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# Seasonal variations of cancer incidence and prognosis

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The overall death rates are highest in the winter season in many countries at high latitudes. In some but not all countries, this is also true for more specific diseases such as cancer, cardiovascular diseases and influenza. For internal cancers we find no consistent, significant seasonal variation, neither of incidence nor of death rates. On the other hand, we find a significant seasonal variation of cancer prognosis with season of diagnosis in Norway. Best prognosis is found for summer and autumn diagnosis; i.e., for the seasons of the best status of vitamin D in the population. There were no corresponding seasonal variations, neither of the rates of diagnosis, nor of the rates of death which could explain the variations of prognosis. The most likely reason for this variation is that the vitamin D status in Norway is significantly better in summer and autumn than in winter and spring. Earlier, seasonal variations have been explained by circannual variations of certain hormones, but the data are not consistent.

## Introduction

Incidence, as well as prognosis, of several types of cancer seem to be related to the vitamin D status. Thus, most case-control epidemiological studies indicate that a high intake of vitamin D reduces the risk.[1-5] Furthermore, several studies of the relationship between 25-hydroxyvitamin D [25(OH)D] concentrations in serum and risk of cancer show low risks for groups with high 25(OH)D levels.[6,7]

Several of these studies may suffer from weaknesses, the most important one being that the "latency" time for internal cancer is likely to be long. Thus, vitamin D consumption and photosynthesis, as well as serum 25(OH)D levels 10–25 years prior to cancer diagnosis, may be more important than those immediately before detection.[8]

Ecological studies are stronger on this point, being based on the fact that photosynthesis in skin is the most important source of vitamin D. Several studies seemingly show that there is a correlation of latitude with internal cancer incidence- or death rates. Under otherwise similar conditions, the annual vitamin D photosynthesis increases by about 50% per 10° decrease in latitude.[9,10] That solar radiation may lower cancer risk was first proposed in 1937.[11] An inverse association between latitude and cancer mortality was found in 1941.[12] Garland and Garland[13] verified this for colon cancer, a finding later confirmed by several other investigators.[14-17] Living in a rural area, as well as migrating southwards,[6] reduces the risk.[7,18]

In a prospective study it was found that low levels of vitamin D may be associated with increased risk of both incidence and mortality.[7]

Norway is a country stretching over a long south-north distance (58–71 N) and with a homogeneous population with respect to skin type and ethnicity. Hence, we decided early in the 1990s to look for latitude gradients of incidence and death rates of common cancers. No such gradients were detected, which was later found to be due to a larger consumption of vitamin D-rich food in the north,[9,19] almost exactly balancing the lower annual vitamin D synthesis by the sun.[9] Since vitamin D levels vary with the season, we decided to study seasonal variations of cancer prognosis, incidence and death rates.

## Results and Discussion

Together with researchers from the Norwegian Cancer Registry, we were the first to investigate the variation of cancer prognosis with season of diagnosis.[21] A better prognosis for cases diagnosed in summer and autumn than in winter and spring was found. This was attributed to the seasonal variation of serum 25(OH)D levels, although contributions from other factors were not excluded. The work was continued, and the findings were confirmed for several types of cancer.[19,20,22-25] In most investigations we found no latitudinal gradient, although for breast cancer and lung cancer a small but not significant gradient was seen.[24,25]

Cutaneous, malignant melanoma (CMM), is a special case, since this cancer is likely to be caused by sun exposure, notably by erythemogenic exposures. As expected, the number of diagnosis was lowest in the months of vacation (July, December) but also for CMM the fatality was lowest for patients diagnosed in the summer season.[26]

Our findings are supported by a similar, recent large investigation in the UK[7] and one from USA.[28] The UK investigators later found that the seasonal variation in prognosis became smaller

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when they adjusted for the generally higher mortality in winter.[29] However, a reduced mortality among women diagnosed with breast cancer in the autumn was still observed.

It has been estimated that an increment of 25 nmol/l in serum 25(OH)D would give a 17% reduction in total cancer incidence and a 29% reduction in total cancer mortality.[7] The fact that the reduction in mortality is larger than that in incidence, indicates that a high 25(OH)D level leads to decreased fatality, as suggested by our data,[9,21,23,24] and the magnitude of the reduction is similar to what we can estimate, using a summer 25(OH)D level throughout the year and assuming that the overall prognosis to be as good throughout the year as found for summer diagnosis, i.e., 20–30% better than for winter diagnosis.

Consistent with our data the five-year case-fatality from colon cancer seems to decrease with latitude in the US population,[30] and the odds ratio for 25(OH)D in serum samples taken in winter and spring had a stronger inverse correlation with colorectal adenomas than did those taken in summer and fall.[31]

The interaction of dietary intake of vitamin D and photosynthesis remains largely unknown. In an attempt to elucidate this problem we extended our first study of colon cancer[9] and divided 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 intake in the population.[20] Since photosynthesis of vitamin D decreases with age, we also investigated different age groups. Attention was paid to frequencies of vacation to southern latitudes and sex differences. We verified that calculated and measured annual UV exposures[9,20] are relevant for real exposures by studying the incidence rates of squamous cell carcinomas of the skin in each of the three regions.

Recently, Holmberg et al. studied the prognosis of breast and prostate cancer and found that for these cancers there was a higher hazard ratio of death for persons diagnosed in the summer, notably in July–August.[32] The time point of this high hazard ratio coincided with a low mean number of diagnosis and a high proportion of advanced cases diagnosed in the summer. Thus, the high hazard ratio was attributed to late presentation, leading to poor prognosis. We tried to look for a similar relationship in our data, but did not find it.[22] As exemplified in the case of colon cancer in Figure 9 in ref. 22 there are small dips in the incidence numbers in July and December (vacations), but no corresponding time points of poor prognosis. In fact the opposite is found: A surprisingly good prognosis for December diagnosis. If the diagnostic rate had been constant throughout the year, the prognosis for December diagnosis would have been even better than shown in our work.[22] We have no explanation for the delay between maximal vitamin D status (July–August) and time point for diagnosis leading to optimal prognosis (November-December, Fig. 9 in ref. 22). We have proposed that the following factors might play roles: seasonal variations of vitamin D intake, rapid winter worsening of the vitamin D status, generally poor health around mid winter (influenza etc.), high intake of fat food around Christmas diluting vitamin D and long-term storage of active vitamin D metabolites in the body. Neither can circannual variations of hormonal status be ruled out. Such factors were proposed to explain seasonal variations of prognosis of breast cancer.[33,34] In these early investigations patterns different from ours was found: Longer survival for spring–summer diagnosis in Australia[34] and for October–June diagnosis in Finland.[33]

The role of vitamin D status for prostate cancer has been studied in Finland[35] and in Norway.[36] In Finland both high (above 80 nM) and low (below 19 nM) vitamin D levels in serum were associated with higher risk. In Norway medium (50–80 nM) and high (above 80 nM) levels were significantly related to better prognosis. Both of these studies support a positive role of vitamin D, but they cannot be directly compared since one study concerns risk and the other one concerns prognosis.

In summary, the Norwegian data support a positive role of vitamin D for cancer prognosis. The prognosis is best for summer and autumn diagnosis and therapy start i.e., for time points of optimal vitamin D status.

## Materials and Methods

The methods of acquiring data on cancer incidence rates, death rates and prognosis from The Cancer Registry of Norway, for the vitamin D status in different seasons within Norway and the statistical methods we used have also been described.[9,20,21]


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