

North-South gradients of melanomas and non-melanomas

A role of vitamin D?

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Abbreviations: UV, ultraviolet; CMM, cutaneous malignant melanoma; SCC, squamous cell carcinoma; BCC, basal cell carcinoma

Incidence rates of skin cancer increase with decreasing latitude in Norway, as in many other countries with white populations. The latitudinal trends of the incidence rates of skin cancer were studied and compared with data for vitamin D-induced by UV and for vitamin D intake. The north-south gradient for CMM incidence rates on sun exposed skin is much smaller than those for BCC and SCC, and that for BCC is smaller than that for SCC. This indicates that SCC and BCC are mainly due to solar UVB, while UVA may play a significant role for CMM and a smaller role for BCC, since the north-south gradient of annual UVB fluences is larger than that of UVA fluences. However, there is an inverse latitudinal gradient of skin cancer in central Europe. This is probably due to a gradient of skin color, since white skin is an important determinant of increased risk of skin cancer. The role of vitamin D for skin cancer risk is difficult to evaluate, since serum levels of 25-hydroxyvitamin D, as well as vitamin D intakes, are widely different from country to country. Still, epidemiological evidence indicates a role: for melanomas arising on non-sun exposed body localizations (uveal melanomas, melanomas arising in the vulva and perianal/anorectal regions) there appears to be no latitudinal gradient, or, a negative gradient, i.e., increasing rates with decreasing latitude as would be expected if UV-generated vitamin D plays a protective role. Both skin cancer risk and vitamin D photosynthesis decrease with increasing skin darkness.

Introduction

UV radiation (UV) from the sun is an important environmental risk factor for all three major forms of skin cancer.¹⁻³ For squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) there is a clear relationship with the UV exposure, and UVB seems to be most important.² The accumulated exposure is a major determinant for SCC, while for BCC the sun exposure pattern may also play an additional role.² The relationship between UV exposure and cutaneous malignant melanoma (CMM) has been debated for decades.²⁻⁷ The exposure pattern (continuous, occupational exposure vs. episodes of intense exposure, often classified as “intermittent exposure”), appears to be of importance for CMM. Furthermore, sunburning in childhood is particularly dangerous. Some investigations even show that lifetime (accumulated) sun exposure is associated with a lower risk of CMM.⁸ In 1990 Garland et al.⁹ concluded that in the US persons with indoor occupations had a higher CMM risk than persons with both indoor and outdoor occupations. CMM is mainly caused by UV radiation, however, genetic factors also

play an important, independent role in CMM generation.¹⁰ A complicating factor is the anticarcinogenic properties of vitamin D which is also generated by exposure to UVB radiation.¹¹ Vitamin D acts in a systemic manner. Therefore, its antimelanogenic action can be elucidated by studying melanoma occurrence on non-UV-exposed body localizations.¹²

Scandinavia is located at high latitudes (> 54°N) where the annual UVB (280–315 nm) exposures are moderate and only of the order of 25% of the Equatorial UVB exposures.⁶ In spite of this, CMM is a significant health problem in Scandinavia. In 2008, the estimated age adjusted incidence rate of CMM for women in Norway was 16.5 as compared with 8.9 in France, 5.6 in Spain, 8.7 in Italy and 12.6 in Germany.¹³

BCC and SCC, like most other cancers, are diseases of old people, with incidence rates increasing sharply with age. In contrast, CMM has for decades been most frequent among middle aged people.² The localization patterns on the body are also different for the three skin cancer forms. These patterns are changing with time, indicating a role of changing habits of sun exposure.²

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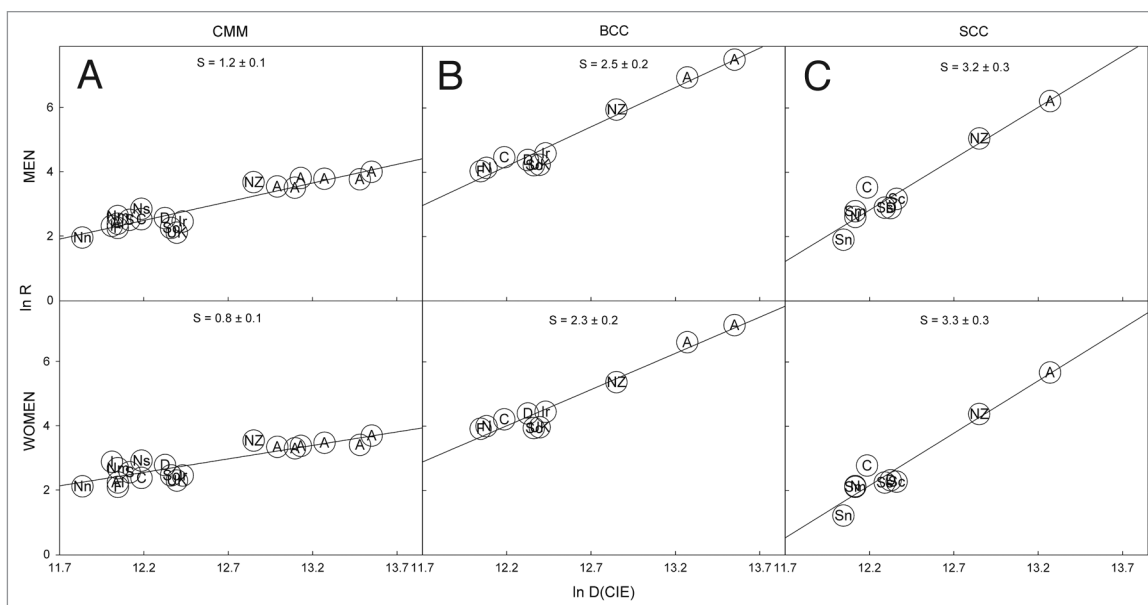


