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Vitamin D and cancer

ABSTRACT
Vitamin D, a fat-soluble prohormone is synthesized in response to sunlight. Experimental evidence suggests that vitamin D may reduce the risk of cancer through regulation of cellular proliferation and differentiation as well as inhibition of angiogenesis. These anticancer properties have been attributed primarily to 1,25-dihydroxyvitamin D [1,25(OH)2D] (calcitriol), the hormonal form of vitamin D. Extensive research has shown that cells, including cancer cells, express specific receptors (VDR) for 1,25-dihydroxyvitamin D. When bound to the VDR, 1,25-dihydroxyvitamin D regulates >60 genes that exert prodifferentiating, antiproliferative and antimetastatic effects on cells, including effects on cell cycle. The amount of exposure to the sun has been found to correlate inversely with cancer mortality and survival in numerous epidemiological studies. An inverse relationship between solar ultraviolet-B (UV-B) exposure and non-skin cancer mortality has long been reported. Several ecological studies suggest that sunlight may protect against prostate, colon, rectal, female breast and ovarian cancer, all diseases that contribute to a substantially higher proportion of cancer mortality in the western industrialized world. Some analytical studies also suggest a protective association between circulating vitamin D in blood, which is largely derived from sunlight, or dietary vitamin D. Paricalcitol (calcitriol analogue) is as effective as 1,25-dihydroxyvitamin D in transactivating the prostatic VDR and in inhibiting the growth of prostate cancer cell lines and primary cultures of prostate cancer cells in vitro. Promising preclinical evaluations of calcitriol and analogues have appeared in prostate cancer animal models.

KEY WORDS: Cancer, vitamin D

Vitamin D refers to a group of fat-soluble prohormones as well as to the metabolites and analogues of these substances. Two major forms of vitamin D are D2 (or calciferol) and D3 or cholecalciferol. Vitamin D3 is produced in skin exposed to sunlight, specifically ultraviolet-B (UV-B) radiation. The primary source of vitamin D for most people in temperate climates, particularly people with light-colored skin, is solar UV-B exposure.[1]

Vitamin D synthesized in response to sunlight undergoes hydroxylation in the liver to 25-hydroxyvitamin D (calcidiol) and then in the kidney to form the physiologically more active metabolite 1,25-dihydroxyvitamin D (calcitriol), the hormonal form of vitamin D.

A better indicator of Vitamin D status is plasma 25(OH)D because it is determined not only by the amount of skin exposure to ultraviolet (UV) light and the quantity of vitamin D consumed through foods and supplements but also by the body’s ability to produce cholecalciferol in the skin and to hydroxylate the cholecalciferol obtained from cutaneous sources and food in the liver.

Plasma levels of 25(OH)D usually range between 10 and 50 ng/ml. In contrast, 1,25(OH)2D acts as a hormone to increase calcium absorption, and plasma levels are regulated at 30 pg/ml to ensure calcium homeostasis.[2]

ANTICANCER MECHANISM
Experimental evidence suggests that vitamin D may reduce the risk of cancer through regulation of cellular proliferation and differentiation and inhibition of angiogenesis. These anticancer properties have been attributed primarily to 1,25-dihydroxyvitamin D [1,25(OH)2D]. However, evidence now suggests that this conversion can be done in other tissues, including the colon, raising the possibility that anticancer effects may also be directly attributed to 25(OH)D.[2]

Extensive research has shown that cells, including cancer cells, express specific receptors (VDR) for 1,25-dihydroxyvitamin D. When bound to the VDR, 1,25-dihydroxyvitamin D regulates >60 genes that exert prodifferentiating, antiproliferative, and antimetastatic effects on cells, including effects on cell cycle.[3]

Vitamin D, acquired primarily through exposure to the sun via the skin, is believed to inhibit tumor development and growth and reduce mortality for certain cancers. It is well established that exposure to sunlight contributes to non-melanoma skin cancer.[1,2]
The amount of exposure to the sun has been found to correlate inversely with cancer mortality and survival in numerous epidemiological studies. An inverse relationship between solar UV-B exposure and non-skin cancer mortality has long been known.[1] Several ecological studies suggest that sunlight may protect against prostate, colon, rectal, female breast, and ovarian cancer, all diseases that contribute to a substantially high proportion of cancer mortality in the Western industrialized world. Some analytical studies also suggest a protective association between circulating vitamin D in blood, which is largely derived from sunlight or dietary vitamin D, and colorectal and prostate cancer.[2]

