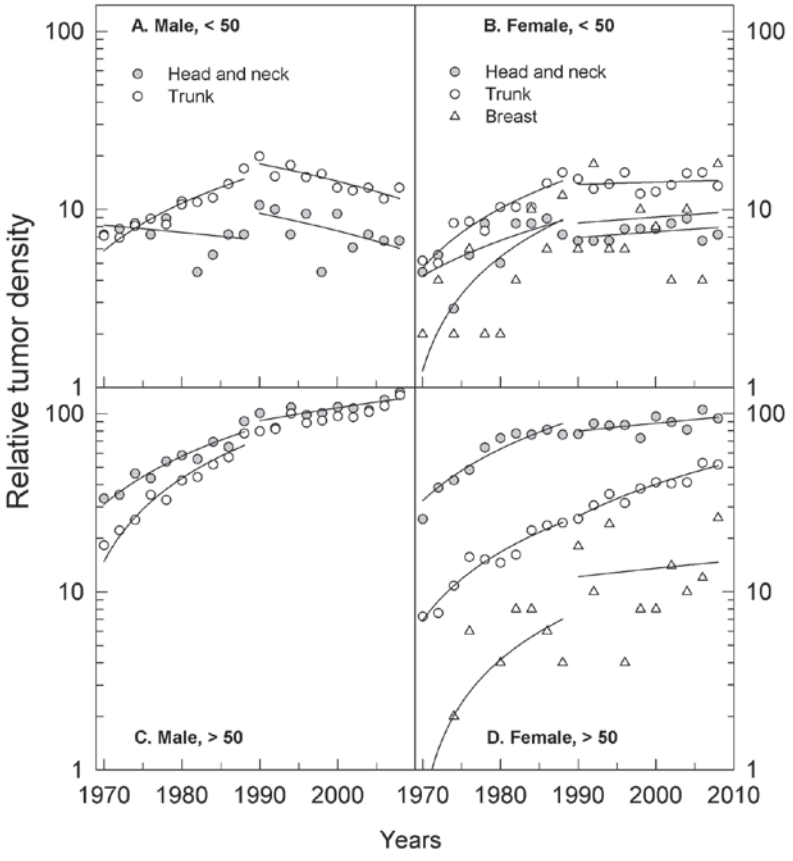

Figure 6. Relative density of cutaneous malignant melanoma (per 100 000 persons) on different body localizations (head and neck, trunk, breast) in Norway from 1970 to 2009: A) Males, < 50 y old, B) Females, < 50 y old, C) Males, ≥ 50 y old; D) Females, ≥ 50 y old.

of the total body area occupied by the given localization. Thus, the higher the RTD is, the more CMMs arise per cm^2 of skin. The values of the fraction of the skin at different sites are 0.09 for head and neck,[93] 0.3 for trunk[93] and 0.025 for breasts.[94]

The data in Figure 6 agree with those in Figure 5, but are more detailed. For men and women older than 50 y the RTD is larger on head and neck than on trunk, and for women the RTD on the breasts is even lower (Fig. 6), as expected in view of the assumed pattern of sun exposure for this generation. However, for men the difference is small and almost non-existent after 1990.

For men younger than 50 y the RTD is generally decreasing after 1990, and is smaller for head and neck than for trunk, in spite of the obvious fact that whenever the trunk is exposed, the head/neck is also exposed. This indicates that an intermittent exposure pattern, which is likely to apply for the trunk, is more melanomagenic than a more constant exposure pattern, which is likely to apply for head/neck. For young women a similar conclusion can be drawn: Also they have a larger RTD on trunk than on head/neck, notably after 1990. Their RTD on breasts is higher than for older women (Fig. 6). This gives valuable information

