Review

Solar Radiation, Vitamin D and Cancer Incidence and Mortality in Norway

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Abstract. *Solar radiation is of fundamental importance for human development and health: On the one hand, too much of it can lead to skin ageing and skin cancer, whilst on the other, too little of it can result in vitamin D deficiency, and, thereby lead to high incidence and poor prognosis of internal cancer as well as a number of other diseases. The following data, mostly from Norway, will be reviewed: Variation of ambient solar ultraviolet radiation (UV) and vitamin D status with season and latitude, variation of incidence rates and prognosis of skin cancer and variation of prognosis of internal cancer with latitude and season. In short, the following issues are discussed: 1) Vitamin D level varies with season, but probably not with latitude in Norway, because of an increased intake of vitamin D in the north; 2) Skin cancer incidence rates increase from north to south, as do annual fluence rates of UV radiation, while there seems to be a slight improvement in prognosis from north to south; 3) Prognosis of internal cancer is best for cases diagnosed in the seasons with the best vitamin D status, i.e. in summer and autumn; 4) Incidence rates of cutaneous melanomas have increased from 1960 to 1990, but have decreased slightly thereafter for young people; 5) Changes in sun exposure habits have taken place; 6) An increase in body mass index (BMI) of the population has occurred, which may have led to a worsening of the vitamin D status.*

All life on earth has developed under the influence of solar radiation. The radiation in the ultraviolet region (UV) of the spectrum is of particular importance. In this region, the atmosphere absorbs all radiation of wavelengths below 280 nm, and only UVB (280-320 nm) and UVA (320-400 nm) radiation reach the ground. The fluence rates of UVA are 10-1,000 times larger than those of UVB. In spite of this, UVB has the major health impacts, since its quantum yields for most biological reactions are much larger than those of UVA.

This review deals with two major health effects of solar radiation: Generation of vitamin D and induction of skin cancer. Vitamin D is produced almost exclusively by UVB (1), and so are both forms of non-melanoma skin cancer: basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) (2-5). Cutaneous malignant melanoma (CMM) is certainly also generated by UVB, but recent research indicates that UVA may play a significant role in its etiology (4, 6, 7). The reason for this difference is that DNA is the main chromophore (molecule absorbing the photon that initiates the effect) for BCC and SCC, while melanin, in particular pheomelanin, in addition to DNA, may act as chromophore for CMM through the generation of free radicals. In this work, CMM will be primarily discussed, since it has a much higher death rate than SCC and BCC (8). Immunological effects of UV may play roles in cancer induction and prognosis, and may have unknown chromophores in addition to DNA and urocanic acid (9, 10). Vitamin D also interacts with the immune system (11, 12), and therefore the action spectrum of vitamin D generation is also important in the immunological effects of solar radiation. From these considerations, it can be understood that the action spectra related to positive and negative health effects may be different. Since the spectrum of solar radiation, as well as its intensity, changes with time and geographical location, the balance point between beneficial and adverse effects of sun exposure will also change. For instance, the UVA/UVB ratio increases with decreasing solar elevation and with increasing latitude. A thin cloud layer, on the other hand, makes the ratio decrease. UVA is

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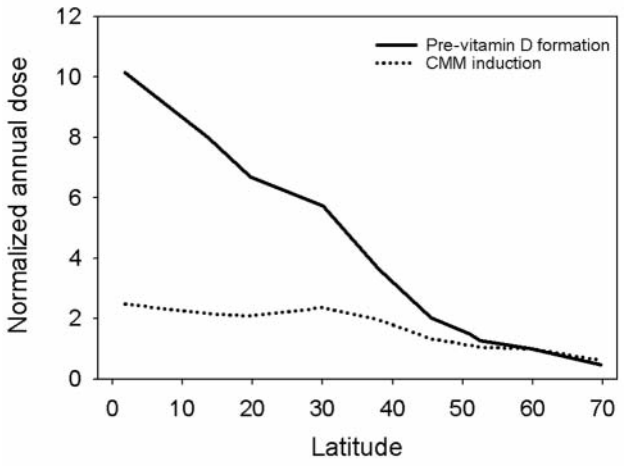