Figure 1. Incidence rates R (for the time period 1997–2007) plotted as functions of $\ln D$, where D is the annual solar UV exposure dose weighted by the CIE erythemal action spectrum: (A) for CMM, (B) for BCC, (C) for SCC. The white populations of the following countries are included: Australia (A), New Zealand (NZ), England (UK), Ireland (Ir), Scotland (Sc), Denmark (D), Sweden (Ss-South, Sn-North, Sm-Middle), Norway (Ns-South, Nn-North, Nm-Middle), Finland (F), Iceland (I), Alaska (Al), Canada (C). The slopes of the curves (the biological amplification factors) are given by S on the figure.

The fact that until recently the incidence rates of CMM increased over many decades was a serious concern for health authorities. Therefore, large campaigns against sun and sunbed exposure and for sunscreen use were launched. An emerging complicating factor associated with such campaigns is that large health benefits of adequate vitamin D levels have been revealed during the last decades. Not only solar UV radiation, but also UV radiation from sunbeds, produces vitamin D,^{14,15} while sunscreens, applied as recommended, eliminate the production.¹⁶

We will summarize basic facts of the epidemiology of skin cancer in Norway and some other countries with white populations, but located at lower latitudes, and concentrate on epidemiological evaluations of north-south gradients of skin cancer, vitamin D photosynthesis and vitamin D consumption.

Results and Discussion

Latitudinal gradients of skin cancer incidence rates. The relationship between annual exposures of solar radiation (weighted by use of the CIE erythema action spectrum)¹⁷ and incidence rates of BCC, SCC and CMM for Scandinavia, England, New Zealand and Australia was analyzed using logarithmic functions (Fig. 1). The populations of these countries are similar with respect to skin types, mostly skin types I, II and III are found. The populations of central Europe have larger contributions (increasing with decreasing latitude, see below) of persons with darker skin types (III and IV), the fraction of the populations with darker skin types increasing with decreasing latitude as indicated below. The rates of all three skin cancer forms, in both men and women, can be represented logarithmically quite well ($p < 0.0001$, Fig. 1). However, the slopes of the curves are

different (Fig. 1). Thus, those for BCC and SCC are between 2 and 4 times larger than those for CMM, in agreement with what we have found for an earlier time period (around 1976 – 1985).² It should also be noted that the gradients of SCC are 1.4 times larger than those of BCC.

Four main factors may explain the difference in slopes between BCC and SCC on one hand and CMM on the other (Fig. 1):

(1) Due to absorption of UVB (but not of UVA) in the ozone layer and to Rayleigh scattering in the atmosphere (its cross section is essentially inversely proportional to the wavelength in fourth power), the latitudinal gradient of UVB is much larger than that of UVA. This is even more evident for a vertical cylinder geometry than for horizontal plane geometry (data not shown). The Rayleigh scattering cross section at 290 nm is a factor of 2.4 larger than that at 360 nm. The annual UVB fluence in south Australia (35 degrees S) is a factor of about 3 larger than that in south Norway (60 degrees N), while the corresponding factor for UVA is about 2. Thus, the relatively small latitudinal gradient for CMM incidence and the larger gradients for SCC and BCC indicate that UVA may be a carcinogen for CMM, but not to the same extent for the non-melanomas. This agrees with our conclusions in an analysis of the data for an earlier time period.¹⁸ The slopes of these curves have remained almost unchanged from the early time period (1978–1982; about 1.1 for CMM, about 2.3 for BCC and about 2.5 for SCC)² to the present period (1997–2007: 0.8–1.2 for CMM, 2.3–2.5 for BCC and 3.2–3.3 for SCC). This indicates that the sun exposure habits have changed similarly in Scandinavia and Australia in the time span from 1978 to 2007. The smaller slope for BCC than for SCC may indicate that UVA also plays a small role for BCC, or, alternatively, that intermittent exposures play a larger role for BCC than for SCC.

