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Vitamin D_3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway)

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Abstract

Objective: To investigate whether prognosis of breast-, colon- and prostate cancer may be related to vitamin D_3, induced from solar ultra-violet (UV) radiation, through studies on geographical and seasonal variations in UV radiation.
Methods: This study includes 115,096 cases of breast-, colon- or prostate cancer, diagnosed between 1964 and 1992. Among these, 45,667 deaths due to the cancer were registered. On the basis of a north–south gradient in solar UV radiation and geographical climatic differences, Norway was divided into eight residential regions. According to seasonal variations in UV radiation, four periods of diagnosis during the year were used. Case fatality according to residential region and to season of diagnosis was estimated using Cox regression. The effects of occupational sun exposure, childbearing pattern and educational level were also evaluated.
Results: No geographic variation in case fatality was observed for the three cancer types studied. A significant variation in prognosis by season of diagnosis was observed. Diagnoses during summer and fall, the seasons with the highest level of vitamin D_3, revealed the lowest risk of cancer death.
Conclusion: The results suggest that a high level of vitamin D_3 at the time of diagnosis, and thus, during cancer treatment, may improve prognosis of the three cancer types studied.

Introduction

The relationship between vitamin D and cancer was first noted by Suda and colleagues in 1981 in studies demonstrating that the hormone form of vitamin D_3, 1,25 dihydroxyvitamin D_3 (1,25$(OH)_2D_3$), inhibits the proliferation of cancer cells and promotes their differentiation [1]. The mechanisms by which vitamin D_3 may have an anticarcinogenic effect have been suggested both by *in vivo* and *in vitro* studies [2–10]. Recently, vitamin D is suggested to interact with therapeutic modalities and improve the outcome of the treatment [11]. Several epidemiological studies indicate a possible protective role of vitamin D_3 in the progression of breast [12–17], colon [18, 19] and prostate cancer [20–22]. With reference to all these studies, a high level of vitamin D_3 might reduce the risk of cancer death.

Ultraviolet (UV) radiation promotes endogenous synthesis of vitamin D_3 [23] and a number of studies demonstrate that UV radiation plays an important role for the vitamin D_3 status in humans, even at northern latitudes [24–30]. Norway, with its homogenous population and its spread in latitude from 58°N to 71°N is well suited for epidemiological studies on cancer forms related to UV radiation, as earlier demonstrated for skin cancer [31]. Furthermore, Norway has pronounced seasonal variations in UV radiation. During the summer season, with long days, the UV radiation is substantial

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while during the winter season practically no vitamin D is generated by UV radiation. The seasonal variation in vitamin D_3 status is 20–50% of its base level, with the highest levels following the sunny summer months.

This study aims to examine whether geographical differences in solar UV radiation in Norway are related to the prognosis of breast-, colon- and prostate cancer, when including information on some potential confounding factors at the individual level. Further, it aims to investigate whether the season of diagnosis, according to seasonal variation in UV radiation and in sun-induced vitamin D_3, are related to the prognosis of the three cancer types studied.

Materials and methods

In 1960, Statistics Norway conducted a national population census. Based on this census, all Norwegian inhabitants, alive in 1960 and born ever since, have been assigned an 11-digit personal identification (ID) number. The ID-number was put into use in 1964 and gave the opportunity to register vital statistics regarding the Norwegian population. From this census, the following individual information is included in the present study: year of birth, place of residence, vital status, reproductive data and data regarding education and occupation. The unique ID-number of every citizen makes it possible to obtain cancer information by linkage to the Cancer Registry of Norway, where all cases diagnosed with a cancer have been registered since 1953. A total of 55,590 men and 59,866 women were included in this study. They were all born in Norway between 1900 and 1966, and were diagnosed with cancer of the breast ($n = 41{,}988$), prostate ($n = 39{,}583$) or colon ($n = 33{,}525$) between the age of 25 and 94 years, during the observation period from 1964 to 1992. Among these, 45,667 deaths were registered with their cancer disease as underlying cause of death. The closing date of follow-up was the date of death, migration from Norway or December 31st 1992.

Norway was divided into eight geographical regions, according to latitude and climatic differences (coast/inland, Figure 1), that influences daily UV exposure. Residential region was classified based on the census data. The mean of annual erythemogenic UV radiation was calculated for region II–VIII relative to region I (Table 1). The methods for clear-sky calculations have been described previously [31]. In the present study, by using the mean of monthly integrated global solar radiation (290–2800 nm) the effect of cloud cover is included. This method has previously been thoroughly described [32].