DEFICIENCY OF VITAMIN D AND RISK OF CANCER
Prostate cancer is the most prevalent (nonskin) cancer among American men and the second most fatal, accounting for >30,000 deaths in 2005. Mortality rates from prostate cancer are inversely related to the levels of UV radiation, the major source of vitamin D.[3]

Vitamin D deficiency could be a risk factor for prostate cancer. It was thought that vitamin D could maintain the differentiated phenotype of prostatic cells and in the presence of low levels of vitamin D, subclinical prostate cancer may progress to clinical disease. This hypothesis was supported by two separate retrospective analyses that measured vitamin D levels in stored sera and showed that mean calcitriol levels were lower in patients who later developed prostate cancer compared with age-matched controls.[4]

The hypothesis that vitamin D may help to prevent colorectal cancer originated with the observation that colon cancer death rates were lowest in the states with the highest mean solar radiation. Epidemiologic research has focused on vitamin D intake from foods and supplements. Among the prospective studies, a 67% lower risk of colorectal cancer was found among women in the highest quintile of consistent vitamin D intake over time. Colorectal cancer is the second leading cause of death in the United States.[2,5]

VITAMIN D AND ITS ANALOGUES
Promising preclinical evaluations of calcitriol and analogues have appeared in prostate cancer animal models. The principal toxicity of calcitriol as an anticancer drug is hypercalcemia. The calcitriol analogue, 19-nor-1-25-dihydroxyvitamin D2 (paricalcitol, Zemplar), was approved by the Food and Drug Administration for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure. Paricalcitol is as effective as 1,25-dihydroxyvitamin D in transactivating the prostatic VDR and in inhibiting the growth of prostate cancer cell lines and primary cultures of prostate cancer cells in vitro.[2,3]

This review details the effect of sunlight and vitamin D and its analogues on cancer; particularly prostrate and colorectal cancer.

MATERIALS AND METHODS
To explore whether mortality from various cancers was associated with exposure to sunlight various surveys were conducted in United States of America.

Survey
Death certificate-based survey
A death certificate-based case-control study of mortality was conducted by Freedman et al.[6] into five cancers: female breast, ovarian, colon, prostate, and non-melanoma skin cancer (as a positive control) to examine associations with residential and occupational exposure to sunlight. Cases were all deaths from these cancers between 1984 and 1995 in 24 states of the United States. Controls, which were age frequency matched to a series of cases, excluded deaths from cancer and certain neurological diseases. Multiple logistic regression was used in a model that included age, sex, race, residential exposure to sunlight (based on region), socioeconomic status, occupational exposure to sunlight, and physical activity (the last three based on usual occupation).

Residential exposure to sunlight was assessed by state residence and birthplace recorded on the death certificate. Occupational exposure to sunlight was based on the usual occupation (as reported by next of kin) in the death certificate and classified by an industrial hygienist into four categories: indoor work, work that combined indoor and outdoor work, outdoor work by non-farmers, and farming (analyzed with dummy variables). Farmers were categorized separately because several studies have suggested that farmers are at increased risk of prostate and other cancers. Those with unidentified occupations or positions that could not be classified were controlled for separately. Occupation was also used to assess socioeconomic status.[6]

Database survey
Cancer incidence and mortality were measured by Boscoe et al.[6] at the county level, using incidence data from the North American Association of Central Cancer Registries’ CINA Deluxe file and mortality data from the National Cancer Institute’s SEER*Stat database. The data consist of approximately 3.1 million incident cancer cases and 3.1 million cancer deaths among white non-Hispanics and 300,000 incident cancer cases and 400,000 cancer deaths among blacks for 32 cancer sites (blacks, with limited sensitivity to geographic variation in solar exposure, serve as a useful comparison group). The included cancer sites were those with at least 4000 incident cases and 4000 deaths, excepting lung cancer as it was used as the basis for adjusting for smoking. Data were stratified
by sex, race/ethnicity, and 10-year age groups, from 35-44 through 85+.[1]

