Chapter

Sun Exposure and Cancer Survival in Norway:
Changes in the Risk of Death with Season of Diagnosis and Latitude

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Abstract

Epidemiological and experimental studies suggest that derivatives of vitamin D may improve prognosis of a number of cancer types. Sun is our most important source of vitamin D. Seasonal variations and latitudinal gradients of calcidiol (the marker of vitamin D status) have been reported. We wanted to investigate if season and latitude play any role for survival from seven different cancer types in Norway. Seasonal and geographical variations of vitamin D were estimated by calculations and were compared with clinical data. For the survival analyses, 249373 cancer patients were followed for three years after diagnosis and the risk of death was analyzed separately for summer- and winter diagnosis, as well as for two geographical regions with different UV exposures. We found a 15-25 % better survival for patients diagnosed during summer and a slight beneficial effect for residents of the high UV region for some of the cancer forms investigated.

Based on our results we suggest that calcidiol concentration at the time of cancer diagnosis is related to survival and discuss briefly ways to improve the vitamin D levels in the general population.

Introduction

Solar radiation, a recognized skin carcinogen,[1] may also reduce mortality from internal cancers. This intriguing suggestion was first published by Apperly in 1941.[2] He observed that cancer patients living at high latitudes in USA had a higher mortality risk compared with those living in the south. Later, in 1980, Garland and Garland[3] surveyed the association between solar exposure and risk of dying from colon cancer and hypothesized that the negative association between these two may be related to the level of vitamin D. A number of similar ecological studies were carried out in the following years, most of them supporting the proposed association.[4-9] The level of solar exposure were either approximated by using latitude, UV satellite measurements, UV indexes (the case of ecological work), assessed through records of personal history of sun exposure or estimated by structural changes in the skin.[10] A number of cancers were investigated throughout this period and in a recent publication fifteen cancer types were found to be sun-sensitive with respect to progression.[11]

A north-south gradient seems to be present in USA as well as in Europe[12,13] and even in Japan.[14]

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These epidemiological observations triggered experimental work aimed at understanding the mechanistic background. As suggested by Garland and Garland a possible link between the level of solar exposure and cancer mortality is vitamin D.[3] It is well known that sun is our main source of vitamin D. Our epidermis and dermis contain 7-dehydrocholesterol (7-DHC), a precursor of both vitamin D and cholesterol.[15] When UVB (ultraviolet B, 280-320 nm) photons from the sun or from artificial sources, hit the skin, 7-DHC absorbs energy and is structurally changed to previtamin D which is unstable and isomerizes in a temperature dependent process to vitamin D. Vitamin D is transported by the blood flow, bound to DBP (vitamin D protein), first to the liver and then to the kidneys. The molecule undergoes steps of enzyme-catalyzed hydroxylation, resulting in the formation of 25 hydroxyvitamin D (calcidiol) in the liver and 1,25 dihydroxyvitamin D (calcitriol) in the kidneys.[15] Calcidiol is used in the clinical vitamin D monitoring, since its formation is not tightly regulated. Therefore it is reflecting the vitamin D status.

The serum level of UV-induced calcidiol is influenced by several factors that modify the biosynthetic pathway. Among these, the level of UVB reaching the ground, the skin properties (pigmentation, thickness), the function of liver and kidneys as primary sources of active vitamin D as well as BMI (body mass index) and possibly hormonal status are the main predictors.[16-19]

The seasonal variation of calcidiol is a well documented fact. In a healthy, adult population living in Norway the percent increase from winter to summer is 15-50%.[20-24] From October to April solar vitamin D synthesis does not take place in this part of the world[25] and vitamin D deficiency will become manifest unless adequate amounts of the vitamin are ingested. The maximal serum levels of calcidiol are usually achieved during the months September-October, reflecting a delay from the maximal solar UVB fluence rate midsummer.

Materials and Methods

The purpose of our work was to study the association between the level of solar exposure and cancer prognosis in Norway. The exposure level changes with season and residential region. Outcome was calculated using Cox proportional hazards regression model and expressed as relative risk of death (RR). The category with the lowest solar exposure was chosen as reference and set to 1. Analyses were adjusted for a number of possible confounders, as outlined below.

