Prostate Cancer Survival Is Dependent on Season of Diagnosis

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BACKGROUND. We have earlier found that the prognosis for several cancers is dependent on season of diagnosis. More recently, both prostate cancer incidence and mortality have been shown to increase with increasing latitude, which probably relates to photosynthesis of vitamin D.
METHODS. The 3 year survival of prostate cancer patients has been analyzed with the Cox regression method for two age groups at different latitudes in Norway.
RESULTS. Patients diagnosed during the summer and autumn had the best prognosis (Ralative risk (RR) death 0.8; 95% CI 0.75–0.85). Similar results were observed in three regions of the country that differ with respect to annual fluences of solar UV radiation, incidence rates of squamous cell carcinoma (SCC) and intake of fish. Furthermore, similar relationship between the season and survival was seen among patients ≤65 years and >65 years old, although the younger group had a slightly larger advantage of summer and autumn diagnosis.
CONCLUSIONS. The seasonal effect on prognosis may be related to the seasonal variations of calcidiol (the marker of vitamin D status). The lack of latitude effect and the similarity of prognosis for different age groups may be related to higher consumption of vitamin D in food in the north region and to increase of such consumption with age. *Prostate 67: 1362–1370, 2007.*

KEY WORDS: **prostate cancer; vitamin D; seasonal variation; prognosis; latitude dependency**

INTRODUCTION

Prostate cancer is the most frequently diagnosed cancer among men in Norway. The annual number and age-adjusted rates are about 2,800 and 80 per 100,000, respectively, which is twice that of lung cancer. Prostate cancer claims 1,100 lives in Norway each year, almost as many as lung cancer (1,200). About 17,000 Norwegian men are living with diagnosed prostate cancer. Although the rates of latent prostate cancer are rather similar throughout the world [1], the death rates can differ as much as 10 from country to country. The highest death rates are found in the USA, Canada, and Scandinavia and lowest in Hong Kong and Japan [2]. Thus, the prognosis is likely to be strongly dependent on racial and environmental factors. Among such environmental factors, ultraviolet radiation (UV) from the sun may be an important one. A latitude dependency of prostate cancer incidence rates has been

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observed [3] and may be related to photosynthesis of vitamin D_3 in the skin. Schwartz and Hulka launched in 1990, the hypothesis that a high prostate cancer mortality may be related to vitamin D deficiency [4]. Later, a number of epidemiological studies, ecological as well as cohort ones, have been carried out, and many of them support the hypothesis [3,5–13]. Two case-control studies that compared measures of acute and chronic sun exposure in prostate cancer patients and patients with benign prostatic hypertrophy in England [14,15] demonstrated a substantial effect of cumulative lifetime sun exposures. The odds ratios of having prostate cancer were 3.03 and 3.21, respectively, when men within the lowest quartile of sun exposure were compared to those in the highest quartiles. Men in the lowest exposure quartile developed prostate cancer at an earlier age than those in the other quartiles. Even childhood sunburns, holidays abroad and adult sunbathing were found to protect against prostate cancer. In a recent study [8], reduced risk of advanced prostate cancer was found to be associated with high sun exposure and outdoor activity, and the risk was related to polymorphisms of the vitamin D receptor (VRD). Furthermore, it has been shown that frequent sun exposure reduced the odds for abnormal levels of serum prostate specific antigen (PSA) [16].

Nevertheless, several studies have failed to show any inverse correlation between prostate cancer risk and vitamin D_3 level [17–19].

We were the first to document a seasonal variation of the prognosis of several cancers [20–24]. Summer and autumn diagnosis were associated with the highest survival, and we tentatively attributed this to the high serum calcidiol levels observed in these seasons. A seasonal variation of the calcidiol level is found in most countries, including Norway [25]. If this explanation is correct, UV exposure, or vitamin D, or one of its derivatives, might be used as adjuvants to standard cancer therapies. Recently, our findings were reproduced in a large study in the UK [26]. Similar findings have been reported for non-small cell lung cancer and even for death risks of melanomas [27,28]. The recent work of Giovannucci et al. [29] indicates that a high calcidiol level reduces the overall death rates more than the incidence rates. An increment of 25 nmol/l calcidiol in serum would give a 17% reduction in total cancer incidence and a 29% reduction in total cancer mortality. Thus, it might seem that vitamin D_3 has a particularly strong effect on tumor progression. One minimal erythematous dose (MED) of UV, i.e. one dose of UV that induces a slight redness of the skin, given to whole body, gives a serum calcidiol increment equivalent to that obtained after ingestion of 10,000–20,000 IU of vitamin D [30].

