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Vitamin D and Cancer — Evidence Suggests This Vital Nutrient May Cut Risk

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A growing body of research suggests vitamin D may play an important role in the prevention of several diseases that previously weren't believed to have a vitamin D connection, including multiple sclerosis, cardiovascular disease, Parkinson's disease, dementia, diabetes, hypertension, obesity, and several types of cancers. Among all the possible associations between vitamin D and disease prevention, the one concerning vitamin D and cancer risk appears to be the most widely studied.

This continuing education activity will evaluate the role vitamin D plays in cancer prevention and provide nutrition professionals with strategies for counseling patients.

Metabolism and Biochemistry

Vitamin D is a fat-soluble vitamin obtained from sunlight exposure, food, and dietary supplements.[1] The vitamin helps regulate calcium absorption, making it a critical nutrient for bone health.[2,3] It also plays a role in maintaining phosphorus levels in the blood, another important nutrient for sustaining bone health. In addition, vitamin D has various functions in the body, including its involvement in gene expression, cell growth regulation, neuromuscular and immune function, and inflammation reduction.

The two forms of vitamin D are D_2 and D_3. Though both are found in supplements and used to fortify foods, vitamin D_3 is more commonly used. Until recently, the two forms were considered interchangeable and equivalent.[2] However, studies suggest vitamin D_3 is more potent than vitamin D_2.

The body produces vitamin D when the skin is exposed to the sun's ultraviolet B (UVB) rays. This causes the compound 7-dehydrocholesterol found in the skin to convert to previtamin D_3 (cholecalciferol). Vitamin D_2 is a synthetic product derived from the irradiation of plant sterols/ergosterol and is used in some supplements.[2]

Both vitamins D_2 and D_3 are converted in the liver to calcidiol, the main form of vitamin D found in the blood that's used to determine vitamin D status. Calcidiol is then converted in the kidneys to 1,25-dihydroxyvitamin D_3 (calcitriol), the biologically active form of vitamin D. It's this form that acts in the small intestine to increase calcium absorption and on bone cells to release calcium to maintain blood calcium levels. Most tissues and cells in the body have a vitamin D receptor and can convert the main form of vitamin D in the blood to the active form.

Plasma parathyroid hormone as well as serum calcium and phosphorus tightly regulate production of 1,25 dihydroxyvitamin D_3 in the kidneys.[1] When blood levels of vitamin D are low, the small intestine absorbs only about 10% to 15% of dietary calcium—not enough to satisfy calcium requirements for bone health and for most of calcium's other metabolic functions and neuromuscular activity.[1] When vitamin D levels are adequate, intestinal absorption of dietary calcium more than doubles, rising to about 30% to 40%. Researchers only recently discovered that cells found in the colon, brain, prostate, and some immune cells also produce biologically active vitamin D.[4]

Cancer Prevention

Vitamin D is considered one of the most potent hormones for the regulation of cell growth.[1] Some evidence suggests that calcitriol helps prevent cancer progression by slowing the development of angiogenesis (the growth of new blood vessels in cancerous tissue), increasing cell differentiation and apoptosis (cancer cell death), and by reducing cell proliferation and metastases.[1] Vitamin D influences more than 200 human genes, many of which encode for proteins that are important for regulating cells. When vitamin D status is suboptimal, these gene activities are impaired.

A relationship between exposure to the sun's UV rays and reduced cancer death rates was first suggested in the 1940s.[5] People living at latitudes farther from the sun are at increased risk for Hodgkin's lymphoma, colon, pancreatic, prostate, ovarian, and breast cancer and are more likely to die from these cancers than people living in latitudes closer to the equator.[6-8]

Both prospective and retrospective studies indicate that blood levels of calcidiol below 20 ng/mL are associated with a 30% to 50% increased risk of colon, prostate, and breast cancer as well as higher mortality rates from these diseases.[9-11] A four-year, double-blind, placebo-controlled trial of calcium and vitamin D supplementation found that improving vitamin D status by supplementing with calcium and 1,100 IU of vitamin D_3 per day substantially reduced all-cancer risk in postmenopausal women.[12] However, some studies indicate that blood levels as high as 60 to 80 ng/mL may be necessary to reduce cancer risk,[13] and that an intake of 9,600 IU/day is estimated to be the supplemental dose needed to ensure that 97.5% of the population achieve a serum calcidiol measure of at least 40 ng/mL.[13] The Recommended Dietary Allowances (RDA) are designed to meet the needs of 97.5% of the population.