Cancer Database

In our study we used data from The National Cancer Registry of Norway, a population-based registry that since 1953 collects data on cancer incidence and survival. Information is obtained from three sources: diagnosing physician, pathology laboratories and Statistics Central Bureau and this assures a high degree of reliability. The Registry records information on patients characteristics (date of birth, sex, residence), date of diagnosis, primary tumor site, stage of diagnosis and follow up for vital status.

After 1960, each Norwegian inhabitant received a unique identification number. This allowed us to link the Cancer Database to The Population Registry whenever we were interested in obtaining further socio-demographic information.

In our work we included all patients diagnosed with prostate-, breast -, colon -, lung-, ovarian- and bladder cancer, as well as with Hodgkin lymphoma. Description of the period of inclusion, number of cases and number of deaths from cancer is presented in Table 1.

Using the date of diagnosis, the season of diagnosis was defined as follows: winter (December 1-May 31) and summer (June 1-November 30).

Solar Exposure in Norway

The main factors influencing the ultraviolet (UV) irradiances at ground level are solar zenith angle (variable with season, latitude and time of day), cloud and snow cover and the thickness of the ozone layer.[26]

In this study, the global solar UV irradiance was calculated using a radiative transfer model.[27,28] Total ozone amounts used in this model were measured by TOMS satellite instruments. The daily cloud cover varies in Norway, with coastal regions being cloudier than the inland regions. The

Table 1. Descriptive of population included

Cancer Type	Period of Inclusion	No Cases	Mean Age ± Std	No Deaths
Prostate cancer	1964-1992	46205	74 ± 8	10090
Breast cancer	1964-1992	49821	62 ± 14	6615
Colon cancer	1964-1992	38541	70 ± 11	14221
Lung cancer	1960-2001	45681	66 ± 10	29856
Ovarian cancer	1964-2000	42096	59 ± 14	7112
Bladder cancer	1964-2000	23890	68 ± 11	5864
Hogkin lymphoma	1964-2000	3139	44 ± 19	769

magnitude of this was estimated for each of the Norwegians counties, from measured reflectivities from an ozone-insensitive channel of the same satellite instruments. The effect of snow cover was estimated by comparing the calculations with UV measurements from the Norwegian UV monitoring network. The calculated annual UV exposures are based on available satellite measurements in the period 1980-2000.

Seasonal UV Doses

The results are partly presented as erythemally effective UV doses (CIE) measured in units of J/m.[2] In some of the analyses we used the efficiency spectrum for vitamin D production giving the relative effectiveness of solar radiation at different wavelengths in converting 7-DHC to previtamin D. Briefly, an efficiency spectrum is calculated by multiplying the intensity of the solar radiation (wavelength by wavelength) with the action spectrum for the vitamin D production for the corresponding wavelength. The vitamin D action spectrum was measured by MacLaughlin et al in ex vivo skin specimens.[29]

Regional UV Doses

The Norwegian mainland covers 13˚ of latitude, from 58˚ N to more than 71˚ N (Fig. 1). In the present study we have investigated the mean annual UV irradiances in each of the Norwegian counties and attempted to correlate them with cancer survival. Additionally, to control for the real UV exposure obtained by different populations, we have plotted the incidence rates (IR) of squamous cell carcinoma of the skin (SCC) vs the calculated UV dose in each of the Norwegian counties, since it is widely accepted that UV from the sun is the main risk factor for SCC.[1] The incidence rates were age-adjusted and the plotted values represent an average of the period 1960-2004. Log—log plots are usually used for incidence—annual UV—dose relationships in the case of skin cancer.[30] The reason for this is that the relationship is not linear, but closer to quadratic. In fact, in most cases it follows the equation log (incidence) = A_b log (Dose), where A_b is the so-called biological amplification factor.[30] The largest city, Oslo, was excluded from all analyses, to reduce errors that may arise from different sun-exposure habits and high immigration rate. Oslo has the highest proportion of immigrants with 18% of its population being of nonwestern origin.[31]

Statistical Analyses

The data were analysed in a multivariate Cox regression model using SPSS Version 10 (SPSS Inc, USA). The dependent variable was death from cancer within 36 months after diagnosis (or 18 months in the case of lung cancer). As independent variables we included in most analyses: age, sex (were relevant), birth cohort, stage of disease and a UV index based on season of diagnosis and residential region. Additionally, for prostate-, breast- and colon cancer, attention has been paid to the level of education, profession and parity as described elsewhere.[32] Since these adjustments did not significantly change the estimates, we did not include them in the analyses of the other cancer forms.

