ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Colorectal Cancer In Focus

Effects of Vitamin D in Colorectal Cancer

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H&O What is the relationship between vitamin D and colorectal cancer?

KN There is a long history of ecologic and observational data demonstrating that vitamin D status affects the risk of developing colorectal cancer (CRC). Studies have evaluated vitamin D intake, both from diet and supplements, as well as vitamin D levels in the blood. Most of these studies suggest that the higher the vitamin D level, the lower the risk of developing CRC. A meta-analysis of 5 epidemiologic studies that evaluated blood levels of vitamin D and CRC found that a higher vitamin D level is associated with an approximately 50% lower risk of developing CRC.

H&O Is one source of vitamin D more effective than another? How much exposure is needed from the various sources?

KN If a fair-skinned individual is in the sun with most of his or her skin exposed and is not wearing sunscreen, approximately 20 minutes of sun exposure (so that skin gets slightly pink) can produce 20,000 IU of vitamin D. In contrast, a standard vitamin D supplement of 400 IU raises blood levels of vitamin D by only 4–5 ng/mL, and a glass of milk contains only 100 IU of vitamin D. Among the 2 forms of vitamin D supplements, D2 and D3, vitamin D3 is more potent. Although sun exposure is the most effective way to increase vitamin D levels, there are obvious concerns about skin cancer.

H&O What are the mechanisms by which vitamin D may prevent CRC or reduce mortality in CRC patients?

KN The active form of vitamin D is 1,25-dihydroxycholecalciferol (calcitriol). To make 1,25-dihydroxycholecalciferol, vitamin D3 from the sun or diet is first modified in the liver to 25-hydroxyvitamin D [25(OH)D], the main circulating form of vitamin D and the functional indicator of vitamin D status. 25(OH)D then travels through the blood to the kidneys, where it is converted by 1-alpha-hydroxylase to 1,25-dihydroxycholecalciferol. 1,25-dihydroxycholecalciferol then binds to the vitamin D receptor (VDR) to affect transcription of target genes. This pathway results in multiple biologic effects, including inhibition of cell proliferation and angiogenesis and induction of cell differentiation and apoptosis—processes that are often dysregulated in cancer. Vitamin D also has several immunologic effects. Although the mechanisms by which vitamin D may reduce or prevent colorectal cancer risk and progression are not fully understood, we now know that VDR and 1-alpha-hydroxylase are expressed in CRC cells, leading to the hypothesis that vitamin D may be important in CRC pathogenesis.

H&O What evidence do we have of the benefits of vitamin D in CRC?

KN One of the earliest studies that suggested a benefit of vitamin D in CRC was an observational study conducted in Norway by Robsahm and colleagues. The investigators evaluated 115,096 cases of breast, colon, and prostate cancer diagnosed between 1964 and 1992. The findings demonstrated that patients diagnosed with CRC in the summer and autumn, when vitamin D levels were higher,

did better than those who were diagnosed in the winter and spring. The investigators hypothesized that the vitamin D status of the patient had some correlation to his or her outcome.

Our group at Dana-Farber Cancer Institute has been focusing on the relationship between vitamin D status and how well a patient does after being diagnosed with CRC. Many other studies have focused on the risk of developing CRC. We have published 2 studies that suggest that the higher the level of vitamin D in the blood, the better the survival after diagnosis. In the study that we published in the *Journal of Clinical Oncology* in 2008, we prospectively evaluated the association between prediagnosis levels of vitamin D and survival in 304 patients who were diagnosed with CRC from 1991–2002. The enrolled patients had all stages of CRC. Our findings showed that there was an approximate 50% decreased risk of overall mortality in those patients with vitamin D levels in the highest quartile. Patients in the highest quartile also had a reduction in the risk of CRC-specific mortality compared to patients in the lowest quartile.

In the other study, published in the *British Journal of Cancer* in 2009, we prospectively examined the effect of postdiagnosis predicted vitamin D levels on survival in 1,017 patients who were diagnosed with all stages of CRC from 1986–2004. In this study, we used a vitamin D score, which uses clinical factors that are known to affect vitamin D levels, to predict patients' vitamin D levels. We found that patients who had vitamin D scores in the highest quintile had a 50% lower chance of dying from CRC than those who had levels in the lowest quintile.

H&O What is the role of the vitamin D test in CRC prevention?

KN It is probably premature to recommend routine testing of vitamin D levels for the purpose of preventing CRC or improving survival after a diagnosis of CRC. However, there are many documented health benefits of a normal vitamin D level in terms of bone health and other outcomes.

Many patients ask their doctors whether or not they should take a vitamin D supplement, and it is reasonable to have a 25(OH)D level checked. If it is low, it is probably beneficial to take a supplement in order to raise it into the normal range (>30 ng/mL). We cannot yet recommend it as a preventative measure for CRC or as a treatment for CRC, but eventually we may be headed in that direction once we collect more data.

H&O What is the typical recommendation for supplementation and sun exposure for a patient who may have low vitamin D levels?

KN The definitions of a sufficient vitamin D level vary depending on the physician and the sources he or she uses. In general, above 30 ng/mL is a good goal to aim for. In the studies of CRC mentioned above, a level of 33 ng/mL or higher was associated with decreased risk of CRC and improved survival. The Institute of Medicine's (IOM) recommendations for vitamin D supplementation are probably insufficient to raise vitamin D levels into the normal range, especially in light of the high prevalence of vitamin D deficiency that has been reported in recent years. Currently, the IOM recommends 200 IU per day for children and adults under 50 years, 400 IU per day for adults 50–70 years, and 600 IU per day for adults over 70 years. These amounts only raise 25(OH)D levels by miniscule amounts. I believe a revision of these guidelines is currently being considered.

H&O What is the future of research for vitamin D and CRC?

KN There has been a lot of interest in characterizing the genetic variation of vitamin D pathway genes and how this genetic variation affects 25(OH)D levels, risk of CRC, and patient outcome after a diagnosis of CRC. So, I think there will be more research in that area. Also, we are interested in further exploring how vitamin D interacts with other pathways that are thought to be important in CRC pathogenesis, particularly the inflammatory and energy balance pathways. Eventually, in order to demonstrate that vitamin D can protect against CRC and cancer progression, randomized clinical trials of vitamin D supplementation will need to be performed.

Suggested Readings

Robsahm TE, Tretli S, Dahlback A, Moan J. Vitamin D3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway). *Cancer Causes Control.* 2004;15:149-158.

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