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The Death D-Fying Vitamin D_3 for Digestive Tract Cancers—The p53 Antibody Connection

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In 2019, Urashima et al[1] reported results of a randomized, double-blind, placebo-controlled clinical trial that evaluated the efficacy of improving relapse-free survival for patients with cancers of the digestive tract who received 2000 IU vitamin D_3 supplementation daily for 8 years. Based on the results from this clinical trial, the authors concluded that vitamin D_3 supplementation did not improve relapse-free survival at 5 years. In this issue of *JAMA Network Open*, Kanno et al[2] report a post hoc subgroup analysis of this clinical trial. They evaluated the p53-immunoreactive subgroup defined by positivity for both anti-p53 antibodies in serum and nuclear accumulation of p53 by immunohistochemistry in more than 99% of cancer cells, which was considered a biomarker for p53-missense mutations. Patients who had detectable serum anti-p53 antibody and received 2000 IU daily had a significant, more than 2.5-fold improvement in relapse or death compared with the placebo group that had detectable p53 immunoreactivity. The observed 27% absolute risk reduction translates to a number needed to treat of 4. In those patients who had no p53 immunoreactivity, 2000 IU of vitamin D_3 daily provided insignificant benefit for 5-year relapse-free survival.

One of the first studies to find an association of sun exposure (a surrogate for improved vitamin D status) with reduced risk of cancer was reported in 1916.[3] A multitude of additional studies found that living at higher latitudes was associated with increased risk for mortality from cancer.[3] In the 1990s, a strong significant negative correlation with colon cancer mortality and mean daily solar radiation in the US was observed. This was quickly followed by the observation in an 8-year prospective case-control study that the risk of getting colon cancer was 3-fold lower in people with a serum 25-hydroxyvitamin D, or 25(OH)D, level greater than 20 ng/mL.[3] Several epidemiologic studies and other clinical studies, including the Women's Health Initiative, observed that vitamin D deficiency was associated with greater risk for development of colorectal cancer.[3] A quantitative meta-analysis on optimal vitamin D status for colorectal cancer prevention reported a 50% risk reduction associated with a serum 25(OH)D concentration of 34 ng/mL.[3] The polymorphisms for the vitamin D receptor (VDR) also have been associated with colorectal cancer risk.[3]

The *TP53* gene produces the protein p53, which suppresses cancer by controlling cell division, DNA repair, and apoptosis, and has been called "the guardian of the genome."[4] Vitamin D_3, through its active form, 1,25-dihydroxyvitamin D_3, or 1,25$(OH)_2D_3$, binds the VDR to regulate cellular proliferation, differentiation, apoptosis, and angiogenesis, all related to its potential anticancer activities.[3]

Approximately 50% of human cancers carry p53 mutations resulting in overproduction of mutant p53 (mutp53). These mutations not only result in loss of tumor-suppressing activities but also inactivate wild-type p53. Interestingly, mutp53 binds to the promoter region of the VDR responsive elements. This interaction is thought to elicit an antiapoptotic state and reduce the 1,25$(OH)_2D_3$-VDR's ability to upregulate expression of proapoptotic genes.[5,6]

The Vitamin D and Omega-3 Trial (VITAL; NCT01169259) evaluated in a randomized double-blind placebo-controlled fashion the effect of 2000 IU of vitamin D_3 and marine omega-3 fatty acids on cancer outcomes and concluded that there was no benefit of vitamin D_3 supplementation for reducing risk of cancer. However, the authors acknowledged that there was a significant 25% reduction in cancer mortality. A secondary analysis of this study[7] revealed that supplementation with 2000 IU vitamin D_3 daily modestly reduced the incidence of metastatic and

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fatal cancer in the overall cohort. However, when this cohort was stratified for body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), those with a BMI less than 25 had a hazard ratio of 0.62 (95% CI, 0.45-0.86), whereas for those with a BMI greater than 30, the hazard ratio was 1.05 (95% CI, 0.74-1.49), demonstrating that normal-weight participants (BMI <25) benefited the most from the vitamin D_3 supplementation.[7] A randomized controlled double-blind clinical trial that assessed the effect of vitamin D_3 supplementation (600, 4000, or 10 000 IU daily for 6 months) on broad gene expression demonstrated a dose-dependent 25(OH)D_3 alteration in broad gene expression, with 162, 320, and 1289 genes upregulated or downregulated in their white blood cells, respectively. In the group that received 10 000 IU vitamin D_3 daily and raised their blood concentrations in the range of 50 to 100 ng/mL, 50% had a robust gene expression of greater than 5% of their genome, whereas the other 50% only expressed 2% to 5% of their genome. This demonstrated individual differences in gene responsiveness to the same vitamin D_3 supplementation dose, with the participants attaining the same serum concentration of 25(OH)D.[8] This observation may help explain why high-dose vitamin D with chemotherapy resulted in a difference in mean progression-free survival that was not statistically significant but with a significantly improved supportive hazard ratio.[9]

The observation by Kanno et al[2] is a game changer for vitamin D and cancer. It provides an additional variable in our understanding of whether improving vitamin D status has any benefit for reducing risk of developing cancer as well as improving relapse-free and mortality outcomes. For more than 100 years, sunlight and vitamin D deficiency has been associated with the risk for many deadly cancers, including colorectal, prostate, and breast.[3] However, there has been great skepticism as to whether this nutrient/hormone provides any benefit for reducing cancer risk and the morbidity and mortality associated with cancer. Several randomized clinical trials supported this skepticism.[1,7] There are a variety of variables that can influence how vitamin D prevents and responds to cancer, including BMI, VDR polymorphisms, enhanced vitamin D catabolism, gene responsiveness to 1,25$(OH)_2D_3$, and the negative interaction that mutp53 has on the 1,25$(OH)_2D_3$-VDR's ability to prevent and control cancer cell growth.[3,5,6,10] It would be worthwhile to retrospectively, when possible, conduct a post hoc analysis for serum p53 antibodies and the immunohistochemistry presence for p53 in histologic cancer samples of studies that evaluated the potential benefit of vitamin D supplementation for improvement in cancer survival and found no benefit. More importantly, future studies evaluating vitamin D supplementation for the prevention of cancer and improvement of cancer outcomes should now include not only many of the variables mentioned above but also a measurement for p53 antibodies and immunohistochemical presence of p53. The results of the study by Kanno et al[2] support the preponderance of association and clinical studies[3,7] concluding that improvement in vitamin D status can be an effective strategy for promoting cancer remission and reducing cancer mortality. It is also important to recognize that most of the studies that have demonstrated a beneficial effect for reducing cancer risk and improving clinical outcomes have used at least 2000 IU vitamin D_3 daily and raising circulating concentrations of 25(OH)D above 30 ng/mL without any significant untoward toxic effects.[1-3,7] It is well documented that to achieve a circulating concentration of 25(OH)D above 30 ng/mL requires a vitamin D intake of at least 2000 IU daily, an amount that can only be obtained from a vitamin D supplement or by being a hunter-gatherer like Maasai herders and the Hadza, who maintain circulating concentrations of 25(OH)D above 30 ng/mL as a result of their daily exposure to sunlight.[3]

This important new observation by Kanno et al[2] requires confirmation. It would be prudent, based on all available evidence, that patients with cancer consider improving their vitamin D status with 2000 IU daily to reduce morbidity and mortality associated with their cancer, except for those patients who have a hypersensitivity to vitamin D, including patients with granulomatous disorders and some lymphomas.

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