Strengths and Limitations of Current Epidemiologic Studies: Vitamin D as a Modifier of Colon and Prostate Cancer Risk

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The existence of an association between latitude and cancer mortality rate had been known since the 1930s, but it was in 1980 that Garland et al.[1] first hypothesized that the potential benefit of sun exposure was due to vitamin D. Initially, the hypothesis focused on colon cancer, but it was later extended to other types of cancer including prostate cancer.[2] Many cell types, normal as well as neoplastic, are now known to express vitamin D receptors and 1-α-hydroxylase, which can convert 25(OH)-vitamin D, abbreviated 25(OH)D, to $1,25(OH)_2$ vitamin D, abbreviated $1,25(OH)_2D$, which is the natural ligand of the vitamin D receptor. Activation of the vitamin D receptor induces or inhibits transcription of a number of genes that influence proliferation, invasiveness, angiogenesis, metastatic potential, differentiation, and apoptosis.[3] The autocrine or perhaps paracrine influences of $1,25(OH)_2D$ acting through these genes could potentially help to retard cancer causation or progression in some tissues. The hypothesis that high circulating levels of 25(OH)D or the two sources of vitamin D, sun exposure and intake, are associated with lower risk of cancer has been examined in epidemiologic studies. A brief summary of results for colorectal and prostate cancer is provided here.

The association between latitude as a surrogate of sun exposure and vitamin D level, first observed in the United States, has now been confirmed in diverse populations such as in Japan.[4] The circulating 25(OH)D level accounts for all sources of vitamin D, plus conversion of vitamin D into 25(OH)D. Circulating 25(OH)D has a relatively long half-life of about 2 to 3 weeks and thus can provide a fairly stable indicator of long-term vitamin D status. Studies that have examined 25(OH)D levels prospectively in relation to risk of colorectal cancer have generally supported an inverse association. In a recent meta-analysis of these studies, individuals with serum 25(OH)D levels equal to or greater than 33 ng/mL (82 nmol/L) had a 50% lower incidence of colorectal cancer than those with relatively low levels ($\leq$ 12 ng/mL or 30 nmol/L).[5] The combined number of colorectal cancer cases in the meta-analysis was 535, and the results were highly statistically significant. Studies that have examined vitamin D intake in relation to colorectal cancer or adenoma risk have also tended to show an inverse association, which, as expected, is smaller in magnitude than that estimated from studies considering 25(OH)D levels.[6] The studies of vitamin D intake tend to support a protective effect of 25(OH)D, but a limitation of these studies is that a confounding effect of calcium intake could not be definitively excluded because of the fairly high correlation between calcium and vitamin D intakes in the United States (where milk is fortified with vitamin D).

The results for prostate cancer are less clear than those for colorectal cancer. Interestingly, studies that have examined sun exposure have generally been supportive of an inverse association. For example, in a case-control study of prostate cancer conducted in the United Kingdom, where vitamin D deficiency is relatively common, regular foreign holidays in sunny climates, a higher sunbathing score, and higher exposure to solar radiation were strongly associated with a reduced risk.[6] Because of the retrospective and subjective assessment of exposure, recall bias is a possibility in this study. However, studies using surrogate measures of recent past or long-term sun exposure, such as prior non-melanoma skin cancer[7] or reflectometry,[8] have also suggested that exposure to sun is associated with a lower risk of prostate cancer. In contrast to the studies that have examined sun exposure surrogates, studies that have examined circulating $1,25(OH)_2D$ or 25(OH)D levels have yielded inconsistent results.[3] Further, although dietary studies have been limited in number, they tend not to support an association between vitamin D intake and lower prostate cancer risk.

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Three factors could contribute to the apparent inconsistent findings for prostate cancer. First, the effect of vitamin D could be more relevant for prostate cancer progression, or for a sub-group of aggressive prostate cancers, than for total prostate cancer. For example, a recent study by Li et al.[9] found that men with low levels of both $1,25(OH)_2D$ and 25(OH)D had an increased risk of aggressive (advanced-stage or high-grade) prostate cancer, but not of non-aggressive cancer. For prostate cancer in general, risk factors for aggressive or advanced cancer appear to be quite different than for total cancer.[10] Most studies of vitamin D have focused on total prostate cancer rather than on aggressive or fatal prostate cancer. Second, the risk associated with low vitamin D status may be conferred earlier in life, and thus studies of circulating levels of 25(OH)D and dietary intake in adulthood may not capture the relevant time period of exposure. For example, some studies find that early life exposure to sun may be most relevant for prostate cancer protection [11] Further, the process of prostate cancer carcinogenesis is likely to begin early in life (by the third decade of life, microscopic neoplastic lesions are already highly prevalent in the prostate gland), and prostate cancer cells appear to lose 1-α-hydroxylase activity and thus the ability to convert 25(OH)D into $1,25(OH)_2D$ early in its natural history.[12,13] In contrast, malignant colorectal cells tend to maintain high 1-α-hydroxylase levels, at least until the most advanced (de-differentiated) stages.[14] These findings suggest that vitamin D levels may be most relevant early in the neoplastic process for prostate cancer.

A final factor that may be relevant for the vitamin D-prostate cancer link is that the dose-response relation may be operative at quite low levels of 25(OH)D. For example, in populations in which severe vitamin D deficiency is uncommon, a higher 25(OH)D level has tended to not be associated with a reduced risk, but evidence of an inverse association is seen in countries (e.g., Nordic countries) where the prevalence of vitamin D deficiency is high because of the high latitudes.[15] Perhaps also supporting an effect at low levels of vitamin D is that low levels of circulating $1,25(OH)_2D$ have also been associated with an increased risk of aggressive prostate cancer.[9,16] Low circulating $1,25(OH)_2D$ typically signifies relatively severe degrees of vitamin D deficiency.

The data on vitamin D and cancer risk are intriguing, but many important questions remain. Although not entirely definitive at this point, the epidemiologic and supporting biologic evidence indicates that vitamin D may have a role in reducing the incidence of at least some cancers, including colorectal cancer. Further observational studies—and randomized trials if feasible—would be useful in testing the hypothesis that vitamin D lowers cancer risk. Serum or plasma-based studies are needed to help establish the dose-response, the optimal level of 25(OH)D, and the length of time required to observe an effect. The time period of life when exposure is most relevant is also important to determine. These studies could help to establish the role of modifying factors such as genetic variants in the vitamin D pathway and other factors such as retinol intake, which may antagonize the actions of vitamin D. Confirming that vitamin D reduces the risk of cancer incidence or mortality is critical, because current health recommendations typically do not encourage high intakes of vitamin D and tend to discourage sun exposure. Current dietary recommendations are geared only to prevent quite low vitamin D levels. If the association between better vitamin D status and reduced cancer risk is a causal one, the levels of intake currently recommended are probably inadequate. Defining what may be the optimal levels of vitamin D for cancer prevention remains a challenge, but further study should be a high priority because the potential for benefit is substantial.

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