

## Vitamin D and Sunlight: Strategies for Cancer Prevention and Other Health Benefits

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Vitamin D deficiency is a worldwide health problem. The major source of vitamin D for most humans is sensible sun exposure. Factors that influence cutaneous vitamin D production include sunscreen use, skin pigmentation, time of day, season of the year, latitude, and aging. Serum 25-hydroxyvitamin D [25(OH)D] is the measure for vitamin D status. A total of 100 IU of vitamin D raises blood level of 25(OH)D by 1 ng/ml. Thus, children and adults who do not receive adequate vitamin D from sun exposure need at least 1000 IU/d vitamin D. Lack of sun exposure and vitamin D deficiency have been linked to many serious chronic diseases, including autoimmune diseases, infectious diseases, cardiovascular disease, and deadly cancers. It is estimated that there is a 30 to 50% reduction in risk for developing colorectal, breast, and prostate cancer by either increasing vitamin D intake to least 1000 IU/d vitamin D or increasing sun exposure to raise blood levels of 25(OH)D >30 ng/ml. Most tissues in the body have a vitamin D receptor. The active form of vitamin D, 1,25-dihydroxyvitamin D, is made in many different tissues, including colon, prostate, and breast. It is believed that the local production of 1,25(OH)<sub>2</sub>D may be responsible for the anticancer benefit of vitamin D. Recent studies suggested that women who are vitamin D deficient have a 253% increased risk for developing colorectal cancer, and women who ingested 1500 mg/d calcium and 1100 IU/d vitamin D<sub>3</sub> for 4 yr reduced risk for developing cancer by >60%.

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Vitamin D is likely to be one of the oldest hormones. It has existed for at least 750 million years, when phytoplankton synthesized it in response to sunlight (1). Throughout evolution, vitamin D played a critical role in the evolution of vertebrates as they left their high-calcium ocean environment for the calcium-deficient *terra firma*. Nocturnal rodents and other rodent-like species that lived underground needed little, if any, vitamin D to survive. It has been speculated that when the asteroid hit the earth 65 million yr ago, one of the survival characteristics for nocturnal mammals was that they did not require sunlight-mediated vitamin D synthesis to survive, unlike the dinosaurs. Dinosaurs likely depended on the sun to satisfy their vitamin D requirement to utilize dietary calcium efficiently for the maintenance of their massive skeletons (1). Thus, the lack of sunlight-mediated vitamin D synthesis after the asteroid impact may have been related to the demise of the dinosaurs.

The industrialization of Europe and the United States in the 17th through the 19th centuries gave birth to the devastating bone-deforming and growth-retarding disease rickets. Although Sniadecki in 1822 suggested that children who were

living in the industrialized cities in Poland were at a higher risk for rickets than children who were living in rural areas as a result of lack of sun exposure, it would take 100 yr before it was reported that exposure to ultraviolet radiation from a mercury arc lamp or sun exposure prevented and cured rickets (2,3).

### Sun-Cancer Connection

The association of sun exposure and latitude with cancer mortality was first noted by Hoffman in 1915 (4). He reported mortality from cancer in cities at various latitudes and observed a gradient decline in the death rate. Peller and Stephenson (5) recognized that people who were exposed to enough sunlight to induce nonlethal, nonmelanoma skin cancers had a decreased incidence of more malignant tumors. They observed that the rate of skin cancer in US Navy personnel was eight times higher, whereas the total number of deaths from other cancers was reduced by >60% in comparison with the civilian population. This was followed by Apperley (6), who reported that people who live at higher latitudes in the United States, including New Hampshire, Vermont, and Massachusetts, were more likely to die of cancer than adults who live in southern states, such as Alabama and Georgia.

In the 1980s to 1990s, Garland *et al.* (7) and Gorham *et al.* (8) completed a number of epidemiologic studies and noted that there was a strong negative correlation between latitude, sun exposure, and poor vitamin D status and the risk for developing many deadly cancers, including colon, breast, ovarian, and

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melanoma (Figure 1). These observations were followed by Grant (9), who noted that several cancers were reduced by adequate exposure to solar ultraviolet B radiation. He estimated that during a span of 24 yr, 1970 through 1994, a total of 566,400 Americans died prematurely from 13 cancers as a result of inadequate sun exposure. This was confirmed by a more recent analysis that concluded that between 50,000 and 63,000 Americans and 19,000 and 25,000 adults who live in the United Kingdom die prematurely from cancer each year as a result of inadequate sun exposure and vitamin D deficiency (10).

