Vitamin D and Cancer Prevention: Strengths and Limits of the Evidence

Key Points

- Vitamin D is essential for the formation, growth, and repair of bones and for normal calcium absorption and immune function. It is obtained primarily through exposure of the skin to ultraviolet radiation in sunlight, but it can also be obtained from some foods and dietary supplements (see Questions 1 and 4).
- Some studies suggest that higher intakes of vitamin D from food and/or supplements and higher levels of vitamin D in the blood are associated with reduced risks of colorectal cancer; however, the research results overall have been inconsistent (see Question 7).
- Whether vitamin D is associated with reduced risks of other cancers, including breast, prostate, and pancreatic cancers, remains unclear (see Questions 8, 9, 10, and 11).
- The National Cancer Institute (NCI) does not recommend for or against the use of vitamin D supplements to reduce the risk of colorectal or any other type of cancer (see Question 14).

Note: The information in this fact sheet is not to be used as the basis for making health claims about products containing vitamin D.

1. What is vitamin D?

Vitamin D is technically not a vitamin. It is the name given to a group of fat-soluble prohormones (substances that are precursors to hormones that usually have little hormonal activity by themselves). Two major forms of vitamin D that are important to humans are vitamin D_2, or ergocalciferol, and vitamin D_3, or cholecalciferol. Vitamin D_2 is made naturally by plants, and vitamin D_3 is made naturally by the body when the skin is exposed to ultraviolet radiation (in particular, UVB radiation) in sunlight. Vitamin D_2 and vitamin D_3 can also be commercially manufactured.

The active form of vitamin D in the body is 1,25-dihydroxyvitamin D, or calcitriol, which can be made from either vitamin D_2 or vitamin D_3. To make the active form, vitamin D_2 and vitamin D_3 are modified in the liver to produce 25-hydroxyvitamin D, which travels through the blood to the kidneys, where it is modified further to make 1,25-dihydroxyvitamin D.

Vitamin D is involved in a number of processes that are essential for good health, including the following:

- It helps improve muscle strength and immune function.
- It helps reduce inflammation.
- It promotes the absorption of calcium from the small intestine.
- It helps maintain adequate blood levels of the calcium and phosphate needed for bone formation, mineralization (incorporating minerals to increase strength and density), growth, and repair (1–3).

Most people get the vitamin D they need through sunlight exposure. It can also be obtained through the diet, but very few foods naturally contain vitamin D. These foods include fatty fish, fish liver oil, and eggs. Smaller amounts are found in meat and cheese. Most dietary vitamin D comes from fortified foods, such as milk, juices, yogurt, bread, and breakfast cereals. Vitamin D can also be

obtained through dietary supplements. Fortified foods and dietary supplements usually contain either vitamin D_2 or vitamin D_3. A person's vitamin D status is usually checked by measuring the level of 25-hydroxyvitamin D in their blood serum.

2. How much vitamin D is needed for health?

A serum level of 25-hydroxyvitamin D lower than 15 nanograms per milliliter (ng/mL)—equivalent to 37.5 nanomoles per liter (nmol/L)—is generally considered inadequate for a healthy person to maintain bone health and normal calcium metabolism (2). However, some experts say that this may be on the low side, and the 2005 *Dietary Guidelines for Americans* notes that the optimal level may be as high as 80 nmol/L. A serum level below 11 ng/mL (27.5 nmol/L) is consistent with vitamin D deficiency in infants, neonates, and young children (2). The Institute of Medicine of the National Academies has developed the following recommended daily intakes of vitamin D (on the assumption that vitamin D_3 is not being made in the skin through sun exposure) (1, 2):

Age	Recommended Minimum Vitamin D Intake (µg/day and IU/day)
Birth to 50 years	5 µg (=200 IU)
51–70 years	10 µg (=400 IU)
71+ years	15 µg (=600 IU)
Pregnancy	5 µg (=200 IU)
Lactation	5 µg (=200 IU)

µg = microgram; 1 µg = 40 International Units (IU)

The 2005 *Dietary Guidelines for Americans* recommends that older adults, people with dark skin, and people exposed to insufficient sunlight should consume extra vitamin D from vitamin D-fortified foods and/or supplements.