Though the Food and Nutrition Board established the Upper Limit (UL) for vitamin D intake at 4,000 IU/day,[3] the National Institutes of Health (NIH) has stated that symptoms of toxicity are unlikely at daily intakes below 10,000 IU/day.[14] Vitamin D toxicity can cause anorexia, weight loss, frequent urination, and heart arrhythmias and raise blood levels of calcium, leading to calcification of tissues and blood vessels.[14] It's unclear whether lower doses can cause problems unrelated to toxicity. The Women's Health Initiative, for example, found a 17% increase in the risk of kidney stones over seven years with only 400 IU/day combined with 1,000 mg/day of calcium.[15] While the format of the study inhibits drawing any conclusions based solely on the consumption of vitamin D, the NIH recommends avoiding excessive vitamin D to help limit kidney stone occurrence. There isn't enough vitamin D present in food to cause toxicity.

In reviewing the latest evidence to establish vitamin D recommendations, the Institute of Medicine (IOM) stated that while the theory that vitamin D may help prevent cancer is biologically plausible, evidence is lacking.[3] A meta-analysis done for the US Preventive Services Task Force, published in the ***Annals of Internal Medicine*** in 2011, concluded that while a few clinical trials have suggested that high doses of vitamin D (1,000 IU/day) could reduce the total risk of cancer, more research is needed.[16] Certain studies have raised concerns that high blood levels of vitamin D possibly could increase the risk of pancreatic, esophageal, and other cancers,[17] while others suggest that people with the highest levels can lower the risk of the following cancers:

• **Colon cancer:** The most convincing evidence for vitamin D's role in cancer prevention comes from studies investigating its effects on colon and rectal cancer.[17] Researchers from the University of California, San Diego, were the first to suggest a connection between vitamin D and colon cancer risk. Subsequent population studies have suggested that vitamin D may help protect against colon cancer. A pooled analysis of people in the Health Professionals Follow-Up Study and the Nurses' Health Study found that those with the highest blood levels of vitamin D had a 34% lower risk of colorectal cancer than those with the lowest levels.[18]

A meta-analysis of five studies, published in the ***American Journal of Preventive Medicine*** in 2007, found a 50% decreased risk of colorectal cancer in subjects with blood levels of at least 33 ng/mL compared with those with blood levels of 12 ng/mL or lower.[6] Despite these findings and others, little evidence exists from clinical trials to support the strong epidemiologic research.[19] Neither a British trial comparing vitamin D_3 with placebo nor the Women's Health Initiative that examined calcium plus vitamin D found any reduction in the incidence of or death from colorectal cancer.[19]

• **Breast cancer:** A study in ***Carcinogenesis*** in 2008 found that breast cancer risk was 70% lower in women with blood levels of vitamin D greater than 30 ng/mL compared with those with blood levels less than 18 ng/mL.[20] In the Third National Health and Nutrition Examination Survey, women with greater sun exposure had only one-half the incidence of breast cancer compared with those with less sun exposure.[21]

Data from the Harvard Nurses Health Study and the St George's Hospital Study found that women with the highest blood levels of calcidiol had a reduced risk of breast cancer. There was a clear dose-response relationship in which those with the lowest blood levels (less than 13 ng/mL) had the highest rates of breast cancer, and rates were successively lower as blood levels increased (up to 52 ng/mL). The blood level associated with a 35% reduction in breast cancer risk can be maintained by taking about 2,000 IU of vitamin D3 per day.[5,22]

However, not all studies have found such a link. A study published in ***Breast Cancer Research*** in 2011 found no link between blood levels of vitamin D and breast cancer risk.[23] Another study showed a 34% increased risk among women who had the highest vitamin D intake at the start of the study (at least 600 IU/day) and who took a supplement containing 400 IU of vitamin D during the study.[19]

• **Prostate cancer:** Several studies suggest that death due to prostate cancer decreases with increased sun exposure. Researchers who examined blood levels of vitamin D in men who participated in the Health Professionals Follow-Up Study and the Physicians' Health Study found that subjects who had the lowest concentrations before they were diagnosed had a higher risk of dying of the cancer.[24] However, several studies have found no association between blood levels of vitamin D and prostate cancer risk. And concerns have been raised that risk may increase at very low levels (8 ng/mL or less) or at higher-than-recommended levels (32 ng/mL or more).[25]

• **Skin cancer:** A history of basal cell carcinoma of the skin (the least dangerous type of skin cancer) increases the risk of melanoma (the most dangerous type). In a randomized placebo-controlled trial of 36,282 postmenopausal women, those with a history of basal cell or squamous cell carcinoma who took 1,000 mg of elemental calcium and 400 IU of vitamin D_3 per day for seven years were 57% less likely to develop melanoma than those who didn't take the supplement.[26]

Sources of Vitamin D

The RDA for vitamin D is 600 IU for people aged 1 to 70. After the age of 70, the RDA increases to 800 IU. These recommendations are designed to prevent rickets in children and promote bone health in adults.[3]

Most at risk of a vitamin D deficiency are people older than the age of 60 and those who live in northern latitudes, have dark skin, are rarely outdoors or always wear sunscreen while outdoors, have chronic kidney disease, take certain medications that interfere with vitamin D absorption, have a medical condition that prevents dietary fat absorption, or who have had part of their stomach or intestine surgically removed.