Additionally, the incidence rates (IR) of squamous cell carcinoma (SCC) of skin, adjusted for age (five-year age groups) and period of diagnosis (10-year periods) are used to illustrate the predictive validity of the UV doses calculated in the region II–VIII relative to region I (Table 1).

The Central Population Registry has registered all migration to or from Norway (1% of the study population), and between municipalities within the country, since 1964. During the study period, the part of the population that has one or more relocations between the residential regions used was less than 4%. Statistical analyses were performed including migration information.

Based on occupational data, registered according to the International standard classification of occupations 1958 [33], three levels of occupational sun exposure were applied: mainly indoor conditions were defined as low, mixed conditions were set to medium, while high level included mainly outdoor working conditions. Unfortunately, a large proportion of the cases lacks the occupational information and thus, they constitute a category of unknown. Educational levels were categorised based on number of years of education: Low (1–9 years), Medium (10–12 years) and High (≥13 years). The Unknown category constitutes cases without educational information. The pattern of childbearing was described by the following categories: nulliparous women, women with the first child born before 25 years, between 25 and 29 years, and 30 years or older. Childbearing history was complete only for cases born after 1934. Cases born before 1935 constitute the category of unknown, which explains its large percentage (Table 2).

The mean monthly values of erythemogenic UV radiation for Tromsø (largest city in region I), together with monthly levels of 25 hydroxy vitamin D_3 ($25(OH)D_3$) [28] are shown in Figure 2. According to this, the dates of diagnoses, obtained from the Cancer Registry of Norway, were categorised into four seasons; winter season from December through February, spring season from March through May, summer season from June through August, and fall season from September through November.

The mean time of follow-up from date of diagnosis was 7.2, 3.9 and 4 years for breast-, colon- and prostate cancer respectively. There was no variation between the regions except for region VIII, which has a slightly longer follow-up for all the three cancer forms (data not shown). The cases diagnosed during fall have more than ten months longer mean follow-up than cases diagnosed during winter (data not shown).