However, neither the relative significance of food intake and photosynthesis of vitamin D, nor the interaction between the two routes (additive, antagonistic, or synergistic) is fully understood. In the present work, we wanted to shed light on this problem by studying prostate cancer more closely and extend our previous work by dividing Norway in regions that differ both with respect to annual solar exposures and documented vitamin D consumption. Furthermore, since photosynthesis of vitamin D in skin decreases with age [31], two separate age groups were considered. Vacations to southern latitudes were also taken in to account, as well as measured calcidiol levels in a non-cancer Norwegian population.

MATERIALS AND METHODS

Cancer Analysis Population

For our epidemiological investigation we used the data on prostate cancer incidence and mortality provided by the Cancer Registry of Norway where all cancer diagnosis since 1953 are registered. Since 1960, every Norwegian inhabitant has a unique personal identification number (11 digits). In 1964, a database including all Norwegians with individual information about year of birth, place of residence, vital status, occupation, education, and number of childbirth was established [20]. The ID number enabled us to link the prostate cancer patients recorded in the Cancer Registry of Norway to this database in order to obtain full sociodemografic information. During the observation period (1964–1992), 46,205 men were diagnosed with prostate cancer. Among these, 6,839 men were $\leq$65 years and 39,366 men were >65 years old at the time of diagnosis. All were born between 1900 and 1966.

The cases were divided into four groups, based on the time points of diagnoses: winter (December 1–February 28), spring (March 1–May 31), summer (June 1–August 31), and autumn (September 1–November 30).

Survival analyses were performed using Cox regression model run by SPSS 11.5 for Windows (SPSS, Chicago, IL). Ralative risks of death (RR) during 36 months after diagnosis were estimated with risk for winter normalized to 1. For the analyses stratified by residential region, two seasons were considered (summer + autumn and winter + spring) to ensure enough cases in each category.

The incidence rate of prostate cancer is known to be higher among old men (65–85 years), but it is also a common malignancy among men of late middle age (50–64 years). While the cancer risk increases with age, the photosynthesis of vitamin D_3 decreases with age [32]. Based on these two facts, all patients diagnosed with prostate cancer were divided in two age groups: ≤65 years (mean age 61) and >65 years (mean age 76).

Calcidiol Analysis Population

Data on seasonal variation of serum calcidiol were provided by the Hormone Laboratory, Aker University Hospital. Calcidiol concentrations in 2,912 men ≤65 and 1,082 men >65 for the period 1996–2001 were analyzed by High Performance Liquid Chromatography after ether extraction, essentially as described in Falch et al. [33] with an inter assay variation of 12%. Donors of these samples were individuals from outpatient clinics that were suspected for different somatic disorders, including those which may result in vitamin D deficiency.

Sun Exposure and Vitamin D Intake

Norway was divided into three geographical regions: north, midwest, and southeast, based on ambient annual UV doses, measured and calculated as described earlier [20,24], and on the age adjusted incidence rate of squamous cell carcinomas (SCC) of the skin averaged for the period 1957–2001 for the different counties [24].

Data on vitamin D and fish intake were obtained from the ''Norkost 1997'' study for men of 16–79 years [34]. The differences in vitamin D and fish intake were used for an additional assessment of vitamin D status in the discussed age groups and geographical regions.

RESULTS

Regional Differences in Annual UV Doses and Vitamin D Intake in Norway

Figure 1 is a map of Norway showing the three regions we have studied: north, midwest, and southeast. Figure 2 shows the age adjusted incidence rates of SCC as a function of latitude. The mean values of annual UV dose, weighted with the CIE reference spectrum and adjusted for different cloud covers [24], are 1.00, 1.18, and 1.44 given in relative numbers for the northern-, the middle-, and the southern region, respectively. We found it informative to determine the SCC incidence rates, since these are related to the UV fluences acquired by the populations [21,35,36]. Due to regional differences in summer temperature, these may be different from the ambient fluences reaching the ground. The average incidence rates for the three regions are well separated (Fig. 2), and we can assume that the UV fluences to the three populations are significantly different, as earlier estimated [20,24].