### Sources and Metabolism of Vitamin D

The major source of vitamin D for most humans is exposure to sunlight (2,11). When the ultraviolet B portion of sunlight enters the skin, 7-dehydrocholesterol in the plasma membrane of both keratinocytes and fibroblasts is converted to previtamin D<sub>3</sub>. Previtamin D<sub>3</sub> rapidly converts within the plasma membrane by a membrane-dependent process to vitamin D<sub>3</sub>, which is then ejected into the extracellular space. Vitamin D<sub>3</sub> from the skin is bound to the vitamin D-binding protein, whereas vitamin D<sub>2</sub> and vitamin D<sub>3</sub> from diet are bound to vitamin D-binding protein and lipoproteins. Both forms are hydroxylated in the liver to 25-hydroxyvitamin D [25(OH)D; D represents D<sub>2</sub> or D<sub>3</sub>]. 25(OH)D is a major circulating form and is the only form used to determine the vitamin D status of a patient (2,11); however, 25(OH)D is inactive and requires hydroxylation in the kidney on carbon 1 to form 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D]. 1,25(OH)<sub>2</sub>D acts in an endocrine manner to regulate calcium metabolism by enhancing intestinal calcium absorption and mobilizing calcium from the skeleton (2,11–13).

There are very few dietary sources of vitamin D. These

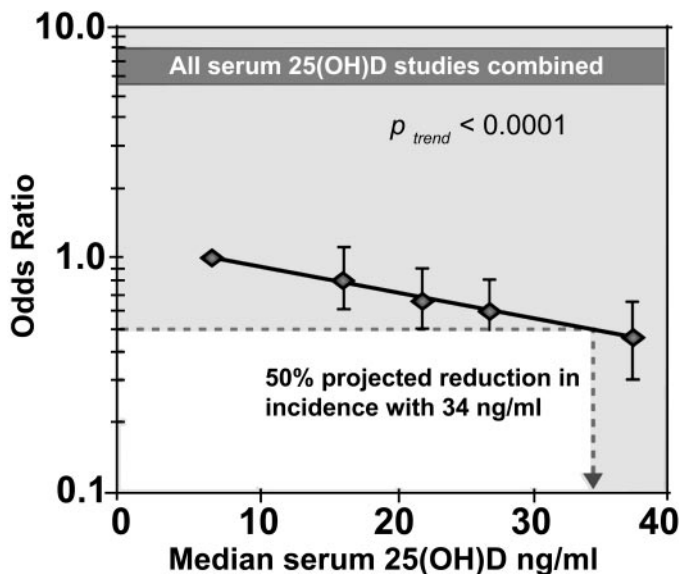


Figure 1. Dose-response gradient for colorectal cancer according to serum 25-hydroxyvitamin D [25(OH)D] concentration of five studies combined. The five points are the odds ratios for each quintile of 25(OH)D on the basis of the combined data from the five studies. Reprinted from reference (8), with permission.

include oily fish, such as salmon, mackerel, and sardines (11). Some foods, including milk, orange juice, bread, cereals, and yogurts, are fortified with vitamin D in the United States. In Europe, margarine and cereals are the major source except in Sweden and Finland, where milk is now fortified with vitamin D; however, there is only 100 IU of vitamin D in an 8-oz serving of milk and orange juice. The content of vitamin D naturally found in food is highly variable. Wild-caught salmon contains approximately 500 to 1000 IU of vitamin D<sub>3</sub> in 3.5 oz, whereas farmed salmon in the United States contains approximately 100 to 250 IU in 3.5 oz (11).

It has been estimated that for every 100 IU of vitamin D ingested, there is an increase in the blood level of 25(OH)D of 1 ng/ml (2.5 nmol/L) (14,15). Limited sensible exposure to sunlight or ultraviolet B radiation is more effective in raising blood levels of 25(OH)D than 1000 IU vitamin D<sub>3</sub> taken daily for adults of most skin types (16) (Figure 2).

### Definition of Vitamin D Sufficiency and the Vitamin D Deficiency Pandemic

Several measures have been used as determinants for defining vitamin D deficiency, insufficiency, and adequacy. A 25(OH)D of <20 ng/ml is associated with suppressible levels of parathyroid hormone when challenged with pharmacologic dosages of vitamin D (17). Parathyroid hormone levels begin to reach their nadir when 25(OH)D levels are >30 ng/ml (18,19). Intestinal calcium absorption in adults is maximized when 25(OH)D is >30 ng/ml (20). Thus, many experts recommend that vitamin D deficiency, insufficiency, and sufficiency are defined as <20, 21 to 29, and >30 ng/ml, respectively. To achieve these levels, a minimum of 1000 IU of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> is needed daily when sun exposure is either unavailable or inadequate to make vitamin D<sub>3</sub>, such as during the winter or when a sunscreen is used (21,22).

In the United States, Europe, India, Asia, Middle East, New Zealand, and Australia, vitamin D deficiency is common (11) in pregnant women (23,24); newborns (23); young and adolescent children (25–28); and young, middle-aged, and older adults (29–32). Vitamin D deficiency is especially common in people of color (25) or who avoid sunlight (32).