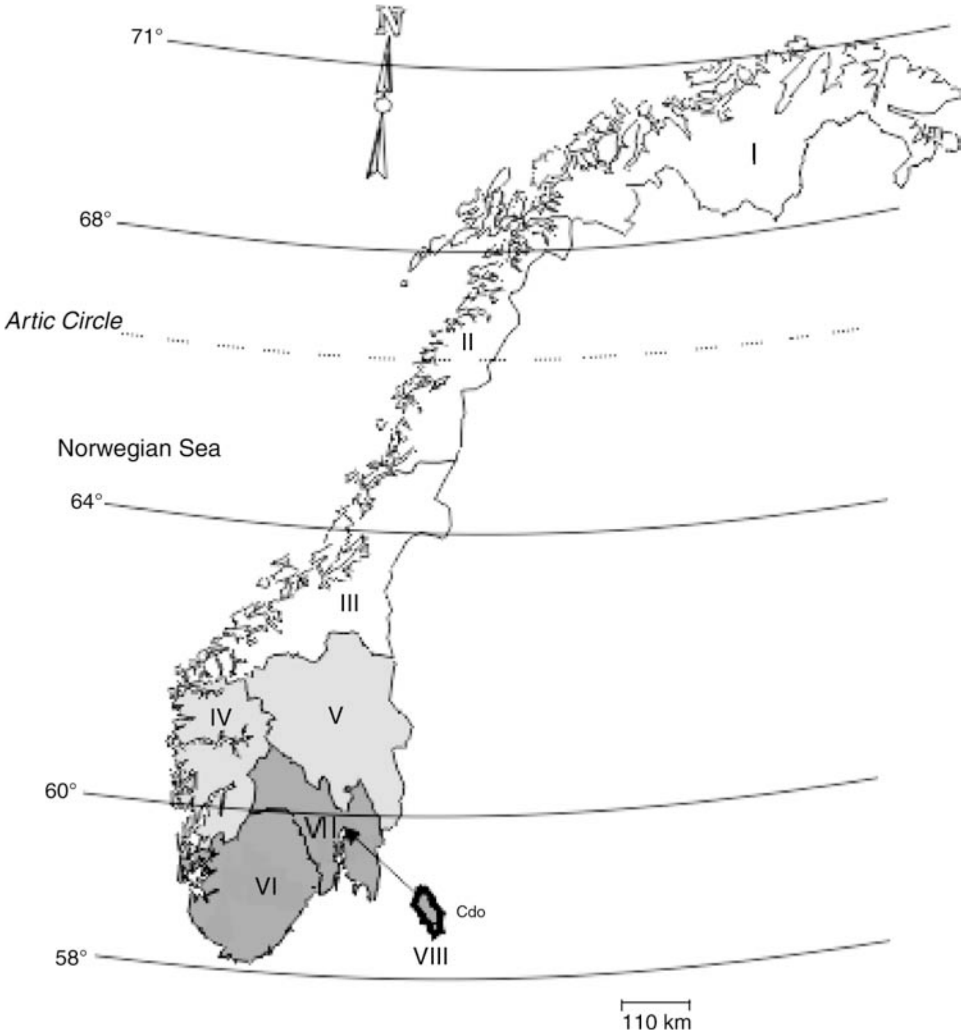

Fig. 1. Map of Norway illustrating the residential regions I–VIII, latitude and level of sun radiation within the regions (low UV exposure □; medium UV exposure (□); high UV exposure (□)).

Statistical methods

To investigate the relationship between residential region, as a surrogate measure of geographical variation of solar UV-radiation, and case fatality from breast-, colon- or prostate cancer, respectively, a multivariate model was applied using Cox regression. Estimations and tests were carried out using the SPSS statistical program package [34]. The risk estimates were calculated as relative risks (RR), with 95% confidence intervals (95% CI). The effect of occupational sun exposure was estimated and the potentially confounding variables available in this study were evaluated by including childbearing pattern and educational level in the analyses. All the analyses of case fatality were adjusted for stage of disease at time of diagnosis.

The fatality among cases with the specified cancer types was estimated according to the season of diagnosis, as a surrogate measure of seasonal variation in UV-induced vitamin D_3, also using Cox regression model (SPSS). An analysis restricted to the first three years of follow-up was performed, to look for short-term effects in a period where the censoring from other causes of death is limited. Due to the hypothesis that high age reduces vitamin D synthesis [35, 36], additional analyses were performed including cases diagnosed before age 68 only.

Results

Table 2 presents the number of cases and deaths, separately. The distribution of occupational sun expo-

Table 1. Relative exposure of erythemogenic UV radiation, and incidence rates (IR) of squamous cell carcinoma of skin (SCC) in men and women, by category of residential sun exposure

Regions	Erythemogenic UV radiation[a]	Squamous cell carsinoma of skin[b]	
		IR[c], men	IR[c], women
I	1.00	9.2	7.7
II	1.04	9.3	7.8
III	1.20	13.6	9.6
IV	1.37	15.9	10.7
V	1.49	12.1	9.3
VI	1.46	21.5	14.3
VII	1.55	15.9	11.7
VIII	1.54	18.7	12.5

[a] Means of annual erythemogenic UV radiation, calculated for region II–VIII relative to region I. The calculations take into account ozone and cloud cover variations [22, 23].

[b] SCC at all anatomical sites, excluding head.

[c] IR, adjusted for age and period of diagnosis.

sure and the available potential confounding variables are presented by cancer site. The major part of the study population belongs to the category of low education, independent of cancer type. The part with a known occupational history has mainly held indoor occupations with only minor work-related sun exposure. There is no seasonal variation in the number of diagnosed cases, regardless of cancer type.

Table 1 gives the regional incidence rates of squamous cell carcinoma (SCC) of the skin, together with the regional erythemogenic solar radiation. Both the UV fluence and the incidence of SCC show a north–south gradient. The rates of daily maximum fluence of UV in the period 1995–2002 for region I, III and VIII are shown in Figure 3 [37]. The variation of UV-radiation during the year is similar in the three regions. However, the difference between summer and winter is larger in the south than in the north. Previously, the data for seasonal variation in $25(OH)D_3$, which is the major vitamin D metabolite and reflects the vitamin level, have been measured for region I [28]. These data are presented in Figure 2 together with the monthly mean of measured integrated daily values of erythemogenic UV radiation, averaged over the years from 1996 to 1999. The peak level of $25(OH)D_3$ is shown to follow the peak of UV, with a delay of about 1–3 months.