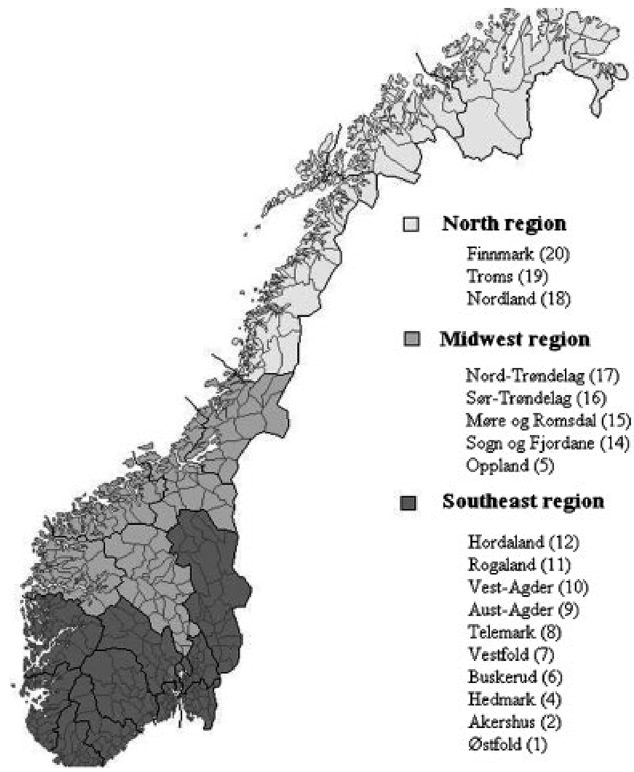

Fig. 1. A map of Norway showing the three geographical regions expended between 58°N and 71°N of latitude.

Data for annual UV doses, incidence rates of SCC, vitamin D photosynthesis in the skin calculated according to the absorption spectrum of 7-dihydrocholesterol [21] and dietary vitamin D intake [34] are shown in Figure 3.

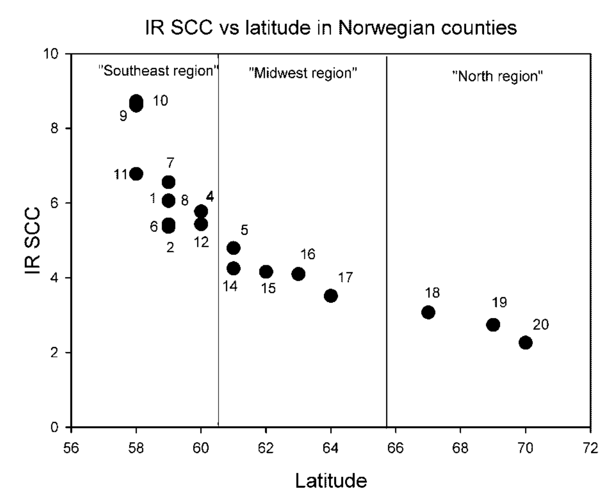

Fig. 2. The average annual incidence rate of squamous cell carcinoma in Norway for the time period 1957–2001 as a function of latitude of the different counties, which are given by numbers (Fig. 1). The rates are given per 100,000 and age adjusted to the standard Norwegian population.