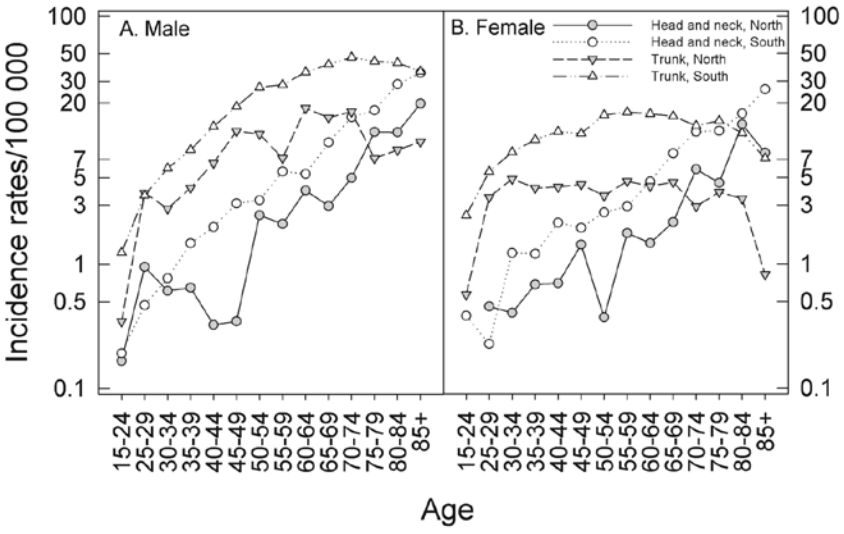

Figure 7. Age specific incidence rates of CMM among males (A) and females (B) in Norway (for the period 1990–2007). Filled symbols for North Norway (counties 18–20) and open symbols for South-East Norway (counties 1, 2, 6–11).

about the impact of the changing pattern of sun exposure. The fact that the RTD on trunk is larger than that on head and neck, which certainly are much more heavily UV exposed, is a clear indication that intermittent UV exposure is a strong carcinogen for CMM, while regular exposure is a much weaker one. Practically no CMMs arose on the breasts of Norwegian women before the advent of the topless fashion at about 1970.[64] As indicated by the curves for the breasts (Fig. 6), the topless fashion may have culminated some time before 1994. These data are in agreement with our earlier findings.[72,82]

The incidence rates of CMM on head and neck and that on trunk have different age dependencies (Fig. 7). While the age specific rates of CMM on head and neck increases uniformly with age (as do those for SCC, BCC and for practically all internal cancers), that for CMM on the trunk has a maximum at an age of 50–70 y. This is true for the North as well for the South part of Norway, and agrees with earlier findings.[72,82] We conclude that the risk of CMM on head/neck, areas regularly sun exposed, increases with age, while that on trunk has a maximum at an age between 50 and 70 y, (or even earlier in the North) when the population as a whole is considered, i.e., at a slightly higher age than found for the period 1976 to 1985.[82] This is certainly related to changing habits of clothing and sun exposure. People who are now 70–80 y did not follow an intermittent exposure pattern when they were young to the same extent as young people do now.

Effects of Sunbeds and Sunscreens

Increased CMM incidence rates were found for sunbed users in Norway.[57,95] However, other investigations indicate decreasing rates as well as increasing rates.[53,96-98] The most recent investigation in UK showed no relationship between sunbed use and CMM.[99] We have recently found that two weekly, moderate (10–15 min, completely non-erythemogenic)

sunbed exposures for 5 weeks increased the serum level of calcidiol (25 hydroxyvitamin D, serum marker of the vitamin D status) significantly, from typical winter values to summer values, and that the earlier recommended vitamin D intake of 200 IU per day was not enough to maintain that level.[100] Furthermore, it has been found that application of a sunscreen with a moderate or high UVB protection factor in recommended amounts almost eliminates the vitamin D synthesis, by sun as well as by sunbeds.[100]

CONCLUSION

Although there are many arguments against the statement that solar radiation is involved in melanomagenesis, our data indicate that UV is, indeed, a carcinogen for CMM, and that that UVA may play a role. CMM incidence rates are twice as high in South Norway as in North Norway, while the ratios of death rates to incidence rates are constant or slightly higher in the North. Comparisons of skin cancer data from Norway, Australia and New Zealand indicate that squamous cell carcinoma and basal cell carcinoma are mainly related to annual solar UVB fluencies, while UVA fluencies may play a significant role for CMM.

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