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Vitamin D Supplementation and Cancer Prevention

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Abstract and Introduction

Abstract

It is estimated that approximately 1 billion people worldwide have blood concentrations of vitamin D that are considered suboptimal. Much research has been conducted over the past 30 years linking low vitamin D serum concentrations to both skeletal and nonskeletal conditions, including several types of cancers, cardiovascular disease, diabetes, upper respiratory tract infections, all-cause mortality, and many others. Several observational studies and a few prospectively randomized controlled trials have demonstrated that adequate levels of vitamin D can decrease the risk and improve survival rates for several types of cancers including breast, rectum, ovary, prostate, stomach, bladder, esophagus, kidney, lung, pancreas, uterus, non-Hodgkin lymphoma, and multiple myeloma. Individuals with serum vitamin D concentrations less than 20 ng/mL are considered most at risk, whereas those who achieve levels of 32 to 100 ng/mL are considered to have sufficient serum vitamin D concentrations. Vitamin D can be obtained from exposure to the sun, through dietary intake, and via supplementation. Obtaining a total of approximately 4000 IU/d of vitamin D_3 from all sources has been shown to achieve serum concentrations considered to be in the sufficient range. Most individuals will require a dietary supplement of 2000 IU/d of vitamin D_3 to achieve sufficient levels as up to 10 000 IU/d is considered safe. Vitamin D_3 is available as an over-the-counter product at most pharmacies and is relatively inexpensive, especially when compared with the demonstrated benefits.

Introduction

It is well known that a causal link exists between severe vitamin D deficiency and rickets in children and the bone disease osteomalacia in adults. It is also well known that vitamin D insufficiency is associated with osteoporosis, a decrease in muscular strength, and increased fall risk. It is less well known, however, that a low serum concentration of vitamin D is also associated with several other diseases and conditions.

It is estimated that 1 billion people worldwide have vitamin D deficiency or insuffiency.[1] Patients ranging from children to elderly are affected by vitamin D deficiency. One study showed that 48% of white preadolescent girls had deficient blood levels of vitamin D.[2] Another study reported that more than half of postmenopausal women taking medication for osteoporosis had suboptimal blood levels of vitamin D.[3] Several other studies report that from 40% to 100% of community-living elderly men and women in both the United States and Europe have deficient levels of vitamin D.[1] The estimated cost to our society of vitamin D deficiency is reported to be between $100 and $200 billion per year.[4]

The recent number of medical publications on the topic of vitamin D is astounding. A PubMed search of the previous 10 years alone using the term "vitamin D" resulted in 17 399 publication displays. The newly appreciated associations between low vitamin D levels and diseases include glucose intolerance, diabetes mellitus, metabolic syndrome, cardiovascular disease, myocardial infarction, hypertension, obesity, heart failure, myopathy, inflammatory bowel disease, multiple sclerosis, psoriasis, tuberculosis, upper respiratory tract infections, polycystic ovarian syndrome, and even all-cause mortality.[5,6] In addition, a great deal of research has been conducted linking low vitamin D levels with several types of cancers. A follow-up PubMed search of the previous 10 years

using the terms "vitamin D AND cancer" resulted in 2870 publication displays, of which two-thirds were published in the past 5 years. The purpose of this article is to briefly review the physiology behind vitamin D, provide an overview of key research linking vitamin D intake with decreased cancer risk, and present the current recommendations for vitamin D intake.

Physiological Facts about Vitamin D

Assessing a patient's vitamin D level can most accurately be measured with serum 25-hydroxyvitamin D, the primary circulating form of vitamin D.[1] Serum 25-hydroxyvitamin D is expressed in ng/mL or nmol/L, where 1 ng/mL is equal to 2.5 nmol/L. Currently, there is no consensus among the medical community with regard to the optimal blood level of 25-hydroxyvitamin D. However, most vitamin D researchers generally agree that <20 ng/mL is considered a deficiency, >32 ng/mL is considered sufficient, and vitamin D intoxication is observed at levels of 150 ng/mL or higher.[1] Table 1 provides a categorical list of serum 25-hydroxyvitamin D levels.