**Patient selection and control**
Safety and efficacy of vitamin D and its analogues was assessed by administering vitamin D in patients suffering from prostrate and colorectal cancer. The patients were selected for the study using the following criteria:

For colorectal cancer
Feskanchor et al. [2] selected 121,700 female participants aged 30-55 years at study initiation in 1976. A mailed questionnaire was sent to participants every 2 years on which they were asked to report disease diagnoses and various characteristics and behaviors that are potential risk factors for cancers and other chronic diseases. Two controls were randomly selected for each case from among the pool of women who had not reported any noncutaneous cancer diagnosis.

Dietary information was first collected in 1980 with a food frequency questionnaire and was updated in alternate follow-up cycles. Blood samples were provided by 32,826 participants, aged 43-70 years, from June 1989 to 1990. The samples were collected in tubes with heparin and sent to us by overnight courier in chilled containers. On receipt, the blood samples were centrifuged, aliquoted, and stored in liquid nitrogen freezers at −70°F.[2]

Wactawski et al. [3] conducted a randomized, double blind, placebo-controlled trial involving 36,282 postmenopausal women, 50-79 years of age, from 40 Women's Health Initiative centers. The protocol and consent forms were approved by the institutional review board at each participating institution. From the group of participants who were free of colorectal cancer, 317 control women were randomly selected. All women provided written informed consent.[4]

For prostate cancer
Lui et al. [4] and Schwartz et al. [5] considered men with confirmed adenocarcinoma of the prostate as having advanced androgen-insensitive disease. If the patients did not have measurable disease but had bone scan abnormalities, a serum PSA > 10 ng/ml was required for inclusion. All patients signed informed consent forms before registration.

**Dose administration and study of toxicity**
For colorectal cancer
Among the 36,282 participants, 18,176 were randomly assigned to receive one tablet of 500 mg of elemental calcium as calcium carbonate combined with 200 IU of vitamin D3 twice daily and 18,106 to receive an identical-appearing placebo tablet twice daily.[2, 5]

For prostate cancer
Eligible patients were given 12.5 µg of 1-OH-D2 (five each of 2.5 µg capsules) continuous once a day p.o. before their a.m. meals. Any grade = “3 toxicity (excluding anemia and alopecia) that was considered to be related to the drug required withholding the drug until the toxicity resolved to < = “2. If the toxicity did not improve to grade < = “2 within 14 days of stopping the drug, the patient was removed from the study.

Dose escalation trial, with paricalcitol doses starting at 5.0 µg (3.0 µg/m²) i.v. thrice per week and escalating at 5.0-µg intervals to 25.0 µg (15.0 µg/m²). Toxicity was assessed after 4 weeks. If no grade 4 toxicities were observed, treatment continued for up to 12 weeks. Dose escalation was not allowed until resolution of any grade 3 toxicity. A complete response was defined as disappearance of all known disease during two observations at least 4 weeks apart, during which no new lesions develop. Samples were immediately stored at 4°C until centrifugation, when the top 1 ml of plasma was isolated and frozen at 70°C in NUNC tubes. These samples were later analyzed for TGFβ1 using a 96-well plate quantitative sandwich immunoassay.[3, 4]

**Evaluation**
For colorectal cancer
All data used in statistical analyses were collected on NHS questionnaires prior to or at the time of the blood draw. 25(OH)D and 1,25(OH)2D concentrations were measured by radio immune assay (RIA) and chemiluminescent radioimmunoassay system. Twenty-one masked triplets of quality control samples from pooled plasma sources were interspersed among the case and control samples.

Serum 25-hydroxyvitamin D levels were measured using 25(OH)D. Comparison of serum 25-hydroxyvitamin D levels in 227 women in the group given calcium with vitamin D and 221 women in the placebo group revealed that the levels were 28% higher in the supplement group.[25]

For prostate cancer
The primary outcome was prostate-specific antigen (PSA) response, defined as a 50% decrease in PSA with confirmatory consecutive measurement at least 4 weeks apart. PSA was assessed monthly. Secondary outcomes were changes in intact serum parathyroid hormone (PTH), evaluation of hypercalcemia, Ca × P product, other toxicities, and survival. Progression was defined as a 50% increase in serum PSA or the appearance of a new metastatic lesion at any site.

