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Colon cancer: Prognosis for different latitudes, age groups and seasons in Norway

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Abstract

The survival of colon cancer patients in Norway, as determined three years after diagnosis, is dependent on the season of diagnosis. This has been attributed to seasonal variations of the vitamin D status. Since solar radiation and food are the human sources of vitamin D, we divided Norway in three regions: The southeast region with a high annual dose of ultraviolet (UV) to the population, as evidenced by a high incidence rate of squamous cell carcinoma of the skin (SCC), the midwest region and the north region with low annual UV doses. The latter region is characterized by a high consumption of vitamin D, mainly through fish intake. Vacations to southern latitudes were equally frequent for all the three geographical regions. Two age groups were analyzed separately ($\leqslant$65 years and >65 years), since the photosynthesis of vitamin D_3 in skin decreases with age.

In all three regions, and in both age groups, the survival was highest for summer and autumn diagnosis. The seasonal effect was slightly, but not significantly, better for the younger than for the older age group. The effect was similar for all three geographical regions, irrespective of SCC incidence.

Keywords: Vitamin D; Solar radiation; SCC incidence; Colon cancer prognosis; Seasonality; Age, Latitude

1. Introduction

Both incidence and prognosis of colon cancer, and of several other cancer types, seem to be related to the vitamin D status. Most case–control epidemiological studies indicate that a high intake of vitamin D reduces the risk of getting colorectal cancer [1–3]. Furthermore, several studies of the relationship between $25(OH)D_3$ concentrations in serum and risk of colorectal cancer show low risks for groups with high $25(OH)D_3$ levels [4–6].

Almost all these studies may suffer from one weakness, namely that the "latency" time for colorectal cancer is likely to be long. Vitamin D_3 consumption and photosynthesis, as well as serum $25(OH)D_3$ levels 10–25 years prior to detection, may be more important than those immediately before diagnosis [2].

Ecological studies are stronger on this point. These are based on the fact that photosynthesis in skin is the most important source of vitamin D_3, and attempt to correlate latitude with colon cancer incidence- or death rates. Under otherwise similar conditions, the annual vitamin D_3 photosynthesis increases by about 50% per 10° decrease in latitude [7]. That solar radiation may lower cancer risk was first proposed in 1937 [8]. An inverse association between latitude and cancer mortality was found in 1941 [9]. Garland and Garland [10] verified this for colon cancer, and

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so did several other investigators later [11–14]. Living in a rural area, as well as migrating southwards [15], reduces the risk [6,15].

In a recent large, prospective study of predictors of vitamin D status and cancer incidence and mortality it was found that low levels of vitamin D may be associated with increased risk of both incidence and mortality [6,16]. Together with researchers from the Norwegian Cancer Registry, we were the first to investigate the variation of cancer prognosis with season of diagnosis [7,17–19] and found a better prognosis for cases diagnosed in summer and autumn than in winter and spring. This was attributed to the seasonal variation of serum 25(OH)D_3, although other factors were not excluded. Consistent with our data are that the five year case-fatality from colon cancer seems to decrease with latitude in the US population [20], and that the odds ratio for 25(OH)D_3 in serum samples taken in winter and spring had a stronger inverse correlation with colorectal adenomas than did those taken in summer and fall [5]. Our findings are in full agreement with those in a similar, recent, large investigation in the UK [21]. Also, for other types of cancer, like non-small cell lung cancer [22], and even melanomas [23], the fatality is lowest for patients diagnosed in the summer season. Recently we found the same for breast cancer [18,19]. It has been estimated that an increment of 25 nmol/l in serum 25(OH)D_3 would give a 17% reduction in total cancer incidence and a 29% reduction in total cancer mortality [6]. The fact that the reduction in mortality is larger than that in incidence, indicates that a high 25(OH)D_3 level leads to decreased fatality, as found by us [7,17–19].

The interaction of dietary intake of vitamin D_3 and photosynthesis remains largely unknown. In an attempt to shed light on this problem we here extend our previous study of colon cancer [7] and divide Norway into three regions, one with a high annual UV dose, one with a low UV dose and one with a low UV dose and a high vitamin D_3 intake in the population. Since photosynthesis of vitamin D_3 decreases with age, we have also investigated different age groups. Frequencies of vacation to southern latitudes and sex differences were paid attention to. Serum 25(OH)D_3 levels, available from another patient population, but for similar age and sex subdivisions, are also presented. We wanted to verify that calculated and measured annual UV exposures [7] are relevant for real exposures, and, therefore, also present SCC incidence rates for each of the three regions.

