

In: *Solar Radiation and Human Health*
Espen Bjertness, editor.
Oslo: The Norwegian Academy of Science and Letters, 2008.

Cancer prognosis depends on season of diagnosis

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Abstract

We have investigated the dependency of incidence rates and prognosis of breast-prostate,-colon-, lung cancer and Hodgkin lymphoma on the season of diagnosis. The incidence rates were constant throughout the year while the prognosis was best for cases diagnosed in summer and autumn. The advantage of summer and autumn diagnosis was largest for the youngest patients and slightly larger in the south than in the north of the country. A recent report from the UK is in full agreement with our work. We also determined the serum calcidiol level in persons hospitalized for a number of non – cancerous diseases, and found a seasonal variation, with highest summer levels. Other investigations in Scandinavia and in a number of other countries agree with our findings. We tentatively relate cancer prognosis with the calcidiol level in serum at diagnosis and therapy start.

Introduction

The total number of new cases of cancer per year in Norway has been steadily increasing since the Cancer Registry was established in the 1950s. The four most common cancer types are prostate-, breast-, colorectal- and lung cancer, accounting for over half of the total number of new cases (1). These cancer types are the ones contributing most heavily to the cancer mortality burden, being responsible for about a half of the number of deaths (1). Prognosis of these cancer forms is dependent on a number of variables: stage at presentation, age, gender and histological type are among the most important ones (2). A number of other modifiable factors like the dietary or environmental ones have been suggested to impact on cancer survival (3-5).

The first indication that environmental UV (ultraviolet) exposure may reduce cancer mortality was made by Apperly in 1941 (6). He observed that cancer patients living at low latitudes in USA had a lower mortality risk from internal cancers compared with those living in the north. Later, in 1980, Garland and Garland (7) analyzed the association between mortality rates of colon cancer and solar exposure and suggested that the inverse association was related to UV-induced vitamin D.

The sun is the most important source of vitamin D for humans even in the Nordic countries. UVB (ultraviolet B, 280 - 320 nm) exposure converts 7 dehydrocholesterol (7-DHC) in skin to previtamin D₃, which isomerizes to vitamin D (8,9). Vitamin D₃ binds to D-binding protein, and is transported to the liver, where hydroxylation to 25-hydroxyvitamin D₃ (calcidiol) takes place. Calcidiol is regarded to be a reliable measure of the vitamin D status (10). Calcidiol is further hydroxylated to 1,25- dihydroxyvitamin D₃ (calcitriol) in the kidney.

Calcitriol is the main hormone involved in maintenance of physiological calcium levels, and acts by activating specific receptors in the bone, kidney and the gut (VDR, vitamin D receptor) (9). Beyond these effects, calcitriol has a proven antiproliferative and pro – differentiating action on a broad spectrum of cells (11,12). Nearly all cell types express VDR, and are, therefore, able to respond to calcitriol activation. In vitro studies demonstrate that the active concentration of calcitriol needed for 50 % growth inhibition exceeds the physiological serum calcitriol concentration (11). For some cell types, more sensitive to calcitriol, the serum concentration of calcitriol may be high enough to activate the VDR, while other cell types may produce locally calcitriol from the more concentrated precursor, calcidiol. In vitro studies have convincingly shown the presence of 1 α hydroxylase (the enzyme that catalyses the conversion of calcidiol into calcitriol) in a number of cell types. Therefore, circulating calcidiol may be even more important than those of calcitriol in mediating the anti – cancer effects. The serum calcidiol level is affected by a number of factors like: the level of UVB reaching the ground (variable with latitude, season and time of the day) (13); skin color (14,15), age (16), BMI (17,18). In Norway, located at 60 – 70° N, season is the main factor influencing the calcidiol production. In contrast, skin color is not a key factor since the population is homogenous with an absolute majority of white Caucasians.

In the present paper we present a synopsis of our epidemiological studies on the seasonal variation of cancer prognosis in Norway.

Materials and methods

All cases of breast, prostate, colon and lung cancer and Hodgkin lymphoma diagnosed during the period 1960 -2000 were identified. The study design and methods are described elsewhere (19,20). The eligible population for the study consisted finally of 183 387 individuals.

In the present study design we did not have the possibility to measure the calcidiol levels at the time of cancer diagnosis. Therefore, we used a proxy measure of the vitamin D status, namely the season of diagnosis. For this purpose, we grouped our patients in two categories: 1) patients diagnosed during summer and autumn (June 1 to November 30) and 2) patients diagnosed during winter and spring (December 1-May 31). Ultimately, we compared the two groups in terms of survival.

The relative risks of death 36 months after diagnosis was computed and compared using the Cox regression model in SPSS (SPSS 13, Inc. USA). Mortality during winter and spring (when calcidiol in the serum is at a minimum level) was set to 1. In the analyses we included a number of variables that affect prognosis like: stage of disease, age at diagnosis and sex.

Results and discussion

Our results can be summarized as follows: patients diagnosed with prostate-, breast- and colon cancer and Hodgkin lymphoma have a 15 – 25 % higher chance to survive for 36 months if they were diagnosed during summer and autumn (19-24). For lung cancer patients there seems to be no seasonal difference in survival (23). We further analyzed if age at diagnosis influences the seasonal pattern. According to the specific age pattern of the cancer forms investigated, we considered the following age threshold: 50 years for breast- and lung cancer (23,24), 65 years for colon- and prostate cancer (21) and 30 years in the case of Hodgkin lymphoma (19).