Only patients completing 8 weeks of therapy were considered evaluable for response. Evidence of progression after 8 weeks was considered a treatment failure. Changes in performance status, PSA, and weight were noted but not used as response criteria. A complete response was defined as disappearance of all known disease during two observations at least 4 weeks apart, during which no new lesions developed.[34]

**RESULTS AND DISCUSSION**
Although sunlight and vitamin D have been positively
associated with non-melanoma skin cancer, ecological studies suggest that sunlight may protect against female breast, ovarian, prostate, and colon cancer. The high prevalence of vitamin D deficiency, combined with the discovery of increased risks of certain types of cancer in those who are deficient, suggest that vitamin D deficiency may account for several thousand premature deaths from colon, breast, ovarian, and prostate cancer annually.

The study by Freedman et al. improved ascertainment of exposure over ecological studies by using individual data on occupation, state of birth and residence at death, socioeconomic status, and physical activity. Inverse associations between both residential and occupational exposure to sunlight and mortality from female breast and colon cancer, which were independent of physical activity on the job was found. Although mortality from ovarian and prostate cancer was inversely associated with residential exposure to sunlight, they were not consistently associated with occupational exposure to sunlight. As expected, a positive association was found between mortality from non-melanoma skin cancer (our positive control cancer) and residential and occupational exposure to sunlight.

Although the study also benefited from the many cases in this data set, death certificate studies such as this, have recognized limitations. These include potential misclassification on the underlying cause of death, occupation and residential exposure (where a lifetime residential history is unavailable), as well as lack of information on other sources of exposure to sunlight, such as leisure activities. Also, death certificates require reliance on crude information, such as usual occupation, for measures of socioeconomic status and physical activity and cannot assess physical activity unrelated to occupation. Thus, there is no independent source of information on socioeconomic status and occupational physical activity and no assessment of recreational physical activity.

Boscoe et al. tried to relate cancer incidence and solar UV-B exposure on a population basis. In so doing, much of the previous research on the relationship between solar UV-B exposure and cancer mortality was corroborated. It was found that there was at least some evidence of an inverse association for 19 cancer sites and no evidence of an association for 8 sites. Five other sites were found to be positively associated with solar UV-B. Ten sites showed strong evidence of an inverse association with solar UV-B exposure: bladder, colon, Hodgkin’s lymphoma, myeloma, other biliary, prostate, rectum, stomach, uterus, and vulva; with two other sites showing this relationship for only one sex (males: esophagus; females: gallbladder). Weaker evidence of an association was seen for six sites (female breast, kidney, leukemia, non-Hodgkin’s lymphoma, pancreas, and small intestine), as well as for female esophagus, male gallbladder, and female thyroid. No evidence of a relationship was seen for eight sites (bone and joint, brain, larynx, liver, miscellaneous sites, nasal cavity, ovary, and soft tissue) as well as for male thyroid. Solar UV-B exposure was positively associated with five sites of cancer (anus, cervix, melanoma, oral cavity, and other skin cancers).

The largest effects were seen for female gallbladder cancer, with nearly doubling of risk for both incidence and mortality; uterine cancer, with about a 50% elevated risk; and stomach cancer, with about a 30% elevated risk. For blacks, there was some evidence of association with solar UV-B exposure, but with great inconsistency between sexes and between incidence and mortality for given sites. The only site with elevated relative risks for living in the northern versus southern United States, that were consistent for both males and females, and for both incidence and mortality, was esophagus, with relative risks in the 1.3 to 1.5 range. Evidence of a north-south gradient was also seen for bladder, colon, kidney, larynx, myeloma, and pancreas for females only and for liver in males only. Female breast cancer was also higher in the north than in the south among blacks, with relative risks of 1.15 (95% confidence interval: 1.11 to 1.19) for incidence and 1.11 (95% CI: 1.06 to 1.16) for mortality.