2. Materials and methods

In the epidemiological investigations the time points of diagnoses are grouped in winter (December 1–February 28), spring (March 1–May 31), summer (June 1–August 31) and autumn (September 1–November 30). In some cases we have grouped winter and spring together and summer and autumn together for statistical reasons.

ID numbers were used in the registration of patients: Since 1960 all Norwegians have an unique personal identification number (11 digits) recorded in The Central Population Registry. Thus, we registered year of birth, living place, occupation, education and number of childbirth, as described in Robsahm et al. [19]. In the Cancer Registry of Norway all cancer diagnosis since 1953 are registered [19]. In our work on colon cancer 12,823 men and 14,922 women with colon cancer are included. All are born between 1900 and 1966. The period of observation is from 1964 to 1992. The relative death risks (RR) during the first 36 months after diagnosis are given as relative numbers. Values for winter (or spring and winter merged) in midwest region are normalized to 1 in all presentations.

Assignment of the Norwegian counties into three regions was based on ambient annual UV doses, calculated and measured as earlier described [7,18], and on the age adjusted incidence rates of squamous cell carcinomas of the skin averaged for the period 1957–2001 for the different counties [18].

In our earlier investigation [7] we considered only persons younger than 68 years at diagnosis. In the present one, we divided the diagnosed patients in two age groups ($\leqslant$65years and >65years). This choice of age groups was made in view of two facts: photosynthesis of vitamin D_3 decreases with age and cancer risk increases with age so that for statistical reasons one has to make the separation of groups at a high age [24] to get enough patients in each group.

The data on serum 25(OH)D_3 are provided by the Hormone Laboratory, Aker University Hospital. Results from the period 1996–2001 from 2912 men aged $\leqslant$65; 1082 men >65 years; 7211 women aged $\leqslant$65 years and 4,411 women >65 years, ordered mainly from outpatient clinics for different diseases were considered. 25(OH)D_3 concentrations were analyzed by high performance liquid chromatography after ether extraction, essentially as described in Falch et al. [25] with an inter assay variation of 12%.

Data on cancer incidence and mortality rates were obtained from GLOBOCAN 2002 for the following eight countries: Finland, Norway, Sweden, Denmark, Iceland, UK, New Zealand and Australia [26]. These countries have populations with roughly similar skin types (nordic–celtic, skin types I–II) but living at different latitudes. The ratio of age-adjusted mortality and incidence rates was used as an estimation of survival [27].

3. Results

Fig. 1 shows the counties of Norway: Vest-Agder is located at 58° N with an annual UV dose about 50% larger than that in Finnmark, located at 70° N. The incidence rates of SCC increases from north to south, and Vest-Agder has a rate that is about three times larger than that Finnmark. The counties are, based on both latitude and SCC incidence rates, assembled in three regions: the southeast, the midwest and the north (Fig. 1).

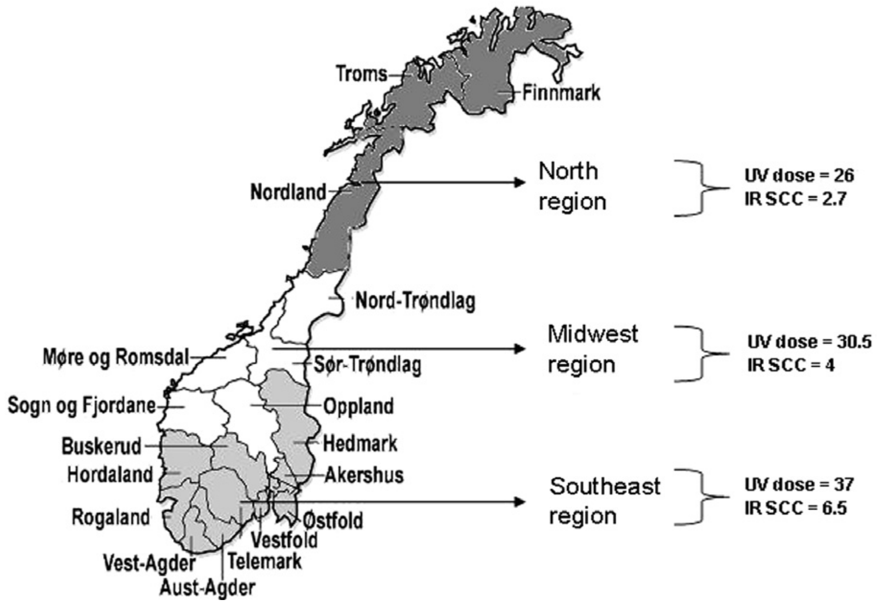

Fig. 1. Map of Norway with averaged values for squamous cell carcinoma incidence rates (IRSCC) and UV doses for north, midwest and southeast region of the country. The cancer data are from the period 1964–1992.