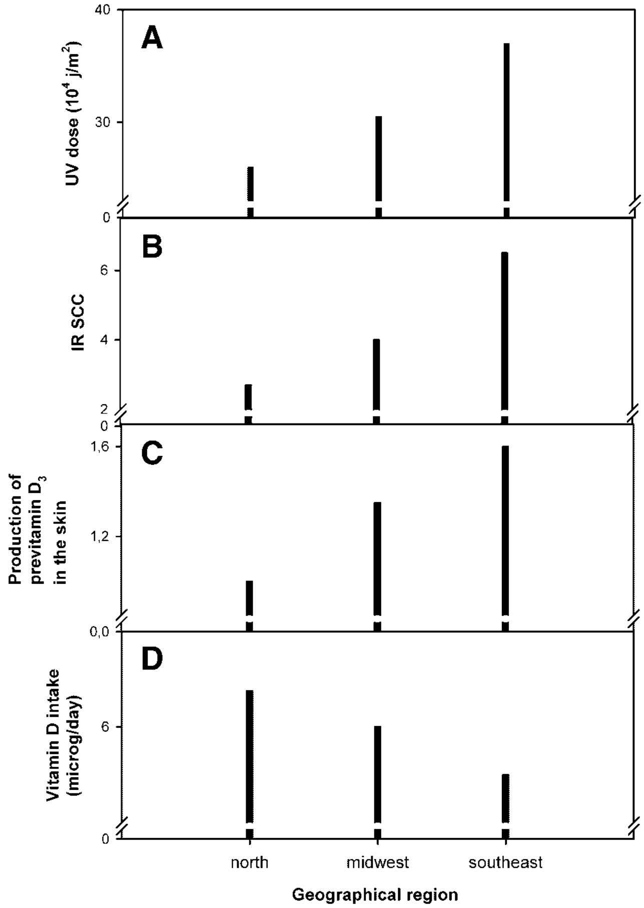

Fig. 3. Relative values for the three regions for annual doses of erythemogenic UV radiation from the sun determined by use of the CIE action spectrum [21] (**A**), for the average annual incidence rates of SCC [21,42] (**B**) as defined under Figure 2, for synthesis of vitamin D determined as described in [20] (**C**), and vitamin D intake (**D**).

The intake of vitamin D from food is also different in the three regions [34]. Compared to the southeast region the vitamin D intake is about 7% and 13% lager in the midwest and the north region, respectively (Fig. 3).

The most important food source of vitamin D_3 in Norway is fat fish. There is 50% increase in fish intake from age 25 to 50–80 years, as shown in Figure 4. However, from age 50 to 80, the age span most relevant in view of prostate cancer, the difference is small and non-significant (Fig. 4).

Contribution of the Region and Age on the Relation Between Season of Diagnosis and Prostate Cancer Survival

As shown in Figure 5, the relative risk of death, assed 36 months after diagnosis, follows a seasonal variation similar to that of serum calcidiol, with the best

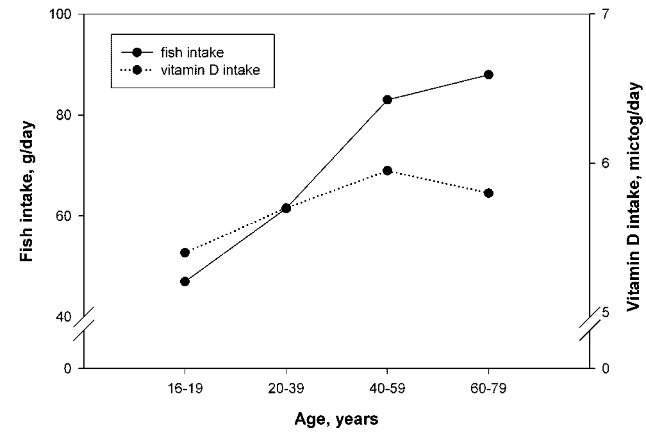

Fig. 4. Fish and vitamin D intake for different age groups of men [34].

prognosis for summer and autumn diagnosis when compared with winter and spring (RR death 0.8; 95% CI 0.75–0.85). Summer and autumn are the seasons with the highest serum calcidiol concentrations in both studied age groups, as shown in Figure 5B.

In order to get more reliable data for comparisons of age groups and regions, summer and autumn data