Table 3 presents the relative risks (RR) of death from breast-, colon- or prostate cancer by residential and occupational category of UV radiation, as well as by childbearing pattern and level of education. No associations between residential UV radiation and case fatality were found for any of the cancer types studied. An analysis including cases diagnosed before the age of 68 only, reveals a similar result (data not shown). Given the large proportion of missing data for the occupation and childbearing variables, a complete-subject analysis was performed, however, with only slight changes of the estimates (data not shown). The test for trend across the regions was not significant (Table 3). Neither was

Table 2. The number of cases and deaths, and percentage distribution of available characteristics by cancer type and sex

Characteristics	Levels	Breast, women		Colon, women		Colon, men		Prostate, men	
		Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Number		41,988	13,826	17,878	8277	15,647	7107	39,583	16,457
Occupational sun exposure (%)	Low	37.4	29.0	35.2	27.8	46.0	41.8	43.7	39.6
	Medium	1.7	1.3	1.0	0.9	14.3	13.0	12.1	10.4
	High	5.7	5.5	0.2	0.2	9.1	8.2	9.2	8.3
	Unknown	55.1	64.2	63.6	71.1	30.7	37.0	35.0	41.8
Childbearing pattern (%)	Nulliparous	2.9	2.2	1.2	0.8	1.9	1.5	0.4	0.2
	Age <25	12.1	8.9	7.1	5.4	3.6	2.6	1.3	1.0
	Age 25–29	13.6	11.4	9.9	7.9	10.0	8.1	6.3	4.3
	Age ≥30	20.4	19.8	18.6	16.1	30.4	28.0	31.1	27.2
	Unknown	51.1	57.8	63.2	69.9	54.2	59.8	60.9	67.3
Educational level (%)	Low	67.9	67.5	72.6	73.0	60.2	62.2	65.4	67.2
	Medium	21.4	17.4	16.2	14.3	23.6	21.1	21.2	19.8
	High	0.9	0.7	0.6	0.6	4.7	4.3	4.4	3.6
	Unknown	9.7	14.3	10.6	12.0	11.5	12.5	9.1	9.5
Season of diagnosis (%)	Winter	25.4	25.8	24.0	24.5	24.7	25.1	25.8	25.8
	Spring	25.5	25.5	26.0	26.6	25.2	25.0	24.8	25.6
	Summer	23.4	23.3	25.1	24.8	25.1	25.5	23.3	24.1
	Fall	25.7	25.4	24.9	24.1	25.0	24.3	26.0	24.4

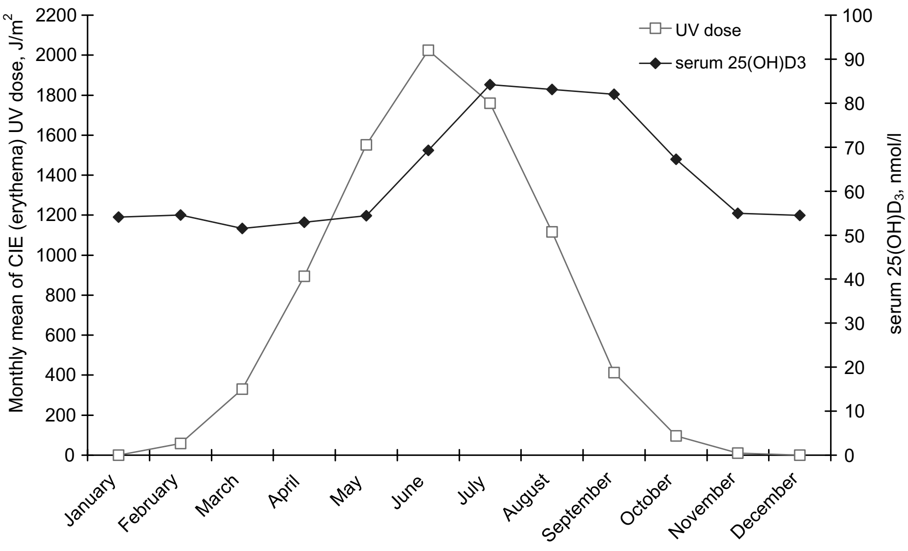

Fig. 2. The monthly variation of vitamin D_3 ($25(OH)D_3$) in region I [28], together with monthly values of erythemogenic UV radiation, averaged over the years 1996–1999.

occupational sun exposure found to be of importance for the prognosis. However, the category 'unknown' seems to have an elevated risk of cancer death.

A medium level of education appears to be beneficial for the prognosis compared to the low level, which applies for all the included cancer sites (Table 3). For males with prostate or colon cancer, a high educational level seems to be beneficial as well. The major part of the category 'unknown' should probably belong to the low level, which would give an even stronger effect of this variable. Furthermore, Table 3 illustrates that men with children tend to have a slightly better prognosis compared to men without children. A similar significant observation is demonstrated for women with breast cancer.

