Solar radiation, vitamin D and survival rate of colon cancer in Norway

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Abstract

Solar radiation contributes significantly to the status of serum calcidiol (25-hydroxyvitamin D3, 25-(OH)D3) in humans, even at the high latitudes of northern Norway. Thus, in late summer the serum concentration of calcidiol is roughly 50% larger than that in late winter, when the solar radiation in Norway contains too little ultraviolet radiation to induce any synthesis of vitamin D3 in human skin. This seems to influence the prognosis of colon cancer. We here report that the survival rate of colon cancer in men and women, assessed 18 months after diagnosis, is dependent on the season of diagnosis. A high serum concentration of calcidiol at the time of diagnosis, i.e. at the start of conventional therapy, seems to give an increased survival rate. This agrees with cell and animal experiments reported in the literature, as well as with epidemiological data from some countries relating colon cancer survival with vitamin D3 synthesis in skin. One possible interpretation of the present data is that, the level of calcidiol, or its derivative calcitriol (1α,25-dihydroxyvitamin D3, 1α,25-(OH)2D3), may act positively in concert with conventional therapies of colon cancer.

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1. Introduction

Cell experiments, as well as animal experiments and epidemiological studies, indicate that vitamin D3 can protect against cancer induction and/or slow down tumor progression [1–8]. In several countries on the northern hemisphere, the death and/or incidence rates of breast cancer, prostate cancer and colon cancer are larger in north than in south [9–16]. Several investigators have related this to vitamin D3, since solar radiation plays a significant role for the status of this vitamin [17].

Norway covers a large distance from north to south and the Norwegian population is relatively homogeneous, both with respect to ethnic origin and clothing and sun exposure habits. Thus, the country is well suited for epidemiological investigations of the relationship between solar radiation and cancer, as we have demonstrated for skin cancer [18–20].

The annual exposure to ultraviolet radiation (UV) is about 50% larger in the south than in the north [18]. This is the main reason for the three times larger incidence rates of skin cancer in the south than in the north.
In any case, the gradient of skin cancer incidence rates clearly indicates that not only the measured UV exposures, but also the exposures obtained by the population, are larger in the south than in the north. It is commonly believed that skin cancer is mainly induced by UVB radiation (280–315 nm) [21], and so is vitamin D3 [22]. Some investigations suggest that UVA may also play a role in the induction of skin cancer [23,24], although this issue is controversial.

In addition to the expected north-south gradient of vitamin D3 induction, there is a clear seasonal variation of the vitamin D3 metabolite calcidiol in Norway [25,26].

In the present work we have attempted to investigate the variation of vitamin D3 induction from north to south, as well as through the year, plays any role for the survival of colon cancer as determined 18 months after diagnosis.

2. Materials and methods

2.1. Calculation of vitamin D3 induction in skin

Since only the overall annual variation of vitamin D3 in Norway, and not specifically the fraction related to solar radiation, has been measured, we attempted to calculate this fraction, using the action spectrum of production of previtamin D3 from 7-dehydrocholesterol [27]. These calculations were compared with the measured annual variation of calcidiol in Norway and Denmark [25,26,28,29]. Calcidiol is present in the nanomolar range in human serum, and, since calcitriol, the active hormone in bone metabolism [17], is present only in the picomolar range, calcidiol is the vitamin D3 metabolite considered in most investigations, as in those cited in the present work [25,26,28,29].

2.2. Calculation of ambient solar UV

The erythema action spectrum [17,27,30] is often used to estimate the skin carcinogenic potential of solar radiation [18–20]. This spectrum is almost similar to the action spectrum we have used for previtamin D3 production. For comparison we have carried out calculations to determine north–south gradient also for erythemogenic exposures. This was done to estimate how dependent our calculations are on the choice of action spectrum. The details of the method of calculation have been described earlier [18–20].

2.3. Epidemiological approach

The epidemiological investigations were carried out as follows: The time points of diagnosis are grouped in four seasons: winter (1st of December–30th of February), spring (1st of March—31st of May), summer (1st of June–31st of August) and autumn (1st of September–31th of November).