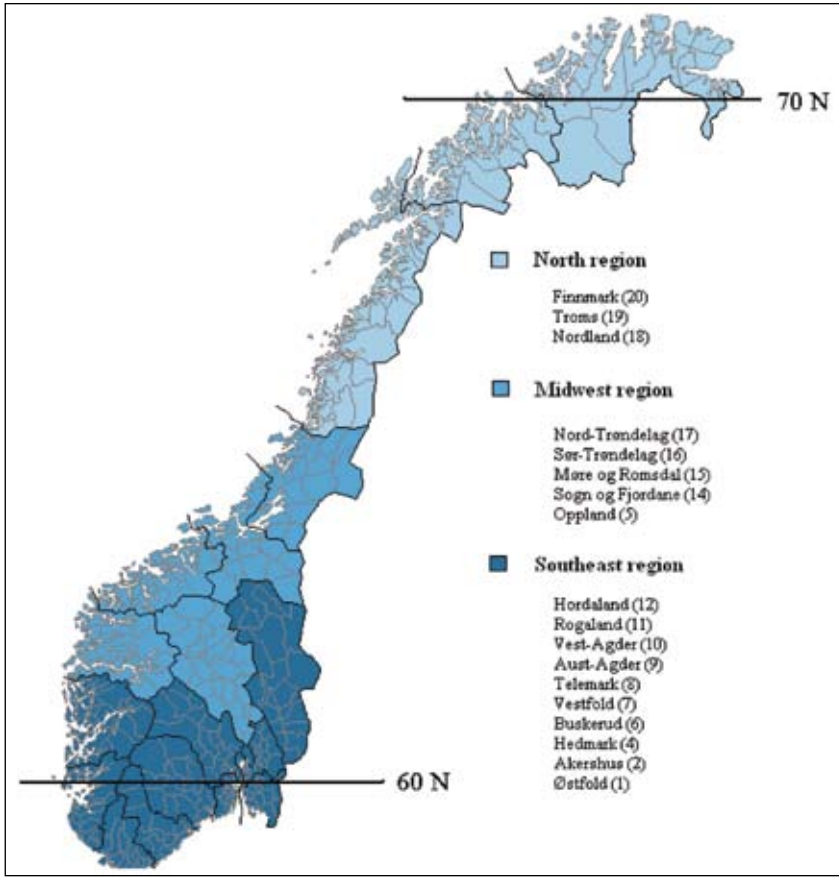

Figure 1. A map of Norway showing its latitude and division into counties. The three different tones of color denote the three regions shown in Figure 5.

In this paper we present the effect of season of diagnosis and/or residential region on the relative risk of death (RR death) from cancer. Concerning the seasonal comparisons, winter (the season with lowest UV doses and the lowest vitamin D levels) was chosen as the reference group. When we included the combined UV variable that took into account both season of diagnosis and residential region, diagnosis in the winter in the midwest region was chosen as the reference category.

Dependency of Survival on Season of Diagnosis

Figure 2 presents the seasonal variation of calculated production of vitamin D in human skin at two geographical locations: north Norway and south Norway.

Seasonal variation of UV doses may be relevant for cancer survival and we hypothesized that the effect may be mediated through vitamin D synthesis in the skin. Figure 3 summarizes the relative risk of death by season of diagnosis for all cancer types included. Significantly reduced RR_s (relative risk) of deaths were found in the summer for cancers of prostate (0,76), breast (0,75) colon (0,79) and Hodgkins lymphoma (0,84). The mortality from ovary-, bladder- and lung cancer showed no seasonal variation.