Table 4 presents estimated case fatality from the specified cancers by season of diagnosis. Cases diagnosed during summer and fall have a significant better prognosis relative to cases diagnosed during winter. Adjustments for age at diagnosis, birth cohort, period of diagnosis, stage at diagnosis, childbearing pattern, level of education, and residential and occupational sun exposure did not affect this result. The analyses restricted to 3 years of follow-up (Table 4) illustrate an even larger variation in case fatality according to season of diagnosis.

Discussion

In the present study, no north–south gradient in cancer prognosis is found. This finding contrasts with a number of other investigations showing a strong negative association between cancer incidence and mortality and geographical latitude [12–14, 16, 17]. There is an inverse relationship between calculated fluences of UV radiation and latitude in Norway (Table 1). Nevertheless, when using the data shown in Figure 3 to make a rough estimate of what would be an expected vitamin D_3 gradient between the north and the south of Norway, this would on the average result in a 8% difference. A major source of vitamin D_3 may be sun-induced synthesis in human skin, however, it is also supplied by intestinal absorption from diet [26, 38]. Thus, the real difference may be smaller than 8%, due to dietary traditions in northern Norway, which consists of more vitamin D rich food as fatty fish and cod liver [39]. This situation may explain why no geographical difference in cancer prognosis is found (Table 3).

The main finding in the present work is that season of diagnosis may influence the prognosis of all the three cancer types studied (Table 4). Cases diagnosed during fall have more than 15% lower case fatality compared to cases diagnosed during winter. The variation in case fatality according to season of diagnosis seems to coincide with the previously shown seasonal variation of $25(OH)D_3$ in serum [23–28]. The results support the suggestion that vitamin D_3 suppresses cancer progression through several growth inhibiting mechanisms [2–4, 7, 10, 15, 40]. It has been suggested that 1,25 $(OH)_2D_3$ stimulate apoptosis, downregulate cell growth factors and upregulate cell cycle regulatory factors. Further, $1,25(OH)D_3$ may inhibit angiogenesis [8]. The beneficial effect of diagnosis during fall was even stronger when