The measured 25(OH)D_3 serum concentrations are shown in Fig. 2 [7]. These data are from the database of the Hormone Laboratory, Aker University Hospital, which is located in southeast Norway. Donors of these samples are mainly non-cancer patients that had their vitamin D status checked for a number of other diseases. These data should, therefore, be used with care in the present context. They mainly serve as a confirmation of seasonal 25(OH)D_3 variations, give valuable indications of age and sex differences, and also as a confirmation of earlier findings [7].

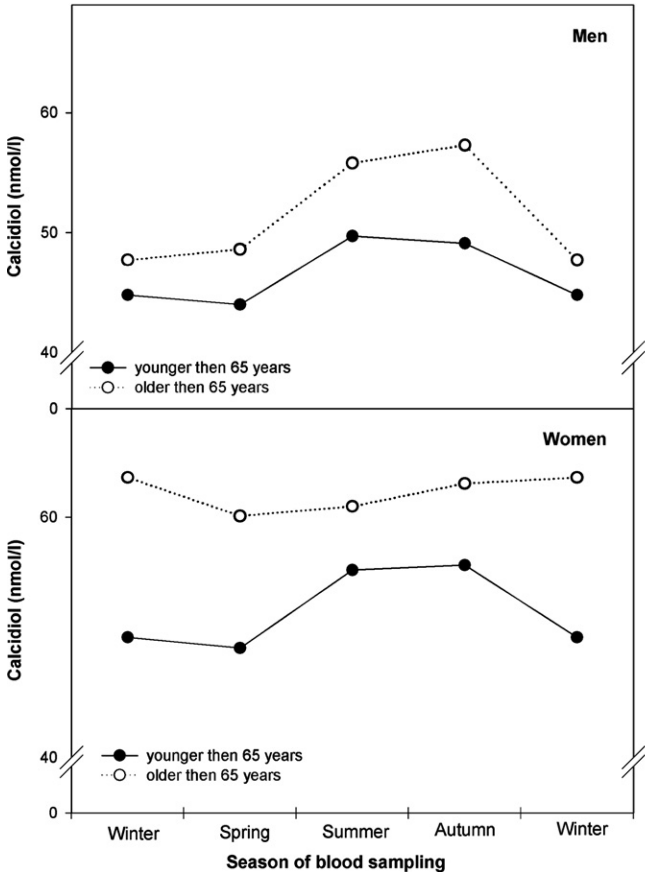

Fig. 2. 25(OH)D3 serum values for different age groups of men and women. The data are provided by analyses performed at the Hormone Laboratory, Aker University Hospital.

In agreement with previous work [7] we found no seasonal variation in the number of diagnosis: 25 ± 1.5% were diagnosed in each season.

The seasonal variation was similar for all data categories: over-all data (Fig. 3), age-grouped and region-grouped data for men and women (Fig. 4). The relative risk of death associated with autumn diagnosis was always lower, by 20–40%, than that for winter diagnosis. For both the southeast and the midwest regions the risk of death was slightly lower for the category of youngest patients.

In order to reveal possible regional differences we combined winter and spring data (called "winter") and summer and autumn data (called "summer"), and normalized the data to the values for diagnosis during "winter" in the midwest region (Figs. 3 and 5).

Unfortunately, no data for colon cancer prognosis in other countries than Norway are available to us. As a very rough estimate, we determined ratios of overall death rates to incidence rates for a number of countries populated by caucasians and located at different latitudes (Fig. 6).

About 60% of the population in all regions annually goes to vacations at southern latitudes for a week or two [28]. The number of passengers traveling for holiday from Norway to southern locations (Greece, Italy, Portugal, Spain, Turkey), was 14 times higher in 2001 than in 1970 [28].