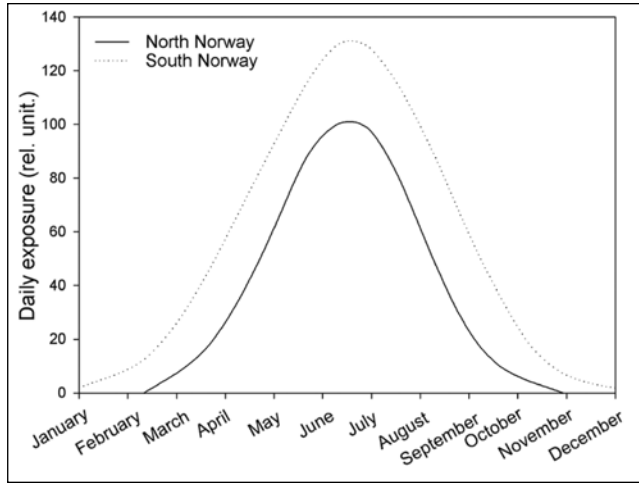

Figure 2. Calculated production of vitamin D (in relative units) in human skin at two different geographical locations in Norway.

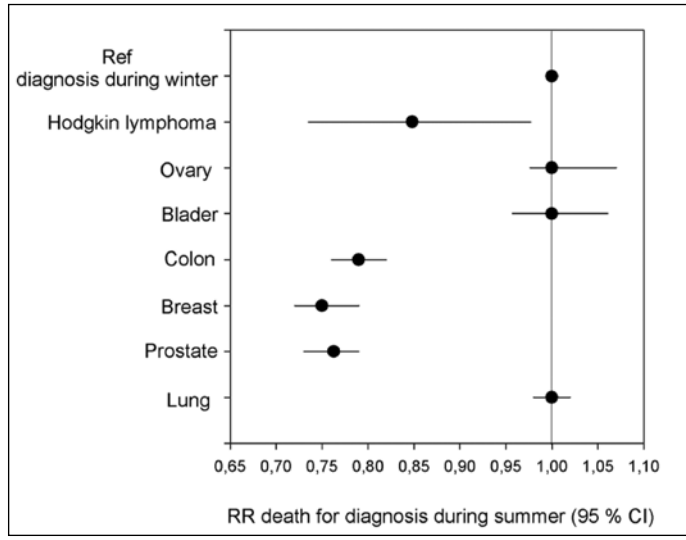

Figure 3. RR death within 36 months after cancer diagnosis for cases diagnosed during summer. Diagnosis during winter is the reference category and is set to 1.

Dependency of Survival on Residential Region

The Norwegian mainland covers 13˚ of latitude, from 58˚ N to more than 71˚ N (Fig. 1) and the UV level decreases with increasing latitude (Fig. 4). The UV exposure rate is roughly 30% higher at 56˚ N than at 70˚ N in the middle of the summer (Fig. 2).

The UV exposure at ground level does not necessarily reflect the exposure achieved by the population. To check the significance of this, we grouped the Norwegian counties according to the incidence rate of SCC, which is known to be strongly correlated with the accumulated UV exposure. When we have plotted the age adjusted incidence rates of SCC in each of the counties against the calculated UV dose, three regions with different UV exposure patterns can be identi-