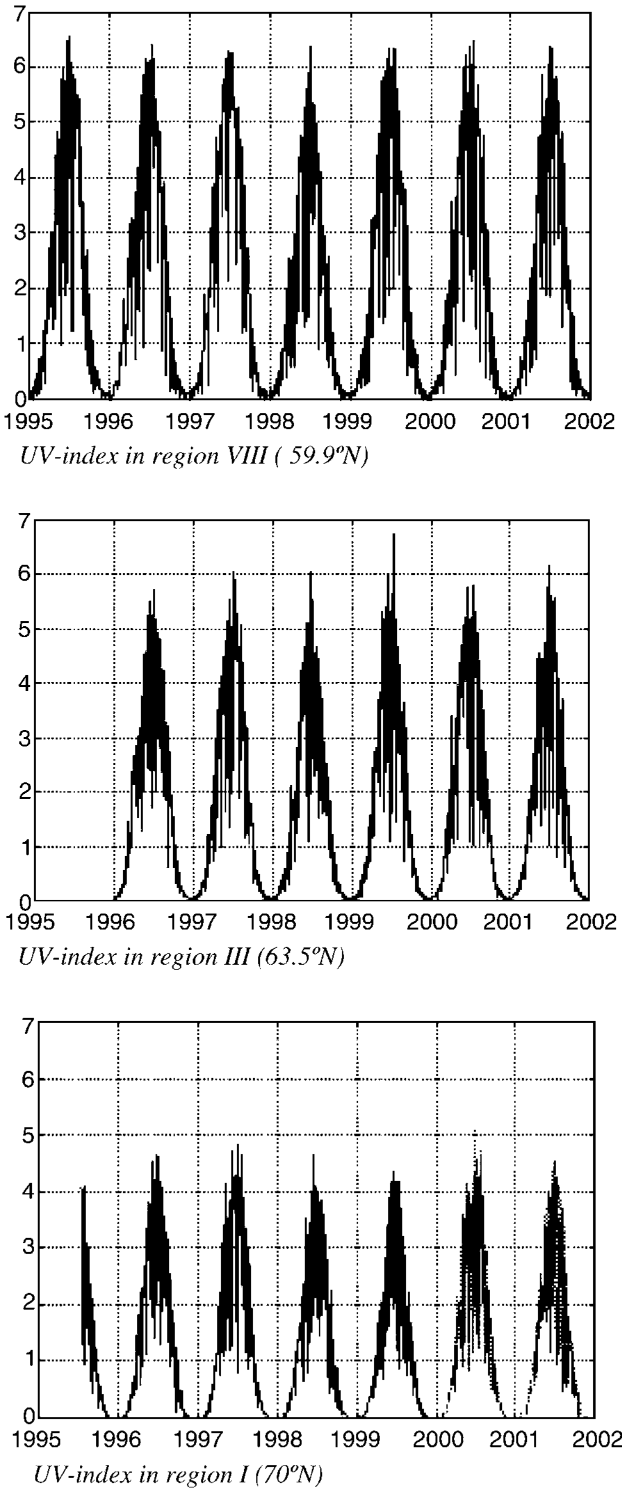

Fig. 3. Annual pattern of daily maximum UV exposure in region I, III and VIII in the period 1995–2002.

case fatality within three years of diagnosis was considered (Table 4). This may indicate that maintaining a high level of vitamin D during the period of cancer treatment can amplify treatment effect. Recently, Sundaram and colleagues have demonstrated that supplementation of vitamin D during radial cancer therapy promotes apoptotic cell death [11].

In Caucasians, the vitamin D_3 status, reflected by the serum level of $25(OH)D_3$, is closely correlated with solar UV radiation [35, 38, 41]. Even in Tromsø, at 70°N, the concentration of $25(OH)D_3$ in serum is about 50% higher during late summer and fall compared to the winter months (Figure 2), and follows the seasonal variation in erythemogenic UV radiation with a delay. In general, the maximum serum concentration of vitamin D_3 is observed to peak one to three months after midsummer, *i.e.*, between July and September.

The serum $1,25(OH)_2D_3$ concentration is not tied to the UV-level, but is tightly regulated due to its role in the calcium homeostasis, hormone regulation and bone mineralization. Although the main production of $1,25(OH)_2$ vitamin D occurs in the kidneys, it has been demonstrated to occur in prostate and colon tissue as well [9, 42]. The effect of vitamin D depends on expression of vitamin D receptors (VDR), as the complex VDR/vitamin D acts as a transcription factor [43]. The expression of VDR has been shown to increase during progression to malignancy [5, 6]. Intracellular VDRs are presented in breast-, colon- and prostate tissue, which strongly indicates a role of vitamin D in growth regulation of these tissues. Thus, cancers of breast-, colon- and prostate may be particularly susceptible to treatment with vitamin D. In spite of this vitamin's potent anticarcinogenic effect it has not been used as cancer treatment due to its hypercalcemic potency [44]. However, as serum $25(OH)D_3$ increases as a response to UV-radiation, which may lead to production of $1,25(OH)_2D_3$ in the tissues in focus, the use of UV radiation might be a supplement to cancer treatment without the risk of hypercalcemia.

Several studies have demonstrated an immunological effect of vitamin D. This effect is related to its ability to prevent, or markedly suppress, autoimmune diseases and inflammatory activity [reviewed in 45]. The action of vitamin D in treatment of immune diseases requires a high intake of calcium [45], but it is unlikely that the variation in calcium intake during a year is of an extent that correspond with the variation in $25(OH)D_3$. Thus, the observations in the present study may not be explained solely by the immunological effect of vitamin D. However, cases diagnosed during fall may benefit from a strengthened immunity [45], and thus, may be better able to handle all kinds of cancer therapies.

The present investigation has several methodological strengths. The cohort includes a large number of cancer

Table 3. Relative risk (RR) of cancer death among cases with breast-, colon- or prostate cancer by categories of residential and occupational sun exposure, childbearing pattern and educational level