Figure 1. *The dependency of annual pre-vitamin D formation and CMM induction on latitude. Calculations are based on known absorption spectra of pre-vitamin D (14), action spectra of CMM induction (6) and known rates of solar radiation, as described elsewhere (23). The curves are normalized to the same value at 60° N (Oslo).*

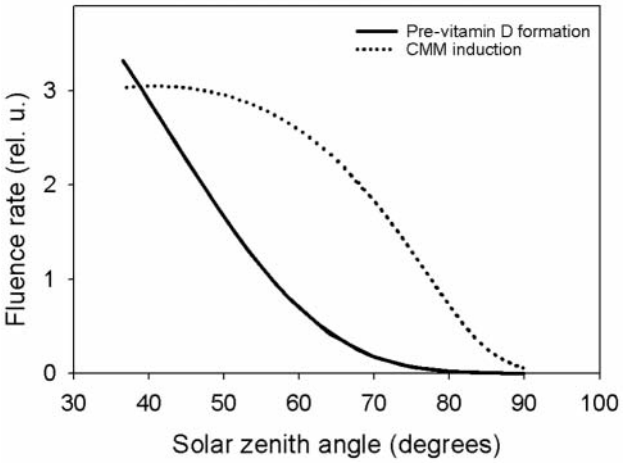

Figure 2. *The dependency of annual pre-vitamin D formation and CMM induction on solar zenith angle.*

significantly less scattered in the atmosphere than UVB, and, therefore, more of it comes in straight lines from the sun. The scattering is much larger at 300 nm than at 360 nm. This means that the UVA/UVB ratio for a vertical cylinder surface (resembling a standing person) increases with decreasing solar elevation, *i.e.* from noon to afternoon, while the ratio changes much less for a horizontal, planar surface as used in most discussions until now (4, 13). These considerations are of fundamental importance for evaluations of health effects of solar radiation, and will therefore be discussed briefly in the first part of this review.

Solar Radiation

The wavelength region responsible for vitamin D photosynthesis, *i.e.* the action spectrum, is known with significant confidence. Thus, the *in vivo* action spectrum and the absorption spectrum of 7-dehydrocholesterol (the precursor of vitamin D) are similar (14, 15). As previously discussed, the action spectrum for generation of non-melanoma skin cancer is likely to be similar to the vitamin D spectrum (2, 15), which, in turn, is similar to the CIE (Commission Internationale de L'Eclairage) erythema reference spectrum (16). For CMM, the radiation around 360 nm is considered, which is in the middle of the action spectrum for CMM in the fish *Xiphophorus* (6). Scientific arguments for this, *i.e.* for UVA as an important carcinogen for CMM, have been discussed elsewhere (13, 17).

Throughout, a vertical cylinder is used as a geometrical representation for the human body, since it is believed that this is a better representation than a planar, horizontal surface. Even lying sun-tanning persons have a significant fraction of their skin in a vertical position. The cylinder geometry is of great importance when it comes to determining UVB/UVA ratios (18).

Figure 1 shows the latitudinal variation of the annual doses of solar radiation generating vitamin D and causing CMM, using the mentioned cylinder representation. It can be seen that the gradient is steeper for vitamin D than for CMM. The gradient for non-melanoma skin cancer is similar to that of vitamin D.

Figure 2 demonstrates that as solar elevation decreases (for instance with time after noon), the fluence rate of UVA decreases much slower than that of UVB (*i.e.* of vitamin D generation). Thus, the best time for sun exposure in view of a high vitamin D yield at a minimal CMM risk, is noon. This is contrary to earlier recommendations of sun exposure, which advised people to wait until the afternoon before going out in the sun.