The differences between incidence and mortality were found to be related to solar UV-B exposure. Several recent studies that focused on the time of diagnosis and death concluded that vitamin D levels are more relevant to disease progression than disease onset. In these studies, little or no pattern was seen in the season of diagnosis (except for a reduction during major holidays, when the level of non-emergency care is reduced), but a strong association was found with the season of death, with death rates higher in the winter months when circulating vitamin D levels are at a minimum. Thus, it may be that one’s overall risk of contracting colon cancer may be moderately influenced by reduced solar UV-B exposure (with an increased risk of 10% to 15% in the northern vs southern United States), while the risk of dying from the disease is more strongly related to reduced solar UV-B exposure (with an increased risk of 25% to 30%).

Finally, this being an ecologic study, all of the usual limitations of an ecologic study apply. The ecologic adjustments that were made for smoking, outdoor occupation, particulate matter, and so on were not optimal, relying on proxy measures, survey data, spatial interpolations, and other imperfect instruments.

In the case-control analysis by Feskanich et al., nested within the NHS cohort of women, it was observed that a statistically significant inverse dose-response relationship existed between plasma 25(OH)D and subsequent risk of colorectal cancer; the risk was 46% lower among the women in the highest vs lowest quintile of 25(OH)D. The benefit was significant for cancers of the rectum and distal colon, whereas there was little evidence that 25(OH)D was associated with a lower risk of cancer of the proximal colon.

The inverse association between 25(OH)D and risk of colorectal
cancer was evident only among the women residing in areas with higher available levels of UV light from the sun. Although plasma 25(OH)D concentrations were positively associated with the amount of UV light available, differences in 25(OH)D between low and high UV groups were too small to account for this difference in association with colorectal cancer risk.

Age seemed to modify the observed association between 25(OH)D and colorectal cancer, being significantly inverse among women of 60 years but null among younger women. Genetic factors in the development of colorectal cancer may play a large role in early diagnoses, superceding the benefits from vitamin D. It is also likely that the benefits of vitamin D are accenteduated as insufficiency becomes more prevalent with age. In older adults, cutaneous production is reduced due to little time being spent in the sun and/or use of sunscreens and a reduced capacity of the skin to manufacture cholecalciferol. In addition, a lower consumption of dairy foods or diminished intestinal absorption of vitamin D add to the likelihood of low 25(OH)D concentrations with age. Multivitamin use; intakes of vitamin D, folate, and alcohol; availability of UV light from the sun; and family history of colorectal cancer were all positively associated with 25(OH)D but unrelated to 1,25(OH)2D. Smokers were more likely to have low levels of 25(OH)D.[2]

Although calcium and vitamin D work together metabolically and both are possible protective agents against colorectal cancer, it is unknown whether they interact in carcinogenesis. In a recent analysis of data from the Calcium Polyp Prevention Study randomized trial, 25(OH)D levels were associated with a reduced risk of recurrent adenoma only among the subjects receiving calcium supplements. Our results with colorectal cancer did not support this finding. Cancer risk decreased with higher 25(OH)D concentrations among those with total calcium intakes above or below 900 mg/day. If the benefit of calcium with vitamin D supplementation is to prevent or slow the progression of colorectal cancer in its early stages and if colorectal cancer has a latency of 10 to 20 years, the average intervention and follow-up of 7 years may have been insufficient to demonstrate an effect. The long latency associated with the development of colorectal cancer, in concert with the 7-year duration of the trial, may have contributed to this null finding as in the case of the study carried out by Wactawski et al.[3]

In order to study the effect of vitamin D analogues on prostate cancer, Lui et al.[4] and Schwartz et al.[5] enrolled patients from January 1999 to October 2000: a total of 26 patients, all at the University of Wisconsin Comprehensive Cancer Center. The median age was 70 years (range: 57-85 years) and the median performance status was 1 (range: Eastern Cooperative Oncology Group performance status 0-1). All patients had stage D2 disease (CT or bone scan positive) with rising PSA before enrollment.