Characteristics	Levels	Breast, women		Colon, women		Colon, men		Prostate, men	
		RR[a]	95% CI[b]	RR[a]	95% CI[b]	RR[a]	95% CI[b]	RR[a]	95%CI[b]
Recidential sun exposure	I[c]	1.00		1.00		1.00		1.00	
	II	1.04	(0.93, 1.16)	1.03	(0.89, 1.20)	0.97	(0.83, 1.14)	1.00	(0.90, 1.11)
	III	0.99	(0.90, 1.09)	1.01	(0.89, 1.14)	1.00	(0.86, 1.14)	1.02	(0.94, 1.12)
	IV	1.02	(0.92, 1.10)	1.02	(0.89, 1.17)	1.00	(0.86, 1.16)	0.99	(0.90, 1.08)
	V	0.98	(0.89, 1.08)	1.02	(0.90, 1.19)	1.02	(0.88, 1.18)	1.16	(1.06, 1.28)
	VI	1.04	(0.95, 1.14)	0.99	(0.87, 1.12)	0.99	(0.86, 1.14)	0.98	(0.90, 1.07)
	VII	1.00	(0.91, 1.09)	1.02	(0.90, 1.15)	1.02	(0.90, 1.17)	1.10	(1.02, 1.21)
	VIII	0.95	(0.86, 1.05)	0.98	(0.86, 1.11)	0.96	(0.83, 1.10)	0.98	(0.88, 1.07)
Test for trend (*p*-values)			$p = 0.10$		$p = 0.36$		$p = 0.33$		$p = 0.28$
Occupational sun exposure	Low[c]	1.00		1.00		1.00		1.00	
	Medium	1.01	(0.86, 1.17)	1.15	(0.91, 1.45)	1.01	(0.94, 1.08)	1.00	(0.95, 1.06)
	High	1.10	(1.00, 1.15)	0.93	(0.60, 1.49)	1.00	(0.91, 1.09)	0.99	(0.94, 1.05)
	Unknown	1.26	(1.20, 1.31)	1.18	(1.12, 1.25)	1.26	(1.18, 1.36)	1.15	(1.05, 1.26)
Childbearing Pattern	Nulliparous	1.15	(1.04, 1.31)	1.00	(0.75, 1.35)	1.12	(0.88, 1.41)	1.10	(0.67, 1.81)
	Age <25[c]	1.00		1.00		1.00		1.00	
	Age 25–29	0.97	(0.89, 1.05)	0.94	(0.83, 1.03)	1.04	(0.88, 1.24)	0.92	(0.77, 1.03)
	Age ≥ 30	0.95	(0.88, 1.04)	0.97	(0.86, 1.06)	1.01	(0.85, 1.19)	0.93	(0.74, 1.09)
	Unknown	1.02	(0.94, 1.11)	1.06	(0.93, 1.20)	1.04	(0.88, 1.23)	0.99	(0.84, 1.17)
Educational level	Low[c]	1.00		1.00		1.00		1.00	
	Medium	0.92	(0.84, 0.98)	0.94	(0.87, 0.99)	0.92	(0.85, 0.97)	0.96	(0.92, 1.00)
	High	0.92	(0.76, 1.12)	1.06	(0.80, 1.40)	0.91	(0.81, 0.99)	0.78	(0.72, 0.86)
	Unknown	2.84	(2.69, 3.00)	1.38	(1.27, 1.49)	1.41	(1.30, 1.63)	1.93	(1.74, 2.13)

[a] Estimated RR adjusted for age at diagnosis, birth cohort, period of diagnosis, stage of disease at diagnosis and each of the other variables in the table.
[b] 95% confidence interval.
[c] Denotes the reference category.

cases that were diagnosed during a follow-up of more than 40 years. The residential history of each case is known, from birth to the end of follow-up, which provides the opportunity to categorise cases according to levels of residential sun exposure. Additionally, information on several available risk factors that may differ between regions is included in the analyses. Other and unknown factors may confound the results, although adjustments of the available factors resulted in very small changes of the risk estimates.

A low educational level tends to increase case fatality, which apply for all the specified cancer types (Table 3). These results may reflect the importance of cognitive resources, the ability to solve problems and to communicate [46]. Furthermore, the economic resources and the availability of treatment may play a role [46]. Despite of the free national health care system, this also could illustrate a lead-time bias; a high diagnostic intensity resulting in a high incidence rate at an early stage of disease, which improves prognosis. However, the analyses were adjusted for stage at diagnosis, which seems not to explain the differences in fatality between the educational levels.

Unfortunately, this study lacks data on parity and occupational history for a large proportion of the cases. Among women, the category of unknown occupation probably consists in a great number of housewives, who belongs to the category of medium occupational sun exposure. Such a misclassification might influence the estimated risk by level of sun exposure at work. However, a conservative analysis has been performed, excluding all cases with missing information, resulting in slightly changed estimates only. Thus, the effect of including the unknown categories seems to be negligible.

A daily ten minute sun exposure of hands and face may be sufficient to maintain an adequate level of vitamin D for calcium regulation and to prevent deficiency diseases [38]. A Norwegian report from the National Council on Nutrition and Physical Activity [47] concludes that Norwegian healthy adults, aged 20–60 years, have an adequate level of vitamin D_3 during the summer, as far as bone metabolism is concerned. However, the level required to reduce the progression of a cancer disease is unknown.