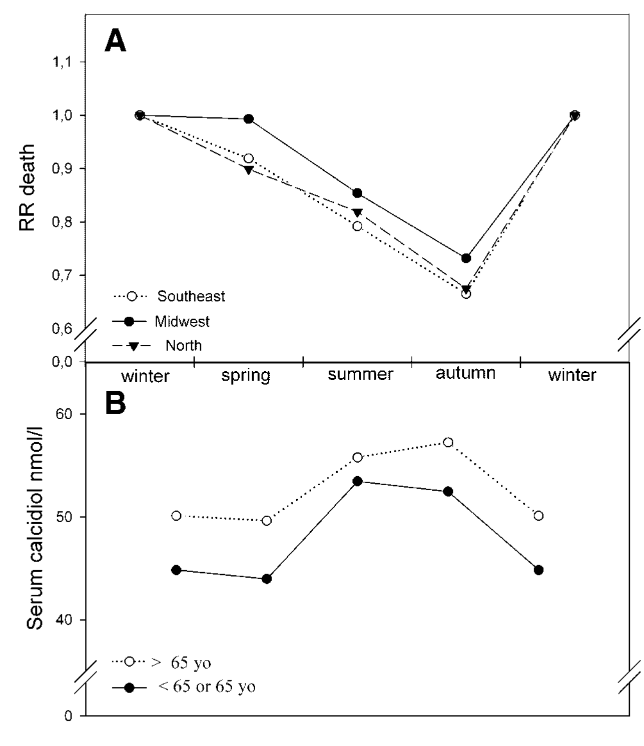

Fig. 5. **A**: Relative risk of death from prostate cancer 36 months after diagnosis in the four seasons. The reference category was diagnosis during winter in the midwest region. **B**: Calcidiol levels in serum for two age groups ($\leq$65 years and >65 years) given for the four seasons.

were grouped together and called "summer," and winter and spring data were combined and called "winter" (Fig. 6). The overall effect of season on cancer-specific survival persisted after stratification by region and age, and there was no significant independent effect neither of region nor of age on this (Fig. 6). There is, however, a trend that the survival advantage of summer diagnosis is larger for younger age group (Fig. 6C,D). This is to be expected since the efficiency of vitamin D_3 photosynthesis in human skin decreases with age [32].

There is no significant difference between the three regions in the frequency of holiday vacations to southern regions [37].

DISCUSSION

Solar UV-B radiation (280–320 nm) is the major source of vitamin D for humans [38,39]. Approximately 80–90% of circulating calcidiol is a result of photosynthesis of vitamin D in the skin and the calcidiol level varies with the exposure to solar radiation [38,40]. At mid latitudes the annual dose of vitamin D-generating solar radiation increases by about 50% when moving 10° southwards [21,41].

The ambient UV dose may not reflect the actual, acquired UV dose due to different behaviors of people in seeking or avoiding solar radiation. Therefore, we used incidence rates of SCC as an indicator of the real acquired UV exposures [21,36,41–43]. There is a decrease in incidence rates of SCC with increasing latitude in Norwegian counties (Fig. 2) [21,43]. The fact that the north–south gradient in SCC incidence rates has not changed significantly during the last 40 years (data not shown) indicates that the duration and frequency of vacations to southern latitudes does not contribute significantly to the north–south gradient in UV exposures.