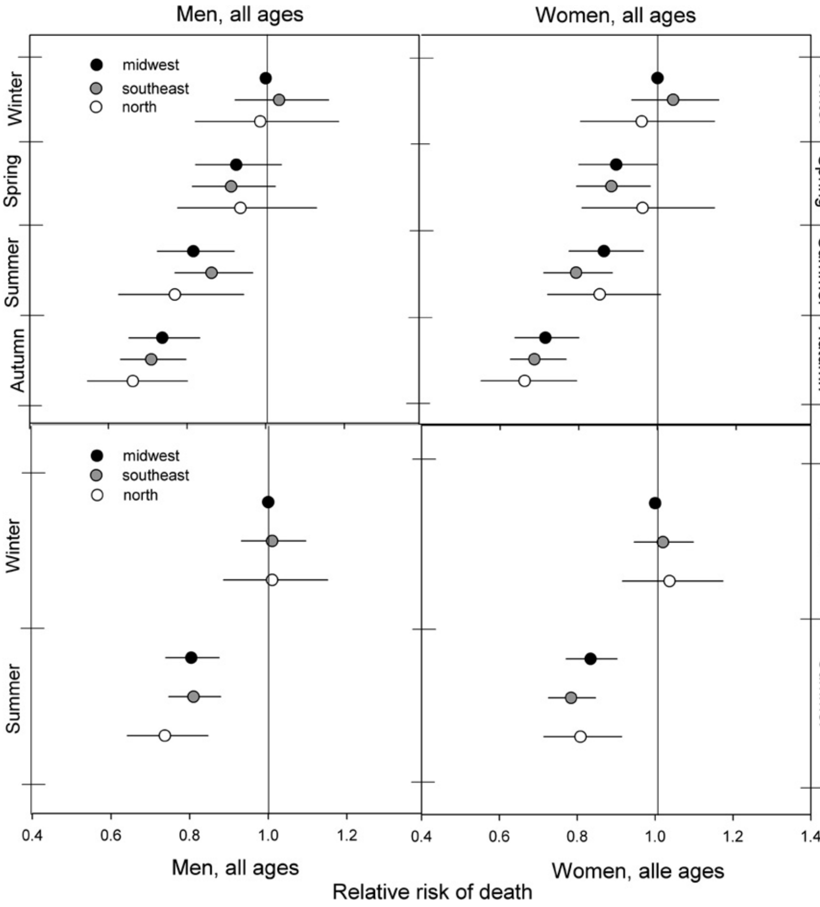

Fig. 3. The seasonal variation of 3 years relative risk of death from colon cancer for men and women in the three regions of Norway delineated in Fig. 1. Death rates are normalized to 1 for diagnosis during winter in Midwest region (see Fig. 1). On the lower panel data are shown for winter and spring (called "winter") and summer and autumn (called "summer").

4. Discussion

The fact that the incidence rates of SCC decrease monotonously with increasing latitude (Fig. 1, right side) indicates that the real personal UV exposures can be approximated by calculated or measured, ambient UV exposures [7,18,29–31]. Vacations to southern latitudes do not influence this, being equally frequent for all regions [28]. Thus, the north–south gradient in SCC incidence rates has not changed significantly the last 40 years (data not shown), while the duration and frequency of vacations to southern latitudes have increased drastically over these years [32,33]. With this in mind we have estimated that the rate of photosynthesis of vitamin D_3 in the summer months is about 20% larger in the southeast region than in the midwest region (Fig. 2). The time period of significant vitamin D_3 photosynthesis is shorter by about one month in the midwest region than in the southeast region. In human skin significant amounts of vitamin D_3 are formed only in the months April–October in the midwest region [34].

Our calculations (Fig. 1), in agreement with those in Lu et al. [35], indicate that annually about 40–50% more vitamin D_3 is synthesized in the southeast region. Assuming a constant baseline level of 50 nmol/l [7] (winter value), the annual average level of 25(OH)D3 should be about 10% higher in the southeast region than in the two other regions, if it is assumed that the vitamin D intake is the same in all regions.