People are more likely to not get enough vitamin D than to get too much. However, excessive intake of any nutrient, including vitamin D, can cause toxic effects (see Question 5). Excessive sun exposure does not cause vitamin D toxicity.

3. What are the health effects of vitamin D deficiency?

Vitamin D deficiency can impair normal bone metabolism, leading to the following conditions:

- Rickets (a condition in children marked by soft and deformed bones; it is caused by undermineralization of bone).
- Osteomalacia (adult rickets).
- Osteoporosis (weak and porous bones) (1, 2).

4. How much vitamin D is in fortified foods and supplements?

Fortification of foods with vitamin D in the United States is carefully regulated (4). Vitamin D fortification is allowed for milk and milk products, cereal flours and related products, margarine, soy-based food products, and fruit juices and fruit juice drinks. Milk is usually fortified with 2.5 µg (100 IU) vitamin D per cup (4). Some yogurts are now fortified with vitamin D. Cheese, ice cream, and other dairy products made from milk are generally not fortified with vitamin D. To see if a food product has been fortified, check the food label.

The amount of vitamin D in multivitamins and other dietary supplements typically ranges from 10 µg (400 IU) to 50 µg (2,000 IU) (5).

5. Is it safe to take vitamin D supplements?

Vitamin D toxicity is more likely to occur from high intakes of dietary supplements than from high intakes of vitamin D-fortified foods. For most children and adults, the tolerable upper intake level (UL) of vitamin D intake from foods and supplements is 25 µg (1,000 IU) per day for those less than 1 year of age and 50 µg (2,000 IU) per day for older individuals (1, 2). The UL is the highest level of daily intake (from all sources combined) that is likely to pose no risk of adverse effects for almost all people.

Excessive vitamin D intake is toxic because it increases calcium levels. Increased calcium levels can lead to calcinosis (the deposit of calcium salts in soft tissues of the body, such as the kidneys, heart, and lungs) and hypercalcemia (high blood levels of calcium). Symptoms of excessive vitamin D intake may include heart rhythm abnormalities; mental status changes, such as confusion; pain; conjunctivitis; anorexia; fever; chills; thirst; vomiting; and weight loss (1, 2, 4).

6. Is there a role for vitamin D in reducing cancer risk?

A large number of scientific studies have investigated a possible role for vitamin D in cancer prevention.

- The first results came from epidemiologic studies known as geographic correlation studies. In these studies, an inverse relationship was found between sunlight exposure levels in a given geographic area and the rates of incidence and death for certain cancers in that area. Individuals living in southern latitudes were found to have lower rates of incidence and death for these cancers than those living at northern latitudes. Because sunlight/UV exposure is necessary for the production of vitamin D_3, researchers hypothesized that variation in vitamin D levels accounted for the observed relationships.

- Evidence of a possible cancer-protective role for vitamin D has also been found in laboratory studies of the effect of vitamin D treatment on cancer cells in culture. In these studies, vitamin D promoted the differentiation and death (apoptosis) of cancer cells, and it slowed their proliferation.

- Randomized clinical trials designed to investigate the effects of vitamin D intake on bone health have suggested that higher vitamin D intakes may reduce the risk of cancer. One study involved nearly 1,200 healthy postmenopausal women who took daily supplements of calcium (1,400 mg or 1,500 mg) and vitamin D (25 µg vitamin D, or 1,100 IU—a relatively large dose) or a placebo for 4 years. The women who took the supplements had a 60 percent lower overall incidence of cancer (6); however, the study did not include a vitamin D-only group. Moreover, the primary outcome of the study was fracture incidence; it was not designed to measure cancer incidence. This limits the ability to draw conclusions about the effect of vitamin D intake on cancer risk.

- A number of observational studies have investigated whether people with higher vitamin D levels or intake have lower risks of specific cancers, particularly colorectal cancer and breast cancer. Associations of vitamin D with risks of prostate, pancreatic, and other, rarer cancers have also been examined. These studies have yielded inconsistent results, most likely because of the challenges of conducting observational studies of diet (7). Information about dietary intakes is obtained from the participants through the use of food frequency questionnaires, diet records, or interviews in which the participants are asked to recall information about their dietary intakes. Information collected in this manner can be inaccurate. In addition, only recently has a comprehensive food composition database with vitamin D values for the U.S. food supply become available. Other dietary components or energy balance may also modify vitamin D metabolism (8).