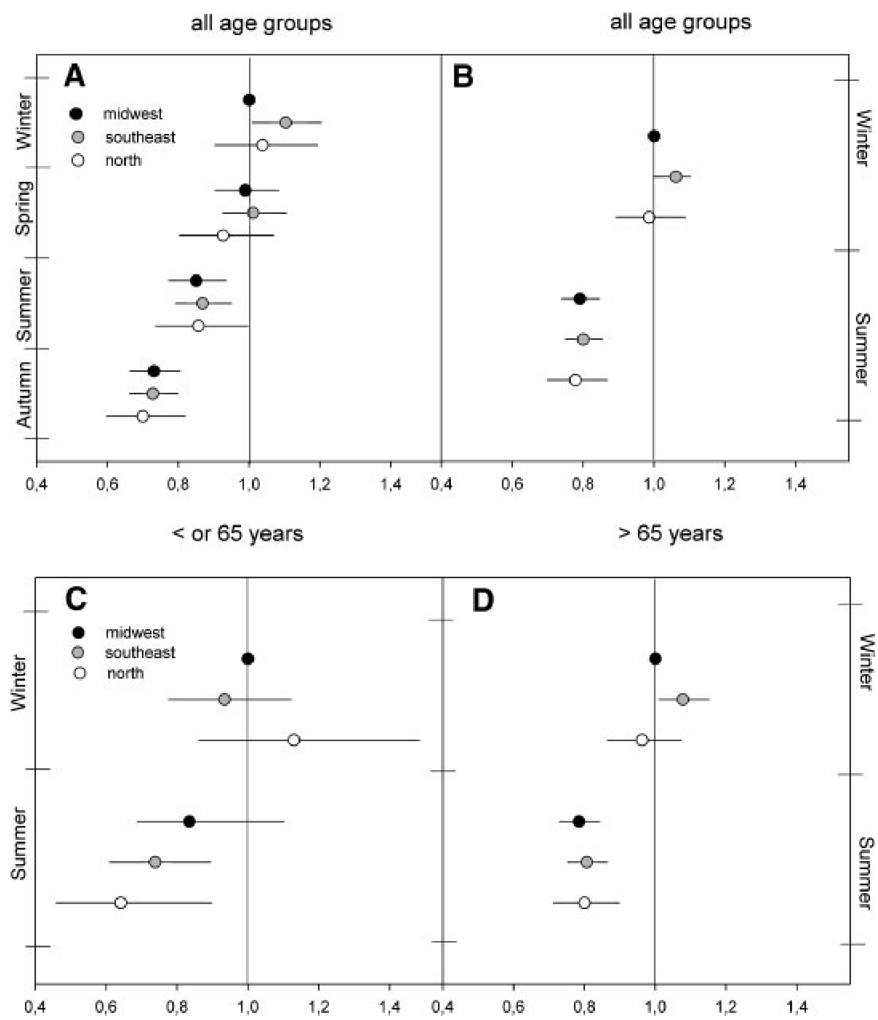

Fig. 6. **A**,**B**: Relative risk of death from prostate cancer 36 months after diagnosis. Data for all age groups and three geographical regions. The reference category was diagnosis during winter in the midwest region. **C**,**D**: Similar data as those shown in **panel B**, but here for the younger category of patients (C) and the older category of patients (D).

In view of these considerations, we feel that it is justified, as a first approximation, to use ambient UV doses to estimate vitamin D-generating doses.

Photosynthesis of vitamin D in the skin decreases with age [32]. Thus, the capacity of the skin to produce previtamin D is about 40% lower in men older then 75 years than in men younger then 60 years [32,44].

Vitamin D is present in a few natural food sources, some multivitamins and supplements. According to Figure 3, based on data from Norkost study [34], the vitamin D intake in the north region is 13% higher than in southeast region and about 7% higher than that in the midwest region (Fig. 4) [34]. Brustad et al. [45] have assessed the seasonality of dietary intake of vitamin D and no variation was observed. Therefore, we assume the 13% higher intake in the north region to be constant throughout the year.

There is a clear seasonality of calcidiol in both age groups (Fig. 2). The winter–summer variation in calcidiol concentration is 11% for men above 65 years and 16% for men below 65 years. The higher winter levels of calcidiol in the oldest age group (12%) may be explained by the fact that intake of fish and fish products increases with age, as shown in Fig. 4. The Norkost study [34] shows an almost 50% higher fish intake in men older than 50 years compared with men of age 16–19 years.

However, the fish intake did not change significantly beyond 50 years.

Our data indicate that inhabitants in the north region have a higher vitamin D intake than inhabitants in the southeast, and that the persons younger than 65 years have a lower vitamin D intake than persons older then 65 years. We assume that this is also true for cancer patients.

The prognosis for prostate cancer patients was better when diagnosed during summer and autumn than during winter and spring (Fig. 5). This was observed for all three geographical regions, with no significant difference between them. Moreover, the survival advantage of summer diagnosis tended to be larger for the younger age group (Fig. 6C,D), in agreement with the fact that the efficiency of vitamin D photosynthesis in skin decreases with age.

All our data, as well as those of our earlier work, are consistent with the hypothesis that cancer prognosis is dependent on the vitamin D level at the time of diagnosis.

In a number of epidemiological studies, cancer incidence and mortality have been related to calcidiol levels. Our work agrees with this, although we focus on prognosis rather than on incidence or mortality.

Tuohimaa et al. [5] recently reported the results of case-control study among Nordic men and showed a U-shaped risk curve for prostate cancer. Both low ($\leq$19 nmol/l) and high ($\geq$80 nmol/l) calcidiol serum levels are associated with higher prostate cancer risk.