For all groups in our 25(OH)D_3 investigation, except for women over 65 years, the measured 25(OH)D_3 level in serum varied with season as earlier found [7,19,36–38]. The reason for the constancy of the values for women over 65 years is not known, but one might speculate that this group is more concerned about proper intake of vitamin D-containing food and supplements than the other groups. The rate of photosynthesis of vitamin D_3 decreases with age [24]. Therefore, it is surprising that we find the highest level for the oldest persons (Fig. 2). Also this may be due to a higher intake of vitamin D_3 in food and supplements in these groups. Alternatively, it is possible that younger people spend more time on indoor work and, therefore, get less vitamin D from the sun. Unfortunately, we are not aware of any investigation on this in Norway.

For all categories the prognosis of colon cancer is better for summer and autumn diagnosis than for winter and spring diagnosis (Figs. 3 and 4). In no case is there any significant difference between the three regions (Figs. 3 and 4).

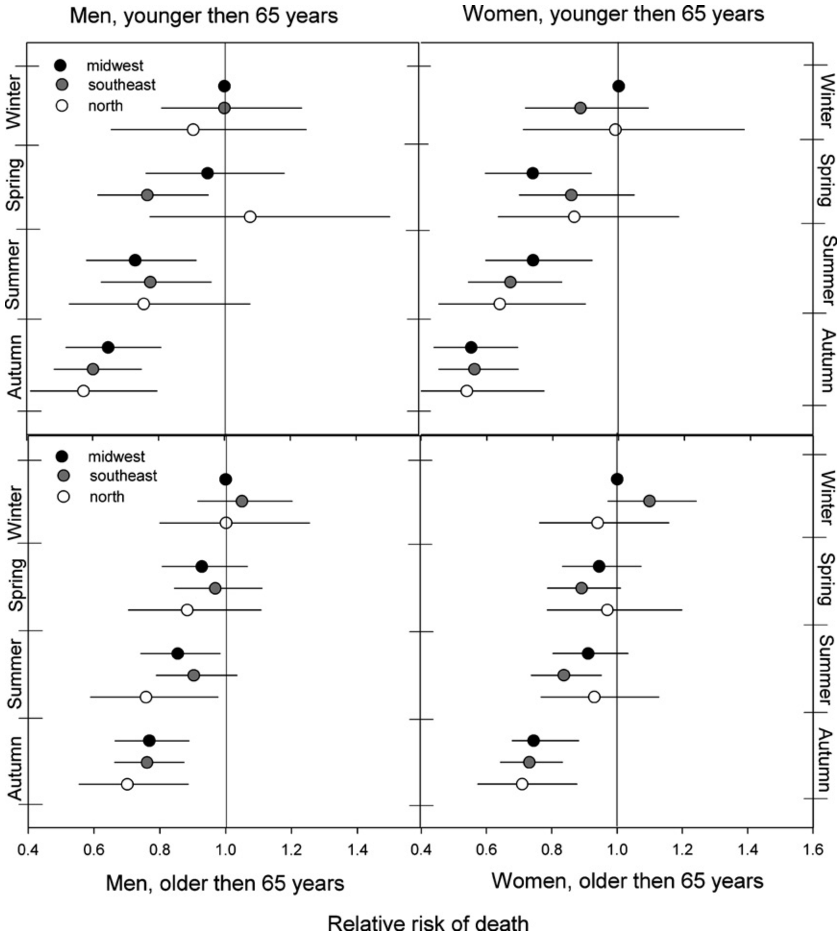

Fig. 4. Similar data as shown in Fig. 3, but here subdivided in two age groups (⩽65 years, >65 years).

We wanted to analyze this more closely, and for better statistics we grouped winter and spring diagnosis together and summer and autumn diagnosis together (Figs. 3 and 5). The only significant difference in prognosis we can detect is that between summer season and winter season diagnosis. The seasonal variation appeared to be slightly, although not significantly, larger for the youngest category of patients (Fig. 5), in agreement with earlier findings [19], and with the decrease in vitamin D_3 photosynthesis with age [24].

In no case should one expect any large age difference, since even in the youngest category (⩽65 years) most patients are older than 55 years. One might not expect any large decrease of the photosynthetic ability of skin from 55 to 65 years [24].

The population of patients, for which the $25(OH)D_3$ level were determined at Aker Hospital, is, as stated, not the same as the population of cancer patients studied. The purpose of analyzing serum samples of the former category was that a low or inadequate vitamin D status might explain their symptoms, and thus, be taken advantage of in therapy. These patients, notably the older ones, are likely to take vitamin D_3 supplements. Furthermore, they do not expose themselves frequently to solar radiation, due to health reasons. Our data (Fig. 2) indicate that this is true at least for women. Colon cancer patients are not likely to avoid sun exposure, notably not before their diagnosis.