Ultraviolet Radiation and Skin Cancer in Norway

For CMM, as well as for SCC, there is a clear dependency on ambient solar UVB-radiation, as shown in Figure 3. The UVB-radiation is given here as annual doses for the different counties, as earlier described (13). The north – south gradient is similar for the two cancer types in Norway, as demonstrated by Figure 2. However, when more data for white populations, spread over a larger span of latitudes, are brought into consideration, the latitudinal gradient of non-melanoma skin cancer incidence rates is much larger than that of CMM incidence rates (19): non-melanomas are much more frequent in Australia than in Norway, while the difference is smaller for CMM. It was previously found that for both men and women, the incidence rates of BCC are 18-20 times larger in Australia than in Norway and the

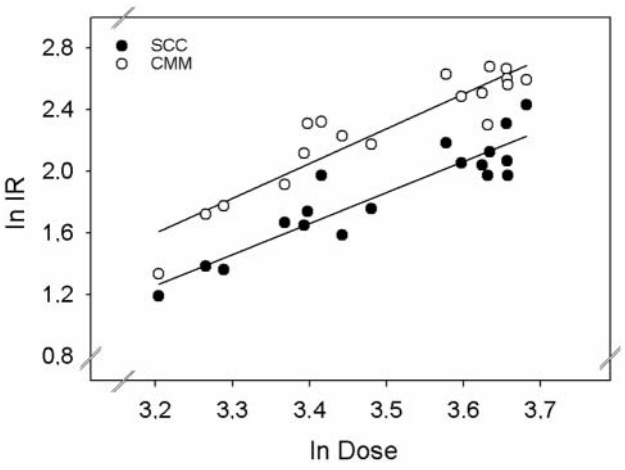

Figure 3. *The dependency of incidence rates of SCC and CMM (age-adjusted for the European population) on UV dose in Norway. Each point represents a Norwegian county. Data are averaged for the period 1960-2007.*

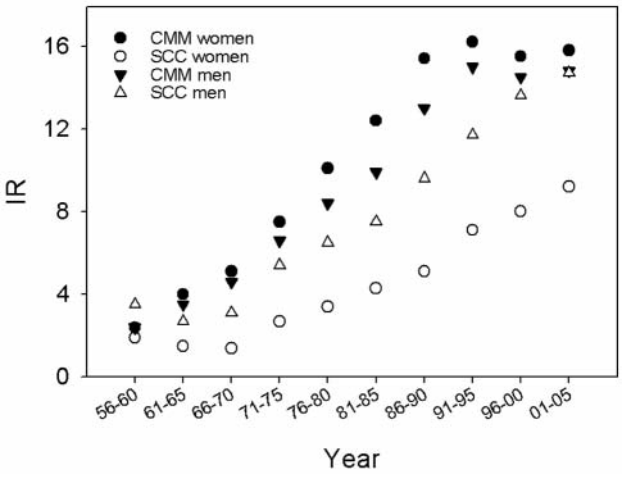

Figure 4. *Time trends of incidence rates of CMM and SCC (age-adjusted for the European population) in men and women in Norway. Values represent averages for five years.*

corresponding numbers for SCC are 30-44 (19), however, those for CMM are only 3.7 to 5. It was found that in the most heavily populated regions, the annual dose of UVB is up to 8 times larger in Australia than in Norway, while the annual dose of UVA is only about 1.7 times larger. This is in agreement with the data shown in Figure 1, since the action spectrum of non-melanomas is similar to that of vitamin D generation, being UVB centered, and strongly indicates that UVA is important for CMM induction but not for non-melanoma induction, in agreement with earlier conclusions (19).

The time trends of CMM and SCC are shown in Figure 4. When stratifying by age groups, it can be seen that for the youngest group (under 50 years), the increasing trend of CMM stopped at around 1990 (Figure 5). After that time there has even been a decrease in the rates of CMM. This indicates that all campaigns against intermittent and vacational sun exposure have had a significant impact. At the same time, the improvement of the prognosis of CMM, here estimated as the ratio of death rate to incidence rate (DR/IR), seemed to stop at about 1990 (Figure 5). This is in agreement with earlier work, in which it is tentatively concluded that decreasing sun exposure (after 1990) may have led to slightly worsening CMM prognosis in agreement with the conclusions of Berwick *et al*. (20).

The fact that the rates of SCC seem to have continued to increase also after 1990 may be explained by the fact that, in contrast to CMM, the risk of SCC increases steadily with age and by the common view that the SCC risk is related to the total, lifelong UVB exposure.