(2) The relatively large RTDs (RTD is the relative density of tumors arising per unit skin area) of CMM on the trunk (and, as earlier found, for RTDs on legs, arms, female breasts)^{18,19} indicate that intermittent exposures may play a larger role for CMM than for the non-melanomas, notably for SCC. Because of lower and more variable temperatures at high latitudes, intermittent exposure may constitute a larger fraction of the total exposure in the south than in the north. For instance, one always exposes head and neck when out-door, but the trunk only when sunbathing at moderate and high temperatures.

(3) The relationship between increase in CMM risk and increase in sun exposure, may be more complicated on the individual level (as first noted by Holman et al.²⁰) than on the population level. Thus, for individuals with skin type III or higher, the CMM risk will increase with exposure up to a maximum, and then decrease upon further exposure. This can be explained by adaptive processes in the skin: pigment induction and skin thickening. Such a reasoning fits with the well known epidemiological observation that persons with out-door work (farmers, fishermen etc) have lower risks of getting CMM than persons with indoor occupations.^{21,22} In agreement with these reasonings are the facts that higher lifetime sun exposures are predominantly associated with a higher SCC risk, to a lesser extent with a higher BCC risk, and in contrast, with a lower CMM risk.⁸

(4) Melanomas sometimes arise on body areas never exposed to the sun.¹² Therefore, melanomas may have other reasons than sun exposure. If the fraction of skin tumors not related to sun exposure is larger for CMMs than for non-melanomas, one would expect to find a smaller latitudinal gradient for CMMs.

Sex differences. For SCC and BCC the gradients are similar for men and women (Fig. 1). For CMM, on the other hand, the gradient is significantly larger for men than for women (Fig. 1). A similar trend was found in an earlier investigation.¹⁸ The reason for this sex difference is likely to be that women in the north tend to expose themselves intermittently to high doses in summer vacations. Such an exposure pattern is probably less common among men.

Effects of skin color and vitamin D. Persons with dark, African skin (types V-VI) have a 20-fold lower risk of getting skin cancers than white people living at the same latitude.²³ Asians have an intermediate risk.²³ In Europe most populations are classified as “white.” However, the average skin color seems to become darker the lower latitude of living is.^{24,25} This is reflected in the CMM incidence rates for Germany (Fig. 2). A recent investigation shows that the CMM mortality decreases with decreasing latitude in Europe as a whole.²⁶

Thus, in Europe as a whole there is an “inverse” latitudinal gradient of CMM compared with in Scandinavia and Australia. This may be related mainly to gradients of skin color or other CMM-related genetic factors.²⁷ Despite the fact that vitamin D-generating UV exposure tends to increase strongly with decreasing latitude (Fig. 3A), there are no latitudinal trends, neither for the winter, nor for the summer vitamin D status (Fig. 3B). Nevertheless, the vitamin D intake tends to increase with increasing latitude (Fig. 3A). We earlier concluded that such an increase in vitamin D intake with increasing latitude

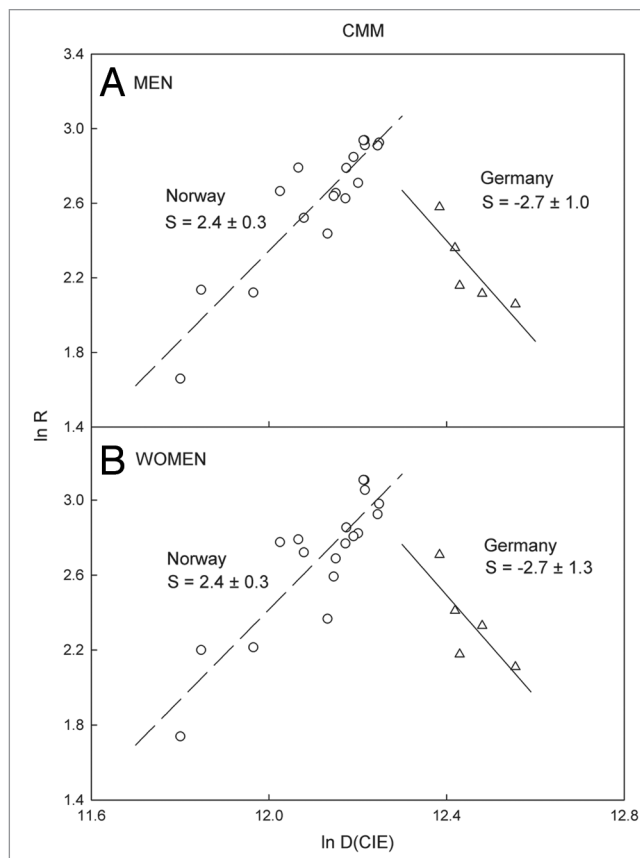


Figure 2. Incidence rates R (for the time period 1997–2007) for CMM at different latitudes in Norway and Germany plotted as functions of $\ln D$, where D is the annual solar UV exposure dose weighted by the CIE erythemal action spectrum.