There is probably not any seasonal variation in fish consumption in Northern Norway. In winter and early spring mainly cod is consumed, and in the summer saithe, herring and other types of fish are consumed. However, overall the population in the north region consume more vitamin D than those in the two other regions (Table 1) [39].

Unfortunately, no direct comparison of $25(OH)D_3$ levels in northern and southern Norway has been performed. However, one can make a rough comparison, based on the literature knowledge of the yield of 25(OH)D3 from photosynthesis and that from consumption. Following similar methods as earlier described [7], we find that the 20% higher vitamin D intake in the north region is about balanced by the 50% larger UV dose per year in the south. This would give roughly a 50% larger annual photosynthesis of vitamin D_3 [7], and, taking the winter values into account, roughly a 15–20% higher overall $25(OH)D_3$ level. Furthermore, the mid-summer photosynthesis of vitamin D_3 is only 20% larger in southeast than in north, according to our calculations [7]. The real differences are likely to be smaller, since large UV doses degrade vitamin D_3 in skin, before it is transported to the liver [40], and since

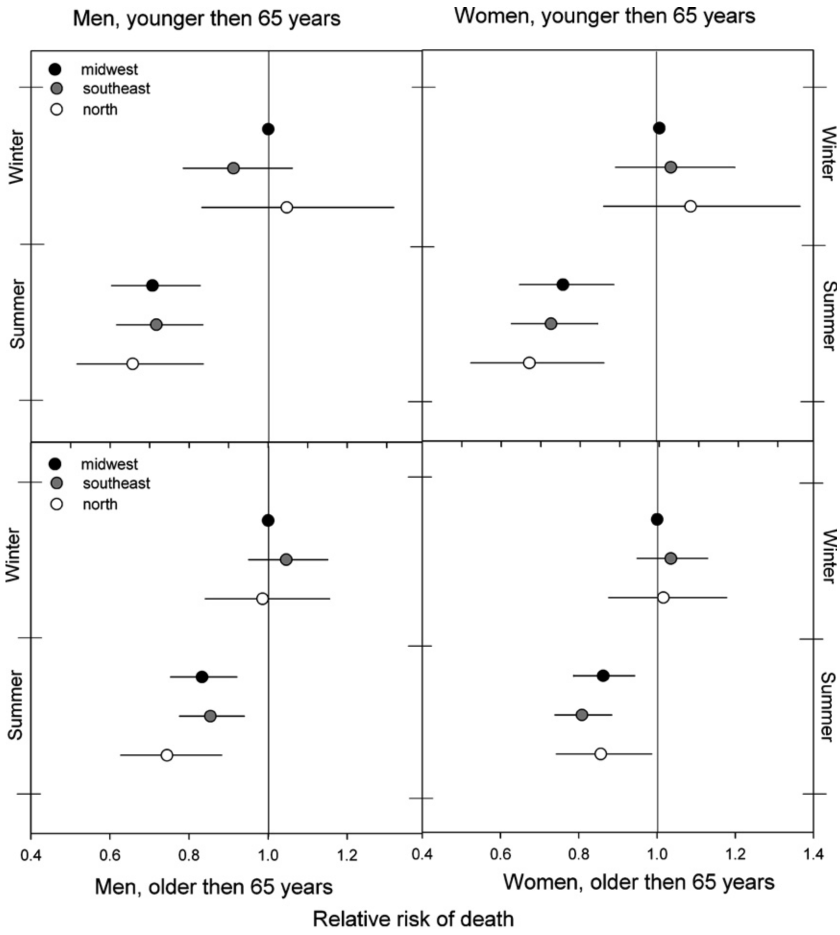

Fig. 5. Regional data for 3 years death rates after summer (June 1–November 30) and winter (December 1–May 31) diagnosis of colon cancer, but here subdivided into two age groups (⩽65 years, >65 years).