The difference between the time trends of CMM for persons above and below 50 years of age seen in Figure 5 is

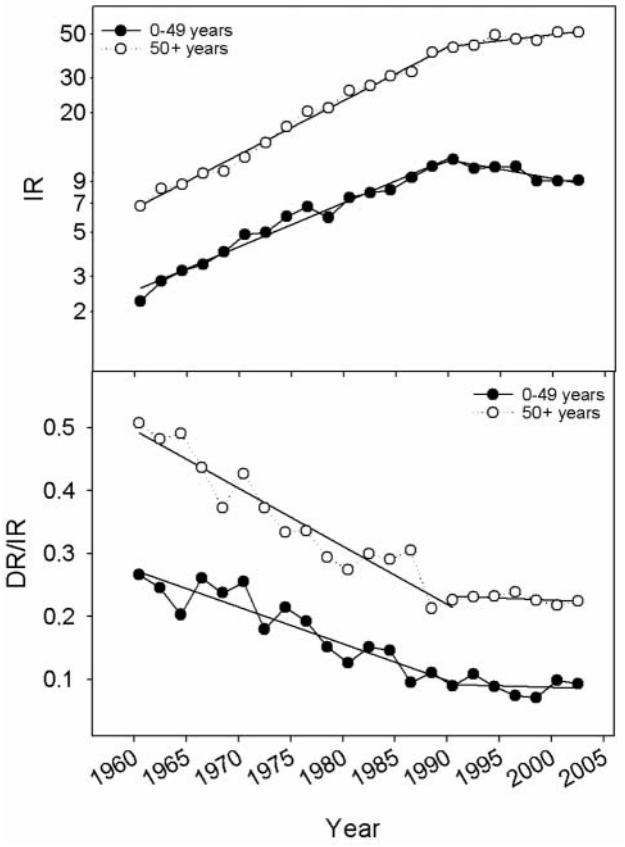

Figure 5. *Incidence rates of CMM and ratio of death rates to incidence rates for two age groups (younger and older than 50 years). The data are for the period 1960-2004 and each point represent the average of two consecutive years. Time trends.*

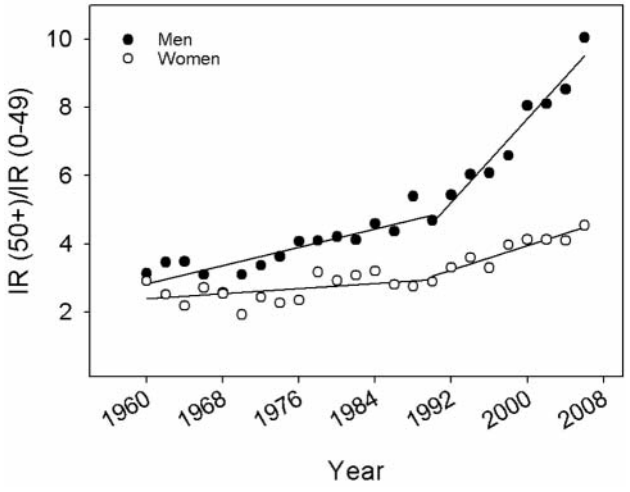

Figure 6. *Ratio of incidence rates of CMM (age-adjusted for the European population) for two age groups (younger and older than 50 years) in women and men. Time trends for the period 1960-2007.*