Table 1. Serum 25-Hydroxyvitamin D Concentrations by Category[1,5,7,8]

Category	25-Hydroxyvitamin D Concentrations, ng/mL (nmol/L)
Deficiency	<20 (<50)
Insufficiency	20-32 (50-80)
Sufficiency	32-100 (80-250)
Excess	>100 (> 250)
Intoxication	>150 (>325)

An individual patient's 25-hydroxyvitamin D level is determined by many variables, including the amount of solar ultraviolet B (UVB) radiation (determined by the time of day, season, latitude, skin pigmentation, use of sunscreen, and age), dietary habits, obesity, and many others.[1] UVB radiation penetrates the skin and converts vitamin D precursors to vitamin D_3. Vitamin D obtained from the skin and diet is metabolized to 25-hydroxyvitamin D. This determines a patient's measured serum level of vitamin D. 25-hydroxyvitamin D is then further metabolized in the kidneys to its active form, 1,25-hydroxyvitamin D. Most tissues and cells in the body possess a vitamin D receptor, and many have the ability to convert 25-hydroxyvitamin D to 1,25-hydroxyvitamin D.[1] This discovery is thought to be the reason such a broad range of diseases and conditions, including cancer, have benefited from vitamin D supplementation.

Cancer and Vitamin D Research

The emerging evidence showing the relationship between decreased cancer risk and vitamin D intake may be relatively new or even unheard of for many health care professionals. But the first article demonstrating a relationship between solar radiation and cancer mortality in North America was actually published in 1941.[9] In 1980, the first article was published proposing that vitamin D may be directly related to cancer risk.[10] Since that time, articles have been published that demonstrate an inverse relationship with solar radiation and cancer mortality for many types of cancers including breast, rectum, ovary, prostate, stomach, bladder, esophagus, kidney, lung, pancreas, uterus, non-Hodgkin lymphoma, and multiple myeloma.[11] Almost all of the evidence that links vitamin D and cancer has come from observational studies. One study, however, published in 2007 by Lappe et al,[11] prospectively looked at the effect of vitamin D intake on the incidence of all cancers.

The purpose of the study was to determine if calcium alone or calcium plus vitamin D has an effect on reducing the incidence of all types of cancer.[11] The study was designed as a 4-year, population-based, double-blind, randomized placebo-controlled trial. The

study participants included 1024 community-dwelling women who were randomly selected from a population of healthy postmenopausal women from 9 rural counties in Nebraska. The participants' mean age was 66.7 years, with a body mass index of 29.0 kg/m^2 and a baseline serum 25-hydroxyvitamin D level of 71.8 nmol/L. Subjects were randomly assigned to 1 of 3 groups: 1400 to 1500 mg supplemental calcium per day alone, 1400 to 1500 mg supplemental calcium plus 1100 IU vitamin D_3 per day, or placebo.[11]

The results showed that both the calcium-only and the calcium plus vitamin D groups had lower rates for all cancers compared with the placebo group ($P < .03$).[11] The relative risk for the development of cancer at the study's end was 0.402 for the calcium plus vitamin D group ($P = .013$) and 0.532 for the calcium-only group ($P = .063$). The Kaplan-Meier plot of the 3 groups showing survival-free cancer over the course of the study revealed a similar time course up to 1 year, which then began to separate. The 12-month serum 25-hydroxyvitamin D level in the calcium plus vitamin D group increased by 23.9 nmol/L to 96.0 nmol/L compared with statistically unchanged levels in the other 2 groups. In multiple logistic regression models, both treatment and serum 25-hydroxyvitamin D concentrations were significant, independent predictors of cancer risk. This translated to a predicted 35% reduced risk of cancer for every 25-nmol/L (10-ng/mL) increase in serum 25-hydroxyvitamin D. The authors concluded that improving vitamin D nutritional status substantially reduced all-cancer risk in postmenopausal women and that baseline and treatment-induced serum 25-hydroxyvitamin D concentrations were strong predictors of cancer risk.[11]

Other studies relating cancer to vitamin D have shown that people living at higher latitudes are at increased risk for Hodgkin lymphoma as well as colon, pancreatic, prostate, ovarian, breast, and other cancers. In addition, people living at higher latitudes are more likely to die from these cancers compared with those living at lower latitudes.[1] Epidemiologic studies, both prospective and retrospective, have shown that individuals who have serum 25-hydroxyvitamin D levels less than 20 ng/mL have an associated 30% to 50% greater risk of colon, prostate, and breast cancer as well as a higher mortality rate from these cancers.[1] In addition, analysis of the Women's Health Initiative showed that women who had a serum 25-hydroxyvitamin D level less than 12 ng/mL (30 nmol/L) had a 253% increase in the risk of colorectal cancer over an 8-year follow-up period.[12]

Vitamin D Intake

The current recommended daily allowance of vitamin D in the United States is 200 IU/d for children and adults up to 50 years of age, 400 IU/d for 51 to 70 years, and 600 IU/d for those older than 70 years.[7] The emerging evidence on the nonskeletal benefits of vitamin D has made these recommendations obsolete. As a general rule of thumb, serum 25-hydroxyvitamin D concentration will increase 1 ng/mL for every 100 IU vitamin D_3.[1,13] Therefore, if a patient has a baseline concentration of 10 mg/mL, an additional 3000 IU/d would be required to achieve a level of 40 ng/mL and put this patient in the sufficiency category.