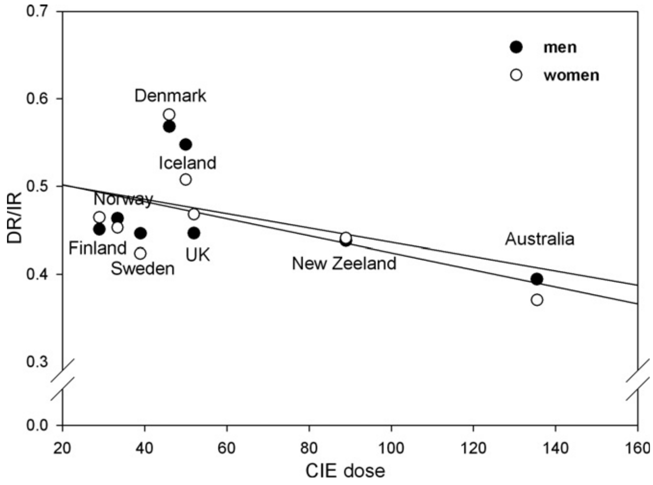

Fig. 6. The ratio of death to incidence rates of colon and rectum cancer for countries with Scandinavian or British origin as a function of annual CIE weighted UV exposure.

Table 1
Vitamin D intake in the three geographical regions (μg/day) [39]

	North region	Midwest region	Southeast region
Men (16–79 yo)	6.3	6	5.6
Women (16–79 yo)	4.5	4.1	3.8

physiological regulation mechanisms may make the fractional increase in 25(OH)D3 smaller than the fractional increase in vitamin D photosynthesis [41]. In agreement with this, levels measured in Denmark (for the winter) are not significantly higher than levels measured in Northern Norway [37].

The present findings are in agreement with the recently published seasonal variation of the fatality of cancers, including colorectal cancer, in the UK [21]. Furthermore, it has been estimated that a 25(OH)D_3 increase of 25 nmol/l would give 29% decrease in cancer mortality but only 17% decrease in cancer incidence [6]. This seems to indicate that high 25(OH)D_3 levels may improve cancer prognosis, in agreement with our data.

No data for cancer prognosis at different latitudes are known to us. However, from data on rates of cancer mortality and cancer incidence one can make a crude estimation. Considering only populations with mainly skin types I and II of Scandinavian or British origin, we have calculated the ratio of mortality rates to incidence rates of colon cancer. Fig. 6 shows that, in fact, there is a decrease in this ratio with increasing annual CIE weighted UV exposure, in agreement with our data.

A number of mechanisms for the significance of vitamin D for protection against carcinogenesis, as well as for cancer prognosis, have been proposed [42–44]. Evidence from cell experiments, animal experiments and epidemiological studies exist for anticarcinogenic action [45]. Our data indicate that cancer progression is inhibited by vitamin D or a derivative like 25(OH)D_3.

The main mechanisms of action of vitamin D metabolites on tumour development and progression are to inhibit proliferation and promote differentiation and apoptosis in numerous cell lines [46]. However, it is possible that 1,25$(OH)_2D_3$ is the only active metabolite, since colon cells may convert 25(OH)D3 to 1,25$(OH)_2$D3. However, significant correlations were shown between serum 25(OH)D_3 levels and epithelial cell proliferation kinetics after 6-month administration of calcium and supplemental dietary vitamin D_3 (400 IU) to patients with increased risk of colonic neoplasia [46]. Cell proliferation decreased as blood levels of 25(OH)D_3 increased, whereas no correlation was found between serum 1,25$(OH)_2D_3$ levels and epithelial cell proliferation [46].

Growth inhibition of colon cancer cell lines is attributable to cell cycle arrest [47]. Moreover, 1,25$(OH)_2D_3$ and its derivatives induce p53-independent apoptosis in both colon adenoma and carcinoma cell lines in a dose-dependent manner [47].

Vitamin D and its derivatives have also anti-invasion, antiangiogenic, and antimetastatic activities [48–51]. Thus, after administration of vitamin D derivatives, the frequency of metastases of chemically induced colon cancer in rats was reduced [48].

Alternative explanations of our cancer survival data should not be overlooked. Higher intakes of fruits and vegetables (notably during summer and autumn) might improve cancer prognosis through their content of antioxidants [52,53].

Moreover, alcohol consumption, which is considered to be one of the risk factors for colon cancer, is higher during winter time. This might affect survival negatively [54,55].

In conclusion we have shown that the prognosis of colon cancer in both sexes is dependent on season of diagnosis. This was true for two different age groups of patients, and for three regions of Norway, different with respect to ambient annual UV exposure, frequency of squamous cell carcinoma of the skin and intake of vitamin D_3. The seasonal effect was slightly larger for the youngest category of patients, but similar for men and women and for the different geographic regions.

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