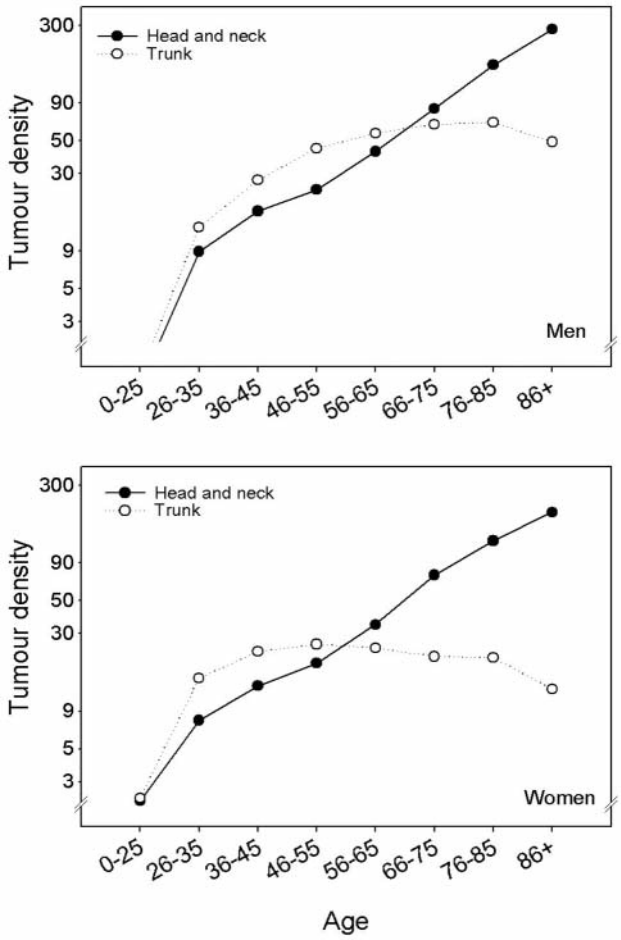

Figure 7. *Relative tumor density of CMM on two body localizations in men and women as a function of age at diagnosis.*

more clearly demonstrated in Figure 6, where the ratio of the incidence rates for these two age groups have been plotted as a function of time. Figure 6 also indicates that the exposure pattern may have changed differently with time for the two age groups and more for men than for women.

It is frequently proposed that the pattern of sun exposure is important for skin carcinogenesis, intermittent exposure patterns being most dangerous for CMM (21, 22). Epidemiological data can be used to elucidate this since different body localizations are differently exposed to the sun: trunk and extremities are supposedly subjected to relatively more intermittent exposures than face and scalp. Age curves for CMM are shown in Figure 7. Those for SCC are known to increase steadily with age, showing that SCC is an "age disease", as most internal cancer forms are. The same is true for CMM on face, scalp and neck, but not for CMM on trunk and extremities, for which the rates are highest around 40-50 years for women and around 55-75 years for men (Figure 7). For BCC, the trends are between those of SCC and CMM (data not shown). It is believed that this can be explained by two factors: intermittent exposure of trunk and extremities has increased in frequency over time, and such exposure patterns are particularly carcinogenic for CMM but not for SCC. For BCC, intermittent exposures may play a role, but not as clearly as for CMM. These conclusions are in agreement with what has been suggested from completely different lines of evidence (4, 13, 21, 22). The changes of exposure patterns (*i.e.* of sun exposure habits) that have taken place over time are further demonstrated by looking at age incidence curves for tumor density on the face/neck and on trunk for two birth cohorts, 1900-1919 and 1940-1959 (Figure 8).

In Figure 8, relative tumor density (RTD) on face and neck and on trunk and extremities are compared. RTD is here defined as the ratio of incidence rate (IR) and fraction f of the skin surface occupied by the studied body localization. The fractions of the total skin surface occupied by the face/neck and by trunk are assumed to be 0.09 and 0.3, respectively, for both sexes. This is clearly only a crude estimation, since neither the hair nor the breasts of women were taken into account. It can be seen that for the "old" birth cohort, RTD is always larger, and in most cases much larger, on the face and neck than on the trunk, while for the "young" birth cohort the opposite is true in most cases. This clearly supports the intermittent exposure hypothesis for CMM, since intermittent exposure relevant for CMM carcinogenesis has certainly increased in frequency with time of these birth cohorts. These findings agree with previous findings (5).