Norway has no tradition of vitamin D-fortification of food items, except for margarine, which has been our

Table 4. Relative risk (RR) of cancer death among cases with breast-, colon- or prostate cancer season of diagnosis

Season of diagnosis	Breast, women		Colon, women		Colon, men		Prostate, men	
	RR	95% CI[a]	RR	95% CI[a]	RR	95% CI[a]	RR	95% CI[a]
Panel A								
Winter[b]	1.00		1.00		1.00		1.00	
Spring[c]	0.96	(0.91, 1.01)	0.94	(0.89, 1.01)	0.94	(0.88, 1.00)	1.01	(0.96, 1.05)
Summer[c]	0.94	(0.89, 0.98)	0.89	(0.84, 0.95)	0.94	(0.89, 1.01)	0.97	(0.93, 1.02)
Fall[c]	0.90	(0.86, 0.94)	0.82	(0.77, 0.87)	0.84	(0.79, 0.90)	0.83	(0.79, 0.86)
Winter[b]	1.00		1.00		1.00		1.00	
Spring[d]	0.94	(0.90, 0.99)	0.91	(0.86, 0.97)	0.93	(0.87, 1.00)	0.96	(0.92, 1.01)
Summer[d]	0.90	(0.86, 0.95)	0.84	(0.79, 0.90)	0.90	(0.84, 0.96)	0.88	(0.86, 0.84)
Fall[d]	0.85	(0.82, 0.90)	0.75	(0.70, 0.79)	0.78	(0.72, 0.82)	0.80	(0.77, 0.84)
Panel B								
Winter[b]	1.00		1.00		1.00		1.00	
Spring[c]	0.92	(0.85, 0.98)	0.89	(0.84, 0.96)	0.93	(0.86, 0.99)	0.98	(0.93, 1.04)
Summer[c]	0.83	(0.77, 0.89)	0.84	(0.80, 0.91)	0.91	(0.86, 0.98)	0.86	(0.82, 0.92)
Fall[c]	0.74	(0.69, 0.79)	0.75	(0.70, 0.79)	0.80	(0.73, 0.84)	0.73	(0.68, 0.78)
Winter[b]	1.00		1.00		1.00		1.00	
Spring[d]	0.90	(0.84, 0.96)	0.88	(0.82, 0.94)	0.92	(0.86, 0.99)	0.93	(0.89, 0.99)
Summer[d]	0.79	(0.73, 0.85)	0.80	(0.75, 0.85)	0.85	(0.80, 0.92)	0.80	(0.75, 0.84)
Fall[d]	0.70	(0.65, 0.75)	0.68	(0.64, 0.72)	0.71	(0.66, 0.77)	0.70	(0.66, 0.74)

[a] 95% Confidence interval.
[b] Denotes the reference category.
[c] Crude estimates.
[d] Estimated RR's adjusted for age at diagnosis, birth cohort, period of diagnosis, stage of disease at diagnosis, childbearing pattern, level of education, and residential and occupational sun exposure.

main supplement from the diet, together with fish and cod liver oil. However, the consumption of margarine and intake of fatty fish have decreased with more than 30% during the last 50 years, from 6.1 to 4.0 μg [47].

In the elderly, the vitamin D_3 status is generally low compared with younger people and it also varies less with season [38]. Ageing may reduce the efficiency of the skin to produce vitamin D_3 [29, 36]. Additionally, a low status in the elderly may be due to insufficient dietary supplement. In the present work, the mean age at diagnosis was 67 years. This is the age of retirement in Norway, which may lead to significant changes in lifestyle. According to this, the material was reanalysed, including only cases diagnosed before the age of 68. This gave no changes in the results.

In conclusion, for breast-, colon- and prostate cancer, the present work shows a significant variation in case fatality according to season of diagnosis. This coincides with the seasonal variation in UV-induced vitamin D_3. Diagnosis during fall is followed by the highest survival rate, and this is most pronounced the first few years after diagnosis. No north–south gradient in case fatality is observed. The study supports the hypothesis that vitamin D may influence cancer specific mortality in a beneficial way. A possible mechanism to explain our results might be a combined action of vitamin D_3 and cancer treatment that amplifies the treatment effect. If confirmed, in addition to traditional cancer treatment, vitamin D would be of particular importance in the primary prevention of death from the cancer types studied. Casual exposure to solar radiation and dietary intake of vitamin D are modifiable lifestyle factors.

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