  Measuring blood levels of 25-hydroxyvitamin D to determine vitamin D status avoids some of the limitations of assessing dietary intake. However, vitamin D levels in the blood vary by race, with the season, and possibly with the activity of genes whose products are involved in vitamin D transport and metabolism. These variations complicate the interpretation of studies that measure the concentration of vitamin D in serum at a single point in time.

  Finally, it is difficult to separate the effects of vitamin D and calcium because of the complicated biological interactions between these substances. To fully understand the effect of vitamin D on cancer and other health outcomes, new randomized trials will need to be carried out (9). However, the appropriate dose of vitamin D to use in such trials is still not clear (10).

7. Is there evidence that vitamin D can help reduce the risk of colorectal cancer?

Epidemiologic studies of the association between vitamin D and the risk of colorectal cancer have provided some indications that higher levels of intake are associated with a reduced risk. However, the data are inconsistent.

In the American Cancer Society's Cancer Prevention Study (CPS) II Nutrition Cohort, the diet, medical history, and lifestyle of more than 120,000 men and women were analyzed (11). Men who had the highest intakes of vitamin D through both their diet and supplement use (greater than 13 µg, or 525 IU, per day) had a slightly

lower risk of colorectal cancer than men who had the lowest vitamin D intakes. However, this association was not observed among women.

In a pooled analysis of data from 10 cohort studies (including the CPS II cohort), individuals with the highest dietary vitamin D intakes had a slightly lower risk of colorectal cancer than those with the lowest intakes, but the reduction in risk was not statistically significant (12).

In the Women's Health Initiative randomized trial, healthy postmenopausal women took daily supplements that contained both calcium (1,000 mg) and vitamin D (10 µg, or 400 IU) or a placebo for an average of 7 years. Supplementation did not reduce the incidence of colorectal cancer (13). However, some scientists have raised the possibility that the relatively low level of vitamin D supplementation and the short duration of participant follow-up might account for the negative results.

At least one epidemiologic study has reported an association between vitamin D and reduced mortality from colorectal cancer. Among the 16,818 participants in the Third National Health and Nutrition Examination Survey, those with higher vitamin D blood levels (≥80 nmol/L) had a 72 percent lower risk of colorectal cancer death than those with lower vitamin D blood levels (< 50 nmol/L) (14).

Most colorectal cancers develop from pre-existing colorectal adenomas, and interventions that reduce the risk of adenoma development or recurrence are likely to reduce the risk of colorectal cancer. Several large studies have investigated the association of vitamin D intake or serum status with adenoma risk.

A cohort from the National Cancer Institute (NCI)-sponsored Polyp Prevention Trial (PPT) was evaluated for the association of vitamin D intake with recurrence of colorectal adenomas in individuals who previously had one or more adenomas removed during a qualifying colonoscopy (15). PPT was a multicenter randomized clinical trial to determine the effects of a diet high in fiber, fruits, and vegetables and low in fat on adenoma recurrence. The detailed dietary information obtained during the trial allowed the researchers to investigate the association between additional dietary factors and adenoma recurrence. Total vitamin D intake (that is, from dietary sources and supplements combined) was not associated with a reduced risk of adenoma recurrence (15). However, individuals who used any amount of vitamin D supplements had a lower risk of adenoma recurrence (15).

In another study, the vitamin D intakes of 3,000 people from several Veterans Affairs medical centers were examined to determine whether there was an association between intake and advanced colorectal neoplasia (an outcome that included high-risk adenomas as well as colon cancer) (16). Individuals with the highest vitamin D intakes (more than 16 µg, or 645 IU, per day) had a lower risk of developing advanced neoplasia than those with lower intakes (16).