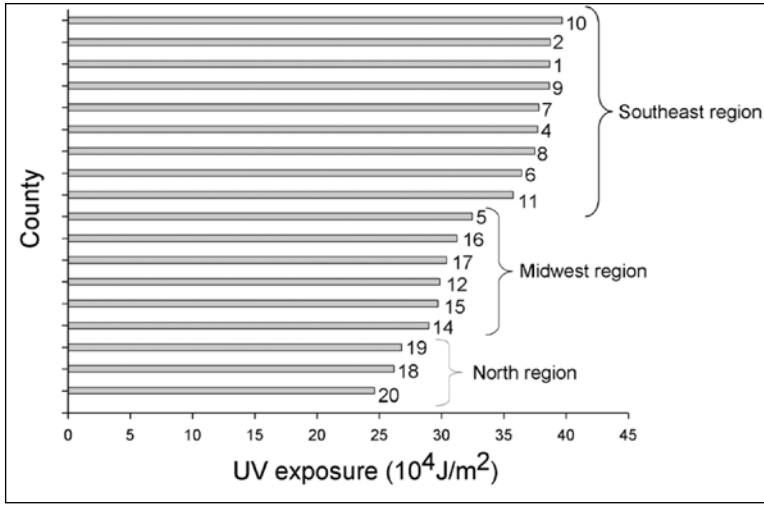

Figure 4. The UV exposure from the sun in Norway, adjusted according to the CIE reference spectrum of erythema. The number in the brackets gives the county's number.

fied: the northern region (counties 18-20); the midwest region (counties 5, 12, 14-17) and the southeast region (counties 1, 2, 4, 6-11) (Fig. 5). A complicating factor in the regional analyses,is the difference in the level of vitamin D intake. People living in the northern region, are exposed to low UV doses but consume high quantities of vitamin D through fat fish.[33] According to Brustad et al[20] the level of fish intake in the north does not show any seasonal variation. Inhabitants of the midwest region receive moderately high doses of both UV and vitamin D through food while those living in the southeast are exposed to high UV doses and have a low vitamin D intake (Table 2).

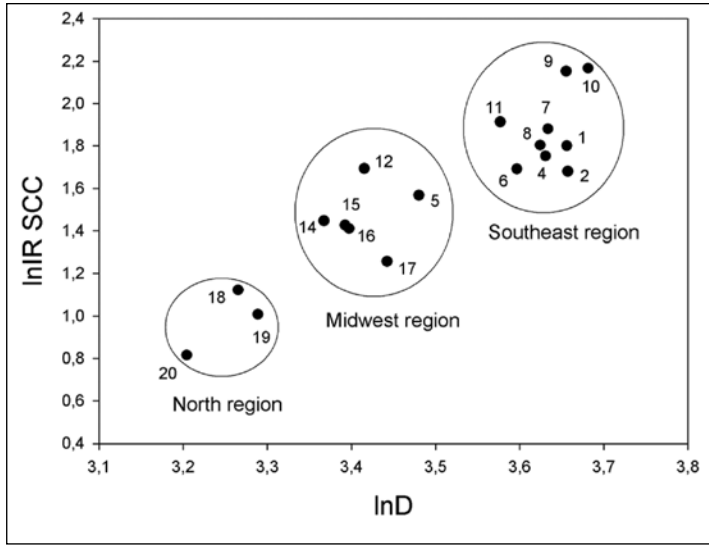

Figure 5. Annual ambient UV exposure (D) vs age adjusted rate of squamous cell carcinoma (R) in Norway (1960-2004). The relationship is described by the relationship lnR = A*lnD, where A is the amplification factor.[30]

Table 2. Relative values for the annual synthesis of vitamin D and the daily intake of vitamin D and fish in the three regions

	North Region	Midwest Region	Southeast Region
Annual vitamin D formation in skin (rel. unit.)[25]	1	1,2	1,5
Vitamin D intake (µg/day)[33]	5,4	5	4,7
Fish intake (g/day)[33]	90	72	59

Table 3. Relative risk of death at 36 months after diagnosis for summer and winter diagnosis in two different regions marked in figure 3. The death rate for winter diagnosis in the midwest region is set to unity. Overall data for all ages and both sexes are presented. Values in parentheses indicate 95% confidence intervals

	Midwest, Winter (Ref)	Midwest, Summer	Southeast, Winter	Southeast, Summer
Prostate cancer	1	0,8 (0,7-0,84)*	1 (0,99-1,1)	0,8 (0,75-0,85)*
Breast cancer	1	0,76 (0,7-0,8)*	0,97 (0,9-1,05)	0,75 (0,7-0,8)*
Colon cancer	1	0,82 (0,7-0,86)*	1 (0,9-1,07)	0,79 (0,7-0,84)*
Lung cancer**	1	1 (0,96-1)	0,93 (0,89-0,96)*	0,93 (0,89-0,96)*
Ovarian cancer	1	1 (0,8-1,3)	1 (0,8-1,3)	1 (0,6-1)
Bladder cancer	1	1 (0,9-1,1)	0,9 (0,8-1)	0,9 (0,9-1)
Hodgkin lymphoma	1	1 (0,9-1,1)	1 (0,9-1)	0,8 (0,9-1,1)