The registration of patients was carried out via ID numbers. Since 1960, all Norwegian inhabitants have been assigned a unique personal identification number (11 digits) and recorded in The Central Population Register. This enabled us to register year of birth, living place, occupation, education and number of childbirths. The Cancer Registry of Norway has registered all cancer diagnosis since 1953 [8]. In the present work 12,823 men with colon cancer are included. The corresponding number for women is 14,922. All were born in the period 1900–1966. The period of observation is from 1964 to 1992. The relative death risks 18 months after diagnosis (RR) are given in relative numbers. A time as short as 18 months was chosen since the effect of therapy on the survival of cancer patients often decreases with time. Whenever seasons are compared, winter is normalized to RR = 1. The incidence rates for the same seasons are also shown. These are normalized so that one on the ordinate equals 25% of the annual rates. 95% confidence intervals are given. Since vitamin D3 synthesis decreases with age [26,31], only persons younger than 68 years at the time point of diagnosis are included.

3. Results

We found no significant annual variation of the incidence rates of colon cancer (Fig. 1(a) and (b)). In each season we found 25 ± 1.5% of the annual incidence rates. However, with respect to death rates, as measured 18 months after diagnosis, there was a clear seasonal variation, with the lowest death rates in the autumn (Fig. 1(a) and (b)). This was true for women (Fig. 1(a)) and for men (Fig. 1(b)). Thus, two parallel sets of data show the same trend. No significant north–south gradient was found for the death rate of colon cancer, neither for men nor for women.

The seasonal variation of calcidiol (25-(OH)D3) is strong in Norway as well as in Denmark (Fig. 1(c)) and in other countries. According to this figure, the maximal concentration of calcidiol is found in July–September and is about 50% larger than the base level of the winter. The time point of maximal measured calcidiol concentration occurs 1–2 months after the time point of calculated maximal induction of previtamin D3 by solar radiation (Fig. 1(d)). A north–south gradient in the production of previtamin D3 is expected (Figs. 1(d), 2). As estimated from Fig. 2, the annual production of previtamin D3 is about 40% larger in south Norway than in north Norway while the erythemogenic dose is about 30% larger in the south. Thus, for the present investigation the choice of action spectrum in the calculation is not crucial.
4. Discussion

There is a clear annual variation in the serum level of calcidiol in the Nordic countries (Fig. 1(c)) as in practically all countries where such measurements have been performed. In most studies, as in those cited here [26,28,29], the maximal calcidiol level is found in July–August. However, it should be noted that the time points of maximal calcidiol levels are different from investigation to investigation (Fig. 1(c)). Nevertheless, there is a lag-time of approximately one month between the time point of the maximal rate of synthesis of previtamin D₃ in the skin and the time point of appearance of the maximal amount of calcidiol in the serum. It is known that some time is needed for previtamin D₃ to be thermally isomerized to vitamin D₃, and that vitamin D₃ stays for some time in the skin before it is bound to D-binding proteins, transported in the blood to the liver and hydroxylated to calcidiol [17]. Surprisingly, the contribution of sun-induced vitamin D₃, as well as the average annual level of calcidiol, is similar in Tromsø and in Denmark, in spite of the large difference in latitude. Assuming a constant, basic level of calcidiol obtained from the food (≈50 nmol/l, Fig. 1(c)) and a latitude-dependent variation of sun-induced production as shown in Fig. 2, we can estimate that the annual mean of calcidiol should be 8–12% larger in Denmark and south Norway than in Tromsø. However, there are at least three mechanisms that contribute to make the difference smaller: First, while they stay in the skin both previtamin D₃ and vitamin D₃ are degraded by large sun exposures [22]. Second, regulatory mechanisms in the body may make the sun contribution of calcidiol smaller than that of vitamin D₃. Thus, after a large single exposure to UV radiation the concentration of previtamin D₃ was found to increase by a factor of 5 while that of calcidiol increased by only 50% [17]. Third, the intake of vitamin D₃ through the food may be larger in Tromsø (and generally in north Norway) than in south Norway and Denmark. According to report No. 30 of The Institute for Nutrition Research of Oslo University (1983), the intake of vitamin D₃ was 13% larger in north Norway than in the southern and mid-regions of Norway. This is certainly related to cod-fishing in the north. Unfortunately, we have no comparable data from Denmark. According to this, we should not expect to find any significant north–south gradient of the annual average of the vitamin D₃ status in Norway. This conclusion is supported by the similarity of the reported values of calcidiol in Norway and Denmark [25,26,28,29].
We found no north–south gradient for the 18 months survival of colon cancer in Norway. Neither did we find any gradient for the 36 months survival nor for the overall case fatality when the closing date of follow-up was date of death, migration from Norway or cut-off date of the follow-up study (31st of December 1992), with an average of 3.9 years [8]. Furthermore, there is no significant north–south gradient of incidence rates of colon cancer in Norway. In fact slightly below average relative incidence rates were reported for the northern regions of Norway and Sweden [32].