A pooled analysis of data from these and a number of other observational studies found that higher circulating levels of vitamin D and higher vitamin D intakes were associated with lower risks of colorectal adenoma (17). Inverse associations were seen with both dietary and total vitamin D intake but not with supplemental vitamin D intake. However, the associations with dietary intake were not statistically significant.

Another large, NCI-sponsored randomized, placebo-controlled trial explored the effects of calcium supplementation and blood levels of vitamin D on adenoma recurrence (18). Calcium supplementation reduced the risk of adenoma recurrence only in individuals with vitamin D blood levels above 73 nmol/L. Among individuals with vitamin D levels at or below this level, calcium supplementation was not associated with a reduced risk (18).

8. Is there evidence that vitamin D can help reduce breast cancer risk?

Epidemiologic studies of the association between vitamin D and breast cancer risk have had conflicting results. Although several studies have suggested an inverse association between vitamin D intake and the risk of breast cancer, others have shown no association or even a positive association (that is, individuals with higher intakes had higher risks). A meta-analysis of six studies that investigated the relationship between vitamin D intake and breast cancer risk found no association (19). However, most women in these studies had relatively low vitamin D intakes, and, when the analysis was restricted to women with the highest vitamin D intakes (>10 µg, or 400 IU, per day), their breast cancer risks were lower than those of women with the lowest intakes (typically <1.25 µg, or 50 IU, per day) (19).

In the Women's Health Initiative, calcium plus vitamin D supplementation for an average of 7 years did not reduce the incidence of invasive breast cancer compared with placebo (20).

The association between blood levels of vitamin D and breast cancer risk was examined in a cohort of postmenopausal women who were enrolled in NCI's Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and from whom blood was drawn at study entry. During the subsequent follow-up period, 1,005 of these women developed breast cancer. When researchers compared the blood vitamin D levels of these women with those of 1,005 similar control women who did not develop breast cancer, they found no association between vitamin D status and risk of breast cancer (21).

9. Is there evidence that vitamin D can help reduce prostate cancer risk?

Some geographic correlation studies (see Question 6) have suggested that men exposed to higher levels of sunlight may have a lower risk of prostate cancer. Although some epidemiologic studies have suggested that men with higher vitamin D levels have an increased risk of prostate cancer, most studies have not shown such an association.

In one relatively large study of men diagnosed 1 to 8 years after their blood was drawn, higher vitamin D blood levels were not associated with a lower risk of prostate cancer overall (22). Indeed, there was some evidence that men with higher vitamin D levels had an increased risk for aggressive disease (22).

In another study, the European Prospective Investigation into Cancer and Nutrition (EPIC), blood samples obtained at study entry were examined for 652 men who developed prostate cancer during follow-up and 752 matched control subjects (23). No association was observed between serum vitamin D levels and risk of prostate cancer, either overall or by cancer stage.

10. Is there evidence that vitamin D can help reduce pancreatic cancer risk?

There is conflicting evidence about vitamin D's relationship to risk of pancreatic cancer. A study of more than 120,000 men and women from the Health Professionals Follow-Up Study and the Nurses' Health Study showed that participants with higher dietary intake of vitamin D had progressively lower risk of pancreatic cancer, compared with those who had the lowest intake (24). The estimates of vitamin D intake were based on detailed dietary information provided through questionnaires. Participants were followed for 16 years for the incidence of pancreatic cancer, and 365 cases were identified.

In a study of men and women enrolled in the PLCO Screening Trial, no association between vitamin D level and pancreatic cancer risk was observed. The PLCO study examined vitamin D levels in blood from 184 individuals who were diagnosed with pancreatic cancer during nearly 12 years of follow-up and 368 matched cancer-free control subjects (25). In contrast, among Finnish male smokers participating in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study (26), higher blood levels of vitamin D were associated with an increased risk of pancreatic cancer. More recently, in the NCI Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (see Question 11), men and women with the highest blood vitamin D levels (greater than 100 nmol/L, or 40 ng/mL) had twice the pancreatic cancer risk of men and women whose blood vitamin D levels were in the normal range of 50-75 nmol/L (20-30 ng/mL).