*indicates statistical significance, $p < 0,05$
**follow-up was restricted at 18 months

In the multivariate analyses of prognosis we have not included data from the northern region because of the high intake of vitamin D and the relatively low population number. Furthermore, we have created a combined variable that accounts for both season of diagnosis and residential region. We consider four categories: winter diagnosis in the midwest region (reference); summer diagnosis in the midwest region; winter diagnosis in the southeast region and summer diagnosis in the southeast region.

Table 3 shows the results of the multivariate regression analyses. The relative risk of death seems to be slightly lower in the southeast region (i.e., high UV doses) for breast-, colon- and lung cancers, while no regional effect is observed for the other cancer types.

Discussion

Our results can be summarized as follows: For prostate-, breast-, colon cancer and Hodgkin lymphoma, patients diagnosed during the summer have a 15-25% reduced risk of death during the first 36 months after diagnosis, compared with those diagnosed during the winter. In addition, residing in southeast Norway seems to add an extra beneficial effect to the improved summer prognosis for breast- and colon cancer and makes apparent a slight protective effect for lung cancer. No seasonal or latitudinal gradient was observed for bladder and ovary cancer.

It is well established that season is an important predictor of the vitamin D level. The seasonal calcidiol variation in humans has been investigated in a number of Norwegian studies and the results show a winter to summer increase of 15-50%.[20-24] which is in accordance with our calculated vitamin D production (Fig. 2).

The fact that the incidence rates of SCC decrease monotonously with increasing latitude (Fig. 5) indicates that the UV exposures achieved by the population can be approximated by calculated or measured ambient UV fluences, as earlier done.[34,35] Unfortunately, no comparison of measured calcidiol levels in north and south Norway has been performed. However, one can make a rough analysis, based on the knowledge of the yield of calcidiol from skin synthesis and that from intake. Following similar calculations as described in[25] we found that a 15% higher vitamin D intake in the fish region (Table 2) is balanced by the 50% larger annual UV fluence in the south (Table 2). Furthermore, the mid-summer photosynthesis of vitamin D is only 30% larger in the south than in the north according to our calculations (Fig. 2) and the real differences in calcidiol levels are likely to be smaller, since large UV fluences degrade vitamin D in skin.[15] Moreover, whole body exposure to one MED (minimal erythema dose) gives a high increase in the vitamin D concentration but only a moderate increase in the serum calcidiol level.[15] Comparisons of our calculation with measured calcidiol levels in Scandinavia confirm that calcidiol concentrations in the south of Scandinavia are not significantly higher than those in the north.[20,24,36,37]

The cancer sites that have been most extensively examined in relation to vitamin D status are colorectal, breast and prostate cancers.[38] For other internal cancers, evidence is limited and comes mostly from ecologic investigations.[9,11,12]

Our study indicates that cancer survival may be affected by the level of UV exposure close to the time of cancer diagnosis in five out of seven cancers types investigated (Table 3). We have suggested that this may be explained in terms of vitamin D-photosynthesis. According to our hypothesis, patients with high levels of calcidiol at the time of diagnosis (summer diagnosis) have a greater chance to survive compared with patients with low levels of calcidiol (winter diagnosis). High calcidiol concentrations in the serum would provide the cancer cells with the precursor for local synthesis of calcitriol, or, alternatively, calcidiol itself may be bind directly to the VDR (vitamin D receptor) and act anticarcinogenic.