Vitamin D can be obtained through exposure to sunlight, food that naturally contains vitamin D, food that is fortified with vitamin D, and prescription and over-the-counter dietary supplementation. Aside from supplementation, the most significant source of vitamin D is through sun exposure. Sensible sun exposure is considered safe and effective for obtaining vitamin D_3. This would entail the exposure of arms and legs for 5 to 30 minutes (depending on season, latitude, and skin pigmentation) between the hours of 10 am and 3 pm 2 times per week. When the body produces excess vitamin D precursors and vitamin D_3, they are destroyed by sunlight; therefore, excessive exposure to sunlight does not cause vitamin D intoxication.[1] Caution should be used when educating patients regarding sun exposure. Health care professionals should counsel patients on the message that sun exposure ad libitum is not acceptable for the purposes of obtaining adequate serum 25-hydroxyvitamin D concentrations and that a balance between the risk for skin cancer and vitamin D intake should be achieved.

A diet high in oily fish such as salmon, sardines, mackerel, and tuna can supply a range of vitamin D_3 from 250 to 1000 IU per

serving. For example, 3.5 oz of fresh, wild salmon can provide 600 to 1000 IU of vitamin D_3, whereas 3.5 oz of fresh, farmed salmon can supply only 100 to 250 IU of vitamin D_3. Likewise, 3.6 oz of canned tuna contains about 230 IU of vitamin D_3. In addition, 8 oz of fortified milk, orange juice, or yogurt contains about 100 IU of vitamin D_3.[1] Most Americans do not consistently take in enough daily vitamin D through their diet to maintain adequate serum concentrations, and therefore supplementation is most often recommended.

As shown in Table 1, the lower level of serum 25-hydroxyvitamin D considered to be sufficient is 32 ng/mL. To achieve a serum concentration of 32 ng/mL or higher, most individuals will need to obtain about 4000 IU/d or more vitamin D_3 from all sources combined.[8] Because most individuals do not get enough vitamin D_3 through their diet and/or live under conditions that prohibit adequate sun exposure, most healthy adults will need 2000 IU/d vitamin D_3 supplementation to achieve a serum concentration of 32 ng/mL or greater. Studies have shown that supplementation with vitamin D_3 over a period of about 90 days is needed to reach steady-state concentrations.[7] Supplementation is available in both vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) formulations. Toxicity and overdose have been related to vitamin D_2 intake but not D_3 intake. Doses of vitamin D_2 of more than 50 000 IU/d have been shown to raise serum 25-hydroxyvitamin D concentrations to greater than 150 ng/mL, causing associated hypercalcemia and hyperphosphatemia. Doses of vitamin D_3 of 10 000 IU/d have been shown to be taken without incidence of side effects and is considered to be the safe upper limit of daily intake.[1] In addition, both vitamin D_2 and D_3 have demonstrated the ability to achieve adequate serum 25-hydroxyvitamin D concentrations; however, vitamin D_3 has been shown to maintain these concentrations for a longer period of time.[14] As a result, supplementation with vitamin D_3 is generally recommended over vitamin D_2.

Table 1. Serum 25-Hydroxyvitamin D Concentrations by Category[1,5,7,8]

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Cost and Availability

Vitamin D_3 can easily be found as an over-the-counter dietary supplement in most pharmacies. As with all supplements, patients should be advised to purchase brands from reputable and well-known companies to ensure quality. Vitamin D_3 is available in a variety of strengths including 400 IU, 1000 IU, 2000 IU, and 10 000 IU. As discussed above, most individuals should take approximately 2000 IU daily, which can be found at most pharmacies, supermarkets, and nutrition stores for less than $10 per bottle of 100 tablets or capsules. This makes vitamin D_3 supplementation relatively inexpensive when compared with the demonstrated benefits.

Conclusion

Reports have shown that a large percentage of our population may have serum vitamin D concentrations that are considered suboptimal. Obtaining adequate amounts of vitamin D is important not only for bone health but also for decreasing the risk for several other diseases and conditions, including cancer. Data support the justification for supplementing vitamin D_3 2000 IU/d in

most adults to decrease the risk for several types of cancers and other conditions. Vitamin D_3 is relatively inexpensive and can be found as an over-the-counter product in most pharmacies.

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