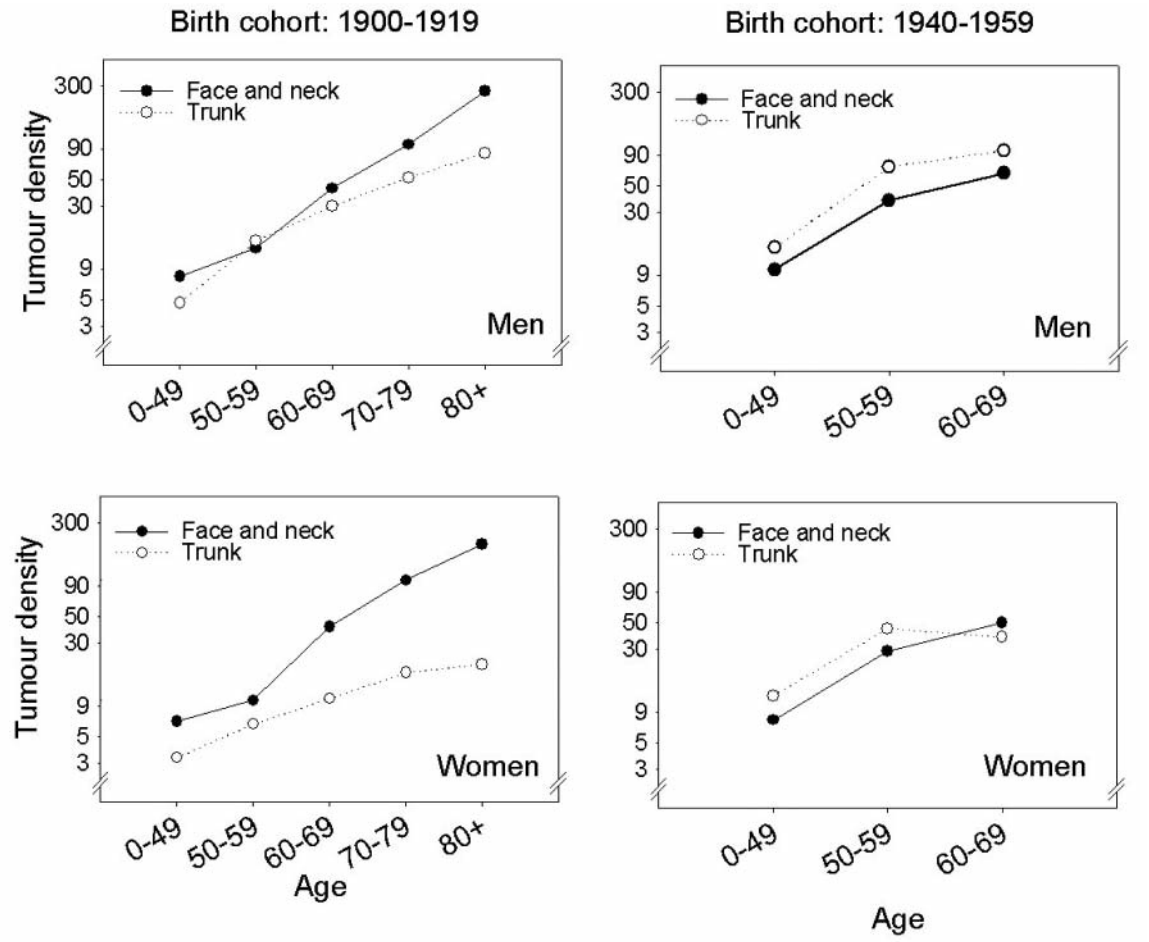

Figure 8. *Relative tumor density of CMM on two body localizations in men and women in two birth cohorts.*

The Vitamin D Status

The vitamin D status has been assessed by determinations of serum 25(OH)D in a number of studies in Norway, as listed in Table I. In all but one study, higher summer values than winter values were found. The summer values are between 10 and 50% larger than the winter values. Due to low solar elevation and a long pathway of the radiation through the ozone layer, there is not enough UVB in the radiation to produce significant amounts of vitamin D between September and March (23). The production rate is largest in midsummer, while the serum level of 25(OH)D reaches a maximum almost a month later (23). The reasons for the delay are partly that most people have their vacation in July, and partly that the biosynthesis of 25(OH)D from pre-vitamin D formed in the skin takes some time (23). The reason why no seasonal variation was found in one of the studies from northern Norway may be that people in that region consume more fish liver products in the winter than in the summer. In fact, people in north Norway consume

Table I. *Seasonal variation of 25(OH)D in different populations studied in Norway.*