Vieth et al. [46] proposed that the increased risk for high calcidiol levels are related to the rapid decline of calcidiol levels in men with high summer levels to low winter values.

Giovannucci et al. [29] found a non-significant decrease in incidence and mortality rates for advanced prostate cancer associated with an increase of 25 nmol/l of calcidiol.

Schwartz et al. [47] demonstrated a gradual decrease in prostate cancer mortality with increasing of latitude and UV radiation in USA with the strongest effect in states north of 40°N, where photosynthesis of vitamin D takes place between April and October.

Since Norway lies between 58°N and 71°N (and significant amounts of vitamin D are formed in the months April–October with latitude gradient [21]) we expected to find a north–south gradient also in the prostate cancer prognosis.

Our data show no such latitude effect, neither for summer nor for winter prognosis. This fact may be explained by the higher vitamin D intake in the north region. This may balance the high UV exposure in the southeast region: the annual vitamin D-generating sun exposure is about 50% lower in the north than in the southeast region, which should result in about 10% calcidiol [21], while the vitamin D intake is 13% higher.

However, other explanations of our cancer survival data should not be overlooked. Thus, diet, physical activity, and alcohol consumption may play a role in prostate cancer prognosis [48–50]. Higher intakes of fruits and vegetables (notably during summer and autumn) may improve cancer prognosis trough their increased content of antioxidants [50]. Moreover, alcohol consumption which is considered to be one of the risk factors for prostate cancer is highly increasing during winter time and this might affect negatively survival [49]. Increasing physical activity during the summer time may also influence cancer prognosis, since a moderate reduction in risk of advance prostate cancer has been observed among patients $\geq$65 years if they had at least 3 hr of vigorous activity weekly [48].

Moreover, it has been shown that not only season of diagnosis may contribute to cancer prognosis, but also the season when anticancer therapy is started may be a predictor of cancer survival. In the recent study on lung cancer patients, surgeries in the summer time were associated with improved cancer survival [51]. Furthermore, some preclinical studies have proven that calcitriol derivatives enchance the effect of established chemotherapeutics for cancer treatment [52]. A large number of in vitro studies with prostate cancer cells support the role of vitamin D in carcinogenesis [53,54].

Since both benign and malignant prostate cells express 1α-hydroxylase which mediates the conversion of 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3, the latter could be produced and act locally in prostate tissue [55].

The mechanisms governing the anti-proliferative and pro-differentiative effects of calcitriol are not fully understood. Calcitriol has been shown to induce cell cycle arrest in G_0/G_1 phase, apoptosis and down-regulation some anti-apoptotic genes, interaction with growth factors, like insulin-like growth factor (IGF), stimulation of differentiation, and inhibition of cell migration and adhesion [56–59]. In vivo studies have shown inhibition of metastasis formation and angiogenesis through influencing endothelial cell growth [60–62]. Finally, active metabolites of vitamin D_3 interact with the immune system in a way that may influence tumor prognosis.

Intracellular levels of calcitriol are tightly regulated, since excess calcitriol is inactivated by the 24-hydroxylase. It's upregulation in many prostate tumor cell lines may result in a decrease of the intracellular calcitriol concentration and its anti-cancer activity [63].

In view of all these effects, and of the interaction with the androgen system, calcitriol, and derivatives thereof, have been launched as prostate cancer therapeutics [52,64]. Improved survival was seen in a randomized placebo controlled trial of docetaxel with (weekly administration) or without calcitirol in patients with metastatic androgen-independent prostate cancer [65]. However, the continuous administration of calcitriol is limited because of the toxicity and secondary hypercalcemia, particularly at doses expected to have a beneficial effect [66]. Therefore, alternative ways to achieve higher vitamin D levels should be considered, especially for long time treatments. Natural sources of vitamin D, such as UV radiation and fish intake, may significantly increase calcidiol concentrations and probably lead to higher intracellular calcitriol production. However, it might be difficult to obtain high levels of calcidiol during the winter time, when no photosynthesis of previtamin D occurs in the skin, while administration of vitamin D_3 supplements may drastically increase serum calcidiol levels and result in better prognosis and outcome of the treatment of prostate cancer [29,67].

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