Deficiencies are common because few foods are fortified with or are naturally rich in vitamin D. Fatty fish such as salmon, tuna, and mackerel and fish liver oils are some of the best sources of vitamin D_3. Smaller amounts are found in beef liver, cheese, and egg yolks. Some types of mushrooms with enhanced levels of vitamin D_2, due to UV light exposure, provide up to 100% of the RDA in a 3-oz serving.

By comparison, most of the vitamin D in the diet comes from fortified foods,[3] while most overall vitamin D comes from sunlight exposure. As mentioned, vitamin D_2 is manufactured through the UV irradiation of ergosterol from yeast and vitamin D_3 through the ultraviolet irradiation of 7-dehydrocholesterol from lanolin. And both are used in over-the-counter vitamin D supplements.[1]

Because few natural food sources of vitamin D exist and not many are fortified, most of the vitamin D in our blood comes from sunlight exposure rather than from food. Dietary sources usually account for no more than 5% to 10% of the vitamin D the body requires.[2] If exposure to sunlight is limited, then vitamin D must come from supplements or fortified foods.

If the vitamin D consumed or obtained from the sun results in adequate levels of vitamin D in the blood, it makes no difference whether the vitamin D comes from the sun or from a

supplement of either form (D_2 or D_3). However, vitamin D from skin synthesis or dietary sources typically is sporadic, and irregular intake can lead to chronic vitamin D deficiency.[1]

Expert Recommendations

It's been suggested that vitamin D deficiency is the most widespread one in developed nations.[2] The term "deficiency" here doesn't refer to clinical disease comparable to a vitamin C deficiency that can lead to scurvy, but increased risk of certain diseases. In other words, seemingly healthy individuals may be "D deficient" and at risk of disease.[2]

While most people get at least some of their vitamin D requirements from sun exposure, the skin's ability to produce vitamin D declines with age.[14] For the skin to produce adequate vitamin D, five to 30 minutes of sun exposure to the face, arms, and legs without sunscreen is recommended between 10 AM and 3 PM twice per week.[14] Moderate use of commercial tanning beds that emit 2% to 6% of UVB radiation also is effective. Complete cloud cover reduces UV energy by 50% and shade by 60%. UVB radiation doesn't penetrate glass, so exposure to sunshine indoors through a window doesn't produce vitamin D.[14]

Testing for Vitamin D Status

Serum calcidiol is the major circulating metabolite of vitamin D that's used to measure vitamin D status.[1] In the blood, vitamin D is expressed as nanograms per milliliter or nanomoles per liter. Most research papers use the latter measurement, nanomoles per liter, which can be converted to nanograms per milliliter by dividing by 2.5. For example, a blood level of 50 nmol/L is equivalent to 20 ng/mL.

In 2010, the IOM recommended target blood levels of 20 to 30 ng/mL for bone health after concluding there was insufficient evidence to suggest higher levels. However, higher blood levels of vitamin D, and therefore higher intakes, may be needed for disease prevention, including cancer. Recommendations for optimal blood levels of vitamin D vary among several professional health organizations and can cause confusion.

Vitamin D inadequacy (less than 20 ng/mL) affects 36% of otherwise healthy young adults aged 18 to 29, 42% of black women aged 15 to 49, 41% of outpatients aged 49 to 83, and up to 57% of inpatients in the United States.[1] And while the deficiency has been reported in healthy children, young adults, the middle-aged, and the elderly, and especially in those with osteoporosis,[1] experts disagree on who should be tested. Plus, there are various testing methods that can produce different results.

Guidance for Clients and Patients

Controversy continues regarding the magnitude of vitamin D deficiency in the United States and whether vitamin D provides nonskeletal health benefits. The use of serum calcidiol concentrations less than 20 ng/mL as a measure to define vitamin D deficiency places approximately one-third of the US population at risk of the deficiency.[27] Serum calcidiol can be expected to rise by about 1 ng/mL for every 100 IU of additional vitamin D intake each day. For example, a patient with a starting value of 15 ng/mL would require approximately 1,500 IU/day to bring his or her serum calcidiol level up to 30 ng/mL. However, this rule of thumb is only an estimate, as blood levels may vary depending on the form of vitamin D (D_2 vs. D_3) and the

various individual responses to standard doses.[2] For conditions that cause low levels of vitamin D, some physicians may need to prescribe doses of D_2 or D_3 that are almost 10 times greater than the RDA.