in Norway probably balanced the decrease in sun-production of vitamin D.²⁸ Vitamin D plays a protective role against CMM induction.²⁹ In addition to protection against melanoma initiation, vitamin D is a presumable agent for lower melanoma mortality in sunnier European countries.²⁶

Materials and Methods

Incidence rates of skin cancer. Online database of The International Agency for Research of Cancer (IARC),^{13,30} The Cancer Registry of Norway (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), Association of Population-based Cancer Registries in Germany,³¹ The Scottish Cancer Registry,³² The Finnish Cancer Registry,³³ The Australian Institute of Health and Welfare,³⁴ The New Zealand Cancer Registry,³⁵ and published articles^{36–50} have been used as sources for presented epidemiological data for incidence rates of skin cancer in different countries (according to the world standard population (ASIR, W)).

Vitamin D data. Serum levels of 25-hydroxyvitamin D and vitamin D intake in different countries were retrieved from published articles.^{51–82}

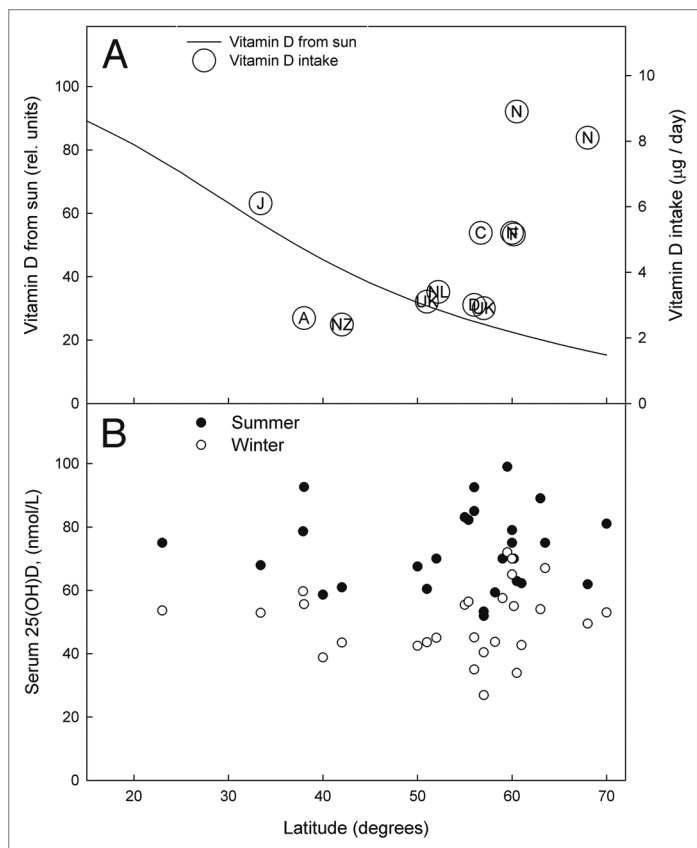


Figure 3. (A) Values for vitamin D intake in different countries, assigned as in Figure 1. The following countries are included: Japan (J), Australia (A), New Zealand (NZ), Canada (C), England (UK), Scotland (Sc), Denmark (D), Netherlands (NL), Finland (F) and Norway (N). The full curve shows the calculated annual vitamin D-generating doses of solar radiation. (B) Measured summer and winter values of 25-hydroxyvitamin D (25(OH)D) in serum at different latitudes.

Radiative transfer calculations. Erythema weighted solar UV spectrum was assumed to be carcinogenically effective, and erythema doses were chosen to be the agent showing the UV effectiveness for skin cancer initiation. The global solar UV (direct and diffuse radiation on a horizontal surface) was calculated with a radiative transfer model.^{83,84} The daily ozone values measured by the TOMS instrument on the Nimbus 7 satellite were used as inputs to the model. The daily cloud cover for each site used in the calculations was derived from measured reflectivities from an ozone-insensitive channel in the same satellite instruments. The calculated annual UV fluences given in this chapter are based on available satellite measurements in the period 1979–1992.

Annual fluences are given, although summer values (May–August) are probably dominant with respect to real fluences obtained by the population. However, as earlier shown by comparisons with SCC incidence rates, the annual fluences are good approximations for the skin cancer generating fluences received by the population.⁸⁵

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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