Ref.	City	Lat (N°)	Age	Gender	Summer 25(OH)D (nmol/L)	Winter 25(OH)D (nmol/L)	Ratio
(54)	Tromsø	70	31.5	M+F	81	53	1.52
(55)	Oslo	60	78	F	70	54	1.29
(56)	Oslo	60	78	M+F	62	43	1.44
(57)	Oslo	60	40	M+F	27	18	1.5
(57)	Oslo	60	60	M+F	79	70	1.12
(58)	Tromsø	70	51	F	61	49.5	1.23
(59)	Andenes[a]	69.2	20-60	M+F	45	44	1.02
(59)	Andenes[b]	69.2	20-60	M+F	41.2	41	1
(29)	Oslo	60	≤50	F	51	44.4	1.14
(29)	Oslo	60	>50	F	62	59.3	1.04
(27)	Oslo	60	≤65	M	52	45	1.15
(27)	Oslo	60	>65	M	58	50	1.16
(28)	Oslo	60	≤65	F	57	50	1.14
(28)	Oslo	60	>65	F	62.5	61	1.02

[a]All participants; [b]participants never using sun bed nor going on holiday in the sun.

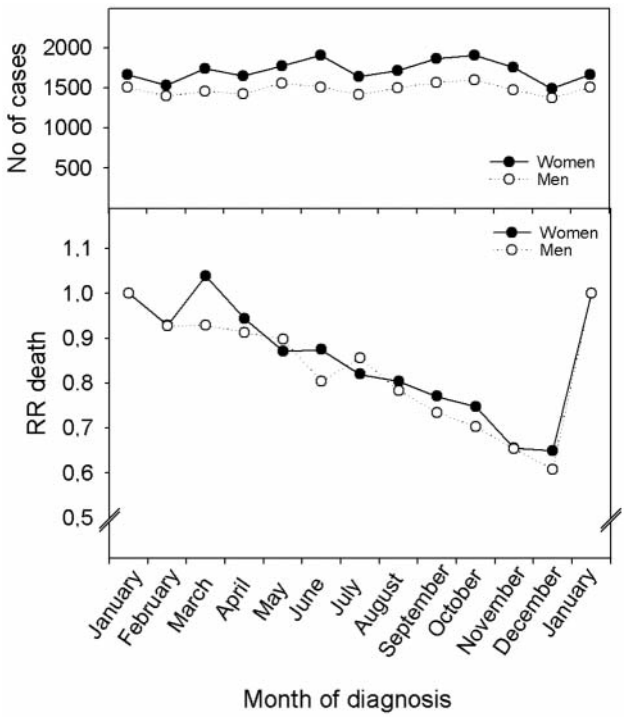

Figure 9. *Monthly variation of colon cancer prognosis in women and men. Cancer prognosis was estimated using a Cox regression model as previously described (40).*

Table II. *Average 25(OH)D levels in two age and BMI groups.*

Gender	Age	BMI	25(OH)D (nmol/L)
Men	<50	20-29	75
		35-40	59
	≥50	20-29	80
		35-40	69
Women	<50	18-29	78
		35-40	67
	≥50	20-29	80
		35-40	72

Table III. *Seasonal variation of 25(OH)D in two BMI groups.*

Gender	BMI	Summer 25(OH)D (nmol/L)	Winter 25(OH)D (nmol/L)	Ratio
Men	20-29	92	64	1.4
	30-40	72	57	1.25
Women	20-29	86	78	1.1
	30-40	75	64	1.2

about 10-20% more fish products with vitamin D than people in south Norway (24). This may be the reason why there seems to be no north – south gradient in the vitamin D status (Table I).

The available data provides no clue as to whether there has been any change of the vitamin D status with time, although an increase in average BMI (body mass index) (25) might suggest a slight decrease. Furthermore, the Norwegian Statistical Bureau gives data showing that young people spend more and more time indoors with PCs and TVs. In 1993- 20% of 15-year-old children spent on average 4 hours with PCs and TVs, while in 2005, the percentage had increased to almost 70.

A study of the relationship between BMI and vitamin D status has recently been performed (26). Essentially, it was found that both summer and winter values decreased with increasing BMI (Tables II and III). There was no significant difference between men and women. The vitamin D status appears to get slightly better with age (Table II), in agreement with previous findings (27-29). Since the efficiency of photosynthesis of vitamin D in skin decreases with age (30), the observed age differences may be related to either sun exposure habits or intake of food or supplements with vitamin D.