Our results show that age modulates the seasonal variation of cancer prognosis. Young patients diagnosed with breast, prostate and colon cancer have a higher amplitude of the seasonal effect compared with old patients (21,24). In the case of lung cancer, a seasonal effect becomes apparent for the young patients (23). The strongest effect of age is observed in the case of Hodgkin lymphoma (19). Patients below 30 years at the time of diagnosis have a 50 % reduced risk of dying from cancer if diagnosed during summer and autumn.

We hypothesize that the seasonal variation found in cancer prognosis can be explained by the variation in the vitamin D levels. A review of the Scandinavian

studies investigating the seasonality of serum calcidiol concentrations indicates that the summer values are 10-100 % higher compared with the winter values (25-38). A high level of calcidiol at the time of cancer diagnosis may act in conjunction with standard treatments, resulting in improved survival. The influence of age on the seasonal pattern supports our theory, since vitamin D synthesis in skin is age-dependent. Holick et al showed that a given UVB dose induces 4 times more serum calcidiol in a young population (20-30 years) compared with in an older population (62-80 years) (39) and that the epidermis content of 7 dehydrocholesterol decreases drastically with age (16). Moreover, elderly are likely to be housebound, and, therefore, less sun - exposed than young people.

Recent in vitro and in vivo studies have provided evidence for a biological explanation and a support of our hypothesis. Breast-, prostate-, colon-, lung and lymphoma malignant cells have both VDR receptors and the capability to convert systemic calcidiol into calcitriol. When activated by the vitamin D ligand (calcidiol, calcitriol or an analog) the VDR induces the vitamin D responsive genes (11). The consequence of this activation is a down – regulation of DNA replication genes, angiogenesis genes and an up – regulation of genes controlling apoptosis and cell adhesion (11).

Our data are supported by a number of epidemiological studies of large cancer populations. A number of authors have used either season of diagnosis or latitude as a proxy measure of the sun – induced calcidiol level. Lim et al (40) studied cancer prognosis in a population of over 1 million cancer patients diagnosed in the UK and showed the same seasonal pattern as ours. In USA, lung cancer patients receiving surgical treatment during summer and autumn had a 50 % higher recurrence - free survival probability compared with cases diagnosed during winter (41). Breast cancer densities (42) and levels of PSA (prostate specific antigen, a biochemical marker of malignant transformation of prostate tissue) have a seasonal pattern of variation (43).

All these published studies, along with clinical investigations showing a negative correlation between calcidiol levels and cancer risk, constituted the background for intervention with vitamin D analogs in cancer patients. The possible toxicity of administration of high concentrations of calcitriol remains an issue not easy to circumvent. A possible approach is the one patented by Beer et al (44,45), in which high doses of calcitriol (45 microg) are administrated weekly per os in combination with docetaxel (standard treatment for androgen-independent prostate cancer). The group reported significantly reduced hazard ratios and increased median survival for patients that had calcitriol in the treatment. In the mean time, hypercalcemia was a minor complication. Authors suggested that calcitriol level, which rises immediately after administration at concentrations approximately 1000 higher than physiological, revert to the base

level within 2-3 days, thus not allowing for hypercalcemia to occur (personal communication).

The same administration pattern was recently tested by Fakhri et al (46) in a phase I clinical trial in which high dose calcitriol was administered intravenously every week in combination with oral gefitinib (standard chemotherapy). Authors reported hypercalcemia in one out of seven patients that received doses of 74 µg/week. Another clinical approach is the administration of high doses of vitamin D (cholecalciferol), the precursor of both calcidiol and calcitriol. This idea was used by Molnar et al (47) in the treatment of myelodysplastic syndromes. The authors administered vitamin D in doses of 2000 – 4000 IU/day for 12 months. No hypercalcemia was reported, calcidiol levels doubled during treatment but no clinical response on the myelodysplastic syndrome was reported.

Our epidemiological observations suggest the usefulness of calcidiol in cancer treatment. From our studies we can not conclude if calcidiol is the primordial ligand for the VDR or if it is converted to calcitriol in the cancer cells. Our studies indicate that an increase in the calcidiol level that is equivalent with the summer-winter difference (from 6 -50 nmol/L in a series of Scandinavian investigations (25-38)) may result in a 15-25 % increased survival from cancer.

Since solar UV is a natural source of vitamin D, we are now testing the efficiency of different UV - doses and sources in inducing a certain level of calcidiol. Sun beds can provide substantial amounts of vitamin D. Even the so-called UVA sun beds are good sources of vitamin D, since they emit some UVB which is orders of magnitude more efficient than UVA both with respect to vitamin D photosynthesis and melanogenesis (13,48).

Conclusion

An adequate vitamin D level may improve survival from major cancer types: prostate-, breast-, colon-cancer, lymphomas. The action mechanisms of vitamin D seem to be related to its antiproliferative and cell-differentiating effects.

We find that the calcidiol level in Scandinavia is 10 – 100 % higher in summer than in winter, and believe this may contribute to the improved survival of a number of cancer forms if treatment is started in the season of high calcidiol levels.

There are mainly two ways to increase the calcidiol level: either by providing its precursor, vitamin D (cholecalciferol) from food or supplements, or by exposure to UVB from sun or sun beds.

Most of the annual 250 cases of death of skin cancer in Norway are due to sun exposure. Nevertheless, one should consider the total health advantages of carefully increased overall sun or sun bed exposure, notably for old persons and immigrants with dark skin and for persons who rarely expose their skin to solar radiation. This may also be an interventional approach in cancer therapy.

Acknowledgements

The present work was supported by Sigval Bergesen D.Y. og hustru Nankis Foundation, by The Research Foundation of The Norwegian Radiumhospital and Helse Sør Health Enterprise.

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