Of all 26 patients enrolled, 6 patients failed to complete = "8 weeks of therapy and were therefore not evaluable for response. Of the remaining 20 (evaluable) patients, no objective responses were seen despite 8 patients having measurable disease. PSA response was not considered a surrogate marker in this study given in vitro data, indicating stimulation of PSA production with vitamin D analogues. Of interest, one of the patients with a PSA decline had a baseline PSA of 44.7 ng/ml and this dropped from the start to a nadir of 29.6 ng/ml at week 12. He had evaluable lymphadenopathy as well as bone scan positivity from the beginning and eventually progressed by bone scan only at week 44, with an associated PSA of 74.7 ng/ml.

The treatment of prostate cancer is being continuously refined as new information regarding the role of prostatectomy, the timing of hormone administration, and use of chemotherapy are studied. Although some improvements in prostate cancer-related mortality have been observed, most of this is likely to be related to better management of treatment and disease-related morbidity, rather than actual impact on the disease itself. Unfortunately, >30,000 patients are estimated to die each year because of prostate cancer and many more are debilitated from advanced disease. It is clear that new therapies are needed. Vitamin D is a secosteroid that has shown extensive laboratory and clinical evidence that it may be useful in the treatment or prevention of prostate cancer.

In a study carried out by Lui et al.[4] no unexpected drug toxicity was observed. Mild, clinically insignificant, hypercalcemia was frequently seen and easily controlled with either dose modifications or brief cessation of therapy. Six of the twenty evaluable patients achieved PFS for >6 months on therapy.

TGFß1; levels were determined at the time of enrollment and then every 4 weeks while the patient remained on protocol. The mean baseline level of TGFß1 in our advanced hormone-refractory prostate cancer population was 4.41 ng/ml (SD: 2.88). The mean levels appeared to increase over baseline in subsequent determinations. TGFßs are multifunctional growth factors that have been associated with both protumorigenic as well as tumor-inhibitory properties. Interestingly, vitamin D and TGFß may share identical actions on the cell’s growth and differentiation because TGFß has been observed to inhibit proliferation of epithelial cells. It has been demonstrated that the inhibitory effect of calcitriol on cell growth could in fact be related to an induction of TGFß synthesis in a paracrine/autocrine loop. Increasing mean TGFß levels over baseline were observed during this trial. Whether this increase is secondary to disease progression or evidence of drug activity is unknown. Theoretically, because TGFß has downstream effects on cell growth, it is conceivable that its level may rise early because of the inducing effect of the vitamin D analogue, before later decreasing because of tumor regression.[3,4]
CONCLUSION

The primary and the most important source of vitamin D is sunlight. Solar UV-B exposure and the amount of exposure to sun is related inversely with cancer mortality and survival in detailed epidemiological studies. Some analytical studies suggest a protective association between circulating vitamin D in blood, which is largely derived from sunlight or dietary vitamin D, and colorectal cancer and prostate cancer.

In an exploratory ecological study, it was observed that sunlight and vitamin D were associated with lower risk of cancer, particularly for prostate and colorectal cancers. Vitamin D is a secosteroid that has shown extensive laboratory and clinical evidence that it may be useful in the treatment or prevention of prostate cancer.

For several sites (breast, colon, rectum, esophagus, other biliary, and vulva) the relative risks of mortality are higher, possibly suggesting that the maintenance of adequate vitamin D levels is more critical for limiting tumor progression than for preventing tumor onset. Although mortality from ovarian and prostate cancer was inversely associated with residential exposure to sunlight, they were not consistently associated with occupational sunlight. Results and supporting evidence suggest that older women with higher circulating levels of 25(OH)D may be at lower risk of colorectal cancer, particularly for cancers at the distal colon and rectum.

In conclusion, Phase I and II trials using vitamin D analogues for the treatment of prostate cancer have shown evidence of drug activity that warrants further investigation. Although the Phase II trial did not have any objective responses, we did observe that disease stability >6 months was observed in 30% of the patients. For a cytostatic drug, this is encouraging, especially because the treatment involves a fairly nontoxic p.o. medication.

Further assessment of vitamin D and its analogues for cancer prevention is being done. From the evidence till date, vitamin D and its analogues seem to be beneficial for cancer prevention and treatment.

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