The evidence for vitamin D and cancer risk is mixed and varies depending on cancer type and the dose of the vitamin. While it's clear that vitamin D's influence goes well beyond bone health, and it's biologically feasible that it could help prevent cancer, it's unclear at this time whether doses of vitamin D greater than the RDA or the UL reduce the risk of certain types of cancer.

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Vitamin D Lexicon

The biochemistry and terminology of vitamin D metabolism is complex. Below are some of the terms and chemical names used most often.

• **Vitamin D_2 (ergocalciferol)** is the form found in nonanimal sources, such as in some mushrooms.

• **Vitamin D_3 (cholecalciferol)** is the previtamin form found naturally in some animal sources, including fish and egg yolks.

• **25-hydroxyvitamin D_3 (calcidiol or calcifediol)** is the form found in blood. Sometimes shortened to 25(OH)D3.

• **1,25-dihydroxyvitamin D_3 (calcitriol)** is the biologically active form of vitamin D. Sometimes shortened to 1,25(OH)2D3.

Food Sources of Vitamin D[14]

• Cod liver oil, 1 T: 1,360 IU

• Salmon (sockeye), cooked, 3 oz: 447 IU

• Tuna fish, canned in water, drained, 3 oz: 154 IU

• Orange juice fortified with vitamin D, 1 cup: 137 IU

• Milk, nonfat, reduced fat, whole, vitamin D fortified, 1 cup: 115 to 124 IU

• Yogurt, fortified with 20% of the Daily Value for vitamin D, 6 oz: 80 IU

• Margarine, fortified, 1 T: 60 IU

• Sardines, canned in oil, drained, 2 sardines: 46 IU

• Egg, 1 large: 41 IU

• Ready-to-eat cereal, fortified with 10% of the Daily Value, 3/4 to 1 cup: 40 IU

• Cheese, Swiss, 1 oz: 6 IU

Classifying Vitamin D Status By 25(OH)D Concentration[14]

The Institute of Medicine concluded that blood levels of 25-dihydroxyvitamin D [25(OH)D] of 20 ng/mL or higher are enough to maintain bone health in the majority of people. However, that recommendation doesn't take into consideration the possible prevention of other diseases with higher levels of vitamin D. There's little agreement among experts about what's an optimum blood level of vitamin D to prevent diseases unrelated to bone health. Nevertheless, a 25(OH)D level of 12 ng/mL or less is considered deficient; 12 to 20 ng/mL, possibly at risk of insufficiency; greater than or equal to 20 ng/mL, optimal for most people; and greater than 50 ng/mL, potential adverse effects.

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Examination

1. Certain studies suggest that people with the highest blood levels of vitamin D have a lower risk of developing all of the following cancers except:
A. colon cancer.
B. breast cancer.
C. melanoma.
D. testicular cancer.

2. Both prospective and retrospective studies indicate that blood levels of calcidiol below which of the following measures are associated with a 30% to 50% increased risk of colon, prostate, and breast cancer as well as higher mortality rates from these diseases?
A. 10 ng/mL
B. 20 ng/mL
C. 30 ng/mL
D. 40 ng/mL

3. Which form of vitamin D in the blood is used to measure vitamin D status?
A. Ergocalciferol
B. Cholecalciferol
C. Calcidiol
D. Calcitriol

4. Research suggests vitamin D may help prevent and slow the progression of cancer by which of the following?
A. Reducing the growth of new blood vessels in cancer tissue
B. Decreasing the spread of cancer
C. Increasing apoptosis
D. All of the above

5. Production of 1,25 dihydroxyvitamin D3 in the kidneys is tightly regulated by which of the following?
A. Insulin
B. Thyroid hormone
C. Parathyroid hormone
D. Adrenaline

6. Which of the following is the current Recommended Dietary Allowance for vitamin D for adults up to the age of 70?
A. 400 IU
B. 600 IU
C. 800 IU
D. 1,000 IU

7. Experts agree that the following people should be tested for vitamin D levels in the blood:
A. Postmenopausal women
B. Individuals with diabetes
C. Everyone
D. No consensus

8. According to the Institute of Medicine, what level of vitamin D in the blood is considered optimal for most people?
A. Less than 10 ng/mL
B. 15 ng/mL
C. 20 ng/mL
D. 50 ng/mL

9. How much is serum calcidiol expected to rise for every 100 IU of additional vitamin D intake each day?
A. 1 ng/mL
B. 10 ng/mL
C. 20 ng/mL
D. 30 ng/mL

10. A patient with a starting value of 15 ng/mL would require approximately how many IU of vitamin D per day to bring his or her serum calcidiol level up to 30 ng/mL?
A. 1,000 IU/day
B. 1,300 IU/day
C. 1,500 IU/day
D. 1,700 IU/day