Sun Beds, Food and Vitamin D

This topic will be thoroughly discussed by Cicarma *et al.* in the present journal. Essentially, it has been observed that moderate sun bed exposures (in non-erythemogenic doses) improve the vitamin D status, and that intake of the recommended doses of vitamin D (200 IU in Norway at the time when the study was performed) is not enough to maintain a summer value of vitamin D in winter times (31-37).

Seasonal Variation of Cancer Prognosis

In a number of publications it has been shown that the prognosis of a number of types of internal cancer is best when diagnosis and therapy commence in the summer and autumn months, *i.e.* when the vitamin D status is optimal (23, 27-29, 38-40). The advantage of summer/autumn diagnosis is generally largest for the youngest patients (27-29, 38, 39), which may be due to the documented decrease in vitamin D photosynthesis with age (30).

The annual doses of ambient solar radiation producing vitamin D is about a factor of 1.5 larger in south Norway than in north Norway (Figures 1 and 3) (23). The ambient doses are probably relevant for real, personal exposures, since the incidence rates of SCC increase uniformly with the ambient UVB doses in the Norwegian counties (Figure 3) (29, 39). In view of this, it was surprising to find no

north–south gradient in cancer prognosis (27-29, 39). The lack of such a gradient was proposed to be due to the higher vitamin D intake in northern Norway (23, 24).

Does Vitamin D Influence Cancer Risk, or Cancer Prognosis, or Both?

This question has been discussed in several papers (41, 42). It was concluded that a good vitamin D status appears to improve survival more than incidence rates. This conclusion is supported by a number of *in vitro* studies which demonstrate the immunological and cell differentiating effects of vitamin D derivatives (43-47). Clinical intervention studies are also in agreement (48-52).

With the exception of CMM (13), no seasonal variation of the number of cancer cases diagnosed can be found. This may seem to indicate that vitamin D does not interfere significantly with cancer induction. However, carcinogenesis is a process believed to proceed over years, so these data do not allow any conclusions to be drawn.

The seasonal variation of cancer prognosis: Speculations on possible artifacts. If the seasonal variations are universal, vitamin D or one of its derivatives, would be an excellent adjuvant in cancer therapy. All the patients that have been studied, by us have received standard treatments (23, 29, 38, 39). Thus, vitamin D seems to act as an adjuvant. In fact, interventional studies also suggest this (48-52). Fundamental findings such as this should be scrutinized with great skepticism, and possible artifacts should be ruled out. One such artifact is the rate of diagnosis which certainly influences prognosis. For instance, if people postpone going to the doctor with dangerous symptoms until after a vacation or a holiday, their treatment would start late, and the prognosis might be unfavorable. If this behavior were common, there would be a seasonal variation of diagnosed cases and a seasonal variation of the distribution of cancer stages. Figure 9 shows that there is no monthly variation of diagnostic rate for colon cancer. Furthermore, the seasonal variation of prognosis is different for different age groups, which is most evident for lymphomas (38). For some cancer forms, such as ovary and bladder cancer, no seasonal variation of prognosis is found at all (53).

In some cases, there are enough data to study monthly variations. This is demonstrated for colon cancer in Figure 9. It can be seen that the time point of diagnosis giving optimal survival is late, in November, and that there is an abrupt worsening from December to January. There is no explanation for this long delay after maximal photosynthesis of vitamin D. Could it be a seasonal variation of intake of vitamin D? Could it be a seasonal variation of the general health condition that might influence cancer prognosis? Could it be an increased intake of fatty foods at Christmas time that might dilute or wash out vitamin D from the body in late winter? Could it be long-term storage of vitamin D derivatives in some locations in the body? These possibilities should be investigated in the future.

Conclusion

Solar radiation is the most important carcinogen for all forms of skin cancer, which causes about 250 deaths in Norway per year. However, by increasing the overall sun exposure of Norwegians, the vitamin D status would be improved. The findings that cancer prognosis varies with season of diagnosis indicate that the advantage of increased sun exposure might be larger than the disadvantage, as far as overall cancer death rates are concerned. In agreement with the known decrease of the efficiency of vitamin D photosynthesis with age, the seasonal variation of prognosis is largest for the youngest patients. The fact that there is no seasonal variation of diagnosed cases and that no seasonal variation of prognosis is found for a few cancer forms (53) argue against the present findings being simple artifacts.

Acknowledgements

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