11. Is there evidence that vitamin D can help reduce the risk of other rare cancers?

A recent large collaborative effort analyzed data from 10 prospective cohort studies to examine whether vitamin D levels in blood were associated with seven rare cancers (27). The NCI Cohort Consortium Vitamin D Pooling Project of Rarer Cancers included information on blood vitamin D levels and incidence of rare cancers in a subset of more than 12,000 men and women. The researchers matched participants on date and season of blood draw and used other statistical techniques to adjust for seasonal variation in blood vitamin D levels. When the data from the different studies were pooled, there was no overall association between vitamin D level and risk of non-Hodgkin lymphoma or cancers of the endometrium, esophagus, stomach, kidney, or ovary. As described in Question 10, an increased risk of pancreatic cancer was observed in those with the highest blood levels of vitamin D (greater than 100 nmol/L or 40 ng/mL).

12. What are the possible mechanisms by which vitamin D may modify cancer risk?

Mechanisms by which vitamin D may modify cancer risk are not fully understood. Laboratory studies have shown that vitamin D promotes cellular differentiation, decreases cancer cell growth, and stimulates apoptosis (28, 29).

Vitamin D acts on cells by binding to the vitamin D receptor (VDR). The VDR is a regulator of gene transcription that is found in the nucleus of cells. Vitamin D-bound VDR binds to the retinoid-X receptor (RXR), and the resulting complex activates the expression of specific genes. Among the many genes regulated by vitamin D are those that produce the proteins calbindin and TPRV6, both of which are involved in the absorption of calcium by intestinal cells (30). Another vitamin D-regulated gene is CYP3A4, whose protein product detoxifies the bile acid lithocholic acid (LCA). LCA is believed to damage the DNA of intestinal cells and may promote colon carcinogenesis. Stimulating the production of a detoxifying enzyme by vitamin D could explain a protective role for vitamin D against colon cancer (31).

Further insight into the mechanisms by which vitamin D might modify cancer risk could come from study of the vitamin D receptor itself. A large number of variant forms of the VDR gene have been identified, some of which are known to alter the structure or function of the VDR protein. Some of these variants have been linked to risk for certain cancers, including prostate, colorectal, breast, bladder, and melanoma (32). The association of VDR variants with cancer risk differs by cancer site and appears to be modified by environmental exposures, such as diet and sun exposure.

13. How can people get enough sunlight for vitamin D synthesis while minimizing the risk of skin cancer?

Although people obtain some vitamin D from dietary sources, most vitamin D is made in the body after the skin is exposed to sunlight. Despite the known and potential health benefits of vitamin D, increasing sun exposure increases the risk of skin cancer. In general, most experts believe that people should continue to use sun protection when UV levels are moderate or higher. Some researchers have suggested that brief daily exposure to UV will ensure adequate vitamin D production, but many variables (such as skin color, latitude, and season) can affect the production of vitamin D, and such recommendations have proven controversial. Other experts recommend vitamin D supplementation to avoid the problem of increasing skin cancer risk.

14. Does NCI recommend the use of vitamin D supplements to prevent colorectal or other cancers?

NCI is a research institute and provides evidence-based results for others to interpret. Therefore, in general, NCI does not make recommendations on supplement use.

Although some evidence suggests that vitamin D may provide some protection against colorectal and possibly other cancers, the evidence of potential benefit is limited and inconsistent. Moreover, some studies have suggested the possibility that higher vitamin D levels are associated with increased risk for some cancers, including pancreatic cancer.

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Related NCI materials and Web pages:

- *Calcium and Cancer Prevention: Strengths and Limits of the Evidence* Fact Sheet (http://www.cancer.gov/cancertopics/factsheet/prevention/calcium)
- *PDQ® Prevention Summary for Health Professionals on Colorectal Cancer* (http://www.cancer.gov/cancertopics/pdq/prevention/colorectal/HealthProfessional)
- Cancer Prevention Home Page (http://www.cancer.gov/cancertopics/prevention)
- Colon and Rectal Cancer Home Page (http://www.cancer.gov/cancertopics/types/colon-and-rectal)
- Energy Balance: Weight and Obesity, Physical Activity, Diet Home Page (http://www.cancer.gov/cancertopics/prevention/energybalance)

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