The anticarcinogenic effects of vitamin D are indicated by a number of experimental investigations with cell lines and animal models. In the case of breast cancer an important amount of research, thoroughly reviewed by Colston et al[39] shows that calcitriol is able to regulate cell cycle progression, induce apoptosis, modulate cell signalling through growth factors and reduce invasiveness and angiogenic activity in breast cancer models.[35] A number of preclinical studies have proven that calcitriol derivatives enhance the effect of established chemotherapeutics for breast cancer treatment.[40-44] Cancer of the prostate also responds to vitamin D therapies presumably by similar molecular mechanisms.[45-48] The same is true for colon cancer.[49,50] In vitro studies, performed with lung-cancer cell lines, have shown that vitamin D derivatives inhibit cell-growth and proliferation[51] Animal studies have demonstrated the capability of these compounds to suppress invasion, metastasis and angiogenesis in vivo.[52-54]

Controversy still exists as to whether only calcitriol, or both calcidiol and calcitriol, have biological functions in humans. Each of these derivatives binds specifically to the VDR receptor (member of the nuclear receptor superfamily), the affinity of calcitriol beeing 600-700 higher than that of calcidiol.[55] On the other hand calcidiol is present in an approximately 1000 times larger concentration in serum and is therefore more bioavailable than calcitriol. Beside the well described role of calcitriol in maintaining calcium homeostasis through processes in the intestine, bones and kidneys, calcitriol and/or calcidiol may act in other normal or pathologic tissues.[56] The effect may either be from the systemic pool or from local ones in tissue, since most tissues are able to produce their own calcitriol.[56] The concentrations at which calcitriol is active in vivo appear to be higher than what has been assumed physiological concentrations, i.e., above 100 pmol/l. However, this effect may at least partly be mediated by locally produced calcitriol or directly by calcidiol taken up from the blood.

Our epidemiological data from Norway point to the importance of calcidiol.[57]

Conclusions

The vitamin D level in serum of Norwegians is 15-50% higher in summer than in winter. Recently, our group hypothesised for the first time that this may be of significance for the prognosis of major cancer forms, like prostate cancer, breast cancer, colon cancer, lung cancer and lymphomas.[25,32,34,58] The relative risk of death three years after diagnosis and start of therapy is estimated to be 15-25% higher for summer diagnosis than for winter diagnosis. A recent study involving over a million cancer patients in the United Kingdom gave similar results.[57] The action mechanism has almost equivocally been attributed to vitamin D production by UV and this view is supported by cell and animal experiments as reviewed in the present chapter.

The health effects of ultraviolet radiation from the sun are now being debated worldwide.[59] Focus of this debate is an understanding that UV has both negative health effects, namely induction of skin cancer[1] and beneficial health effects through induction of vitamin D.[60] Solar UV is a well-established skin carcinogen being responsible for more than half of all cancers and causing about 250 deaths per year in Norway.[61] Large sun-safety campaigns have been launched, which seems to have had a significant impact since the increasing trend of skin cancer incidence rates observed from 1960 or earlier is reversed for young persons after about 1990 (for more details, see chapter 8 in this book). However, in the same time period, i.e., after 1990, vitamin D deficiency has developed in many populations. Since solar UV is a main source of vitamin D, this deficiency may, at least partly, be due to reduced sun exposure. Another important source of vitamin D is supplemental/dietary intake. From evolutionary, epidemiological and experimental perspectives, the optimal nutritional intake vitamin D may be defined as the amount equivalent to what an adult can acquire through exposing the whole skin surface to summer sunshine.[62] Based on this, a physiologic intake of vitamin D for an adult might range up to 250 μg/day (i.e., 50 times the daily recommended dose in Norway).[63]

Implementation of public health policies to optimise the vitamin D nutritional status would be relatively inexpensive but would meet various limiting factors such as: risk of toxicity in susceptible populations (infants, individuals suffering from hyperparathyroidism, sarcoidosis, tuberculosis, lymphomas, William's syndrome, etc), inability to reach vulnerable populations with different dietary preferences or aversions against specific foods such as milk, higher prevalence of lactose intolerance and low milk consumption in African-Americans (population at high risk of vitamin D deficiency), need for thorough labelling of all food items containing vitamin D. Any public health strategy requires both safety- and efficacy-testing.[64] Controlled use of UV exposure might be evaluated as a supplemental and safe source of vitamin D. Due to the seriousness of both vitamin D deficiency and skin cancer induction, more research is needed on the topic of UV and health.

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