The present work shows a strong seasonal variation of the 18 months death rates of colon cancer in Norway (Fig. 1(a) and (b)). The lowest death rates were found for diagnosis in the autumn. The annual variation of the 18 months data was slightly larger than those of the 36 and 45 months (Fig. 1(a) and (b)). The latter data correspond to the over-all data (average follow-up 45 months) [8]. The annual variation of death rates clearly decreases with increasing observation times. This is not unexpected, since many forms of cancer therapy have a delaying effect on prognosis rather than a curative effect. Since the incidence rates are constant through the year, the seasonal variation of prognosis cannot be due to variations in the detection rates, i.e. to variations of the level of progression at the time point when diagnosis is made.

It is tempting to associate the good prognosis for colon cancer diagnosed in the autumn with the high calcidiol levels in the season (Fig. 1). This association is supported by a number of cell and animal experiments, as well as by epidemiological and clinical reports [1–7,14]. Clearly, the present data constitute no solid proof for the role of vitamin D3 in cancer progression, but should contribute to initiate further research. Other factors than vitamin D3 may play significant roles for colon cancer prognosis, and some of these might vary with the season. For instance, the intake of vegetables and fruit, which is known to reduce colon cancer risk [33,34], might be largest in summer and autumn. Alcohol intake is a risk factor [35] and may be highest in the winter season, notably during Christmas [36,37]. Finally, the level of physical activity may be lower in the winter than in summer. Physical activity is also considered a protective factor for colon cancer [38–40]. To our knowledge no investigation of the seasonal variation of the above mentioned factors (intake of fruits, vegetables, alcohol and physical activity) have been performed in Norway.

Calcitriol, rather than calcidiol, is known to be the vitamin D3 derived hormone that is involved in bone metabolism and calcium homeostasis [17]. Calcitriol was earlier believed to be formed mainly in the kidneys, but, in fact, is produced in a number of tissues [41]. However, its serum level is about one thousand times smaller than that of calcidiol and is quite tightly regulated [17]. Thus, an UV exposure leading to a five-fold increase of the serum level of vitamin D3, and a 50% increase of the level of calcidiol, gave only a minor increase of the level of calcitriol [17]. In view of the present data (Fig. 1) it should, therefore, be considered if serum calcidiol, rather than serum calcitriol, is the protective agent with respect to colon cancer progression. Calcidiol may act either directly [42,43] or by being hydroxylated to calcitriol in the tumors [44–46].

5. Abbreviations

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\begin{align*}
1\alpha,25-(OH)_2D_3 & \quad \text{calcitriol} \\
25-(OH)D_3 & \quad \text{calcidiol} \\
\text{ID numbers} & \quad \text{personal identification numbers} \\
\text{RR} & \quad \text{relative death risk} \\
\text{UV} & \quad \text{ultraviolet} \\
\text{UVA} & \quad \text{ultraviolet A (400–315 nm)} \\
\text{UVB} & \quad \text{ultraviolet B (315–280 nm)}
\end{align*}
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References