### Vitamin D and the Cancer Connection

It was perplexing as to how sunlight and the vitamin D connection could be associated with decreasing the risk for developing common deadly cancers. It was known that 1,25(OH)<sub>2</sub>D<sub>3</sub> was one of the most potent hormones for inhibiting both normal and cancer cell proliferation and inducing maturation (11,33,34). Although the exact mechanism by which 1,25(OH)<sub>2</sub>D is able to regulate cellular proliferation and differentiation is not fully understood, a large number of genes control proliferation, differentiation, apoptosis, and angiogenesis and are either directly or indirectly influenced by 1,25(OH)<sub>2</sub>D<sub>3</sub> (11,33–35). 1,25(OH)<sub>2</sub>D<sub>3</sub> increased inhibitors and decreased activators of cyclin-cyclin-dependent kinase complexes in addition to increasing levels of cyclin-dependent kinase inhibitors Cip/Kip proteins P21 and P27. These proteins are known to keep the cell cycle in the G1/S phase, preventing

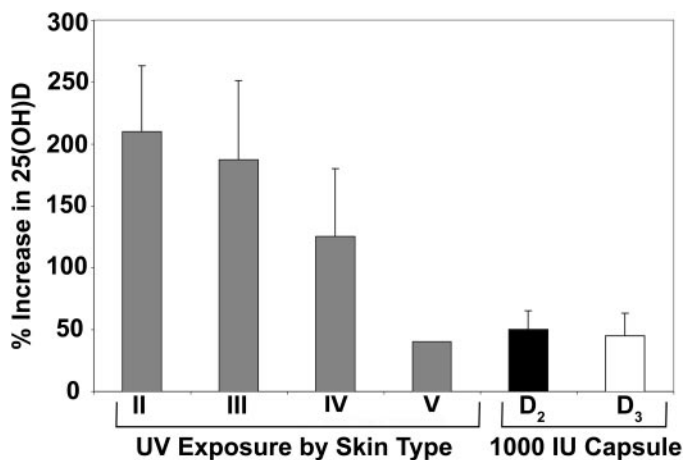


Figure 2. Comparison of the percentage increase in serum 25(OH)D levels of healthy adults who were in a bathing suit and exposed to suberythemal doses (0.5 MED) of ultraviolet B radiation once a week for 3 mo with healthy adults who received either 1000 IU of vitamin D<sub>2</sub> or 1000 IU of vitamin D<sub>3</sub> daily during the winter and early spring for a period of 11 wk. Fifty percent increase represented approximately 10 ng/ml from baseline  $18 \pm 3$  to  $28 \pm 4$  ng/ml. Skin type is based on the Fitzpatrick scale: Type II always burns, sometimes tans; type III always burns, always tans; type IV sometimes burns, always tans; type V never burns, always tans. Data are means  $\pm$  SEM. Reprinted with permission, copyright Michael F. Holick, 2008.

DNA synthesis and, therefore, cellular growth (33). A human colon cancer cell line that expressed the vitamin D receptor (VDR) HT-29 responded to 1,25(OH)<sub>2</sub>D<sub>3</sub> by a dosage-dependent inhibition of cellular growth and induction of differentiation. A wide variety of other tumor cell lines including leukemia; melanoma; and lung, breast, and prostate cancer cells have been shown to respond to the antiproliferative and prodifferentiating activity of 1,25(OH)<sub>2</sub>D<sub>3</sub> (33–38). In addition, 1,25(OH)<sub>2</sub>D<sub>3</sub> induced apoptosis and has been demonstrated to be antiangiogenic both *in vivo* and *in vitro* (33,39).

It is well established that the kidneys are the major source of 1,25(OH)<sub>2</sub>D that is present in the circulation and is responsible for regulating the efficiency of intestinal calcium absorption and mobilizing calcium stores from the skeleton (11). In nephrectomized patients, circulating levels of 1,25(OH)<sub>2</sub>D are undetectable. Thus, it had been assumed that only the kidneys were capable of producing 1,25(OH)<sub>2</sub>D. It was recognized that keratinocytes in skin expressed the 25-hydroxyvitamin D-1-hydroxylase (CYP27B1; 1-OHase) (40); however, it was not until 1995, when it was observed that human prostate cells that were recovered from prostate biopsies not only expressed 1-OHase but also converted 25(OH)D<sub>3</sub> to 1,25(OH)<sub>2</sub>D<sub>3</sub>, that it was realized that the body had other resources to produce 1,25(OH)<sub>2</sub>D in an autocrine manner (41). It has been reported that many tissues and cells in the body, including activated macrophages, colon, prostate, breast, and brain, among others, have the ability to express 1-OHase and make 1,25(OH)<sub>2</sub>D<sub>3</sub> (11,37). With this new revelation, it was appreciated that there was another function for vitamin D that was unrelated to

calcium metabolism, and it was important not only for regulating cellular proliferation and differentiation but also for a wide variety of other biologic processes, including regulation of immune function, modulating vascular tone, and influencing renin and insulin synthesis, among other functions (11). Thus, although increasing vitamin D intake or sun exposure will not lead to an increase in the renal production of 1,25(OH)<sub>2</sub>D, it is believed that raising blood levels of 25(OH)D >30 ng/ml provides an adequate amount of substrate for the nonrenal conversion of 25(OH)D to 1,25(OH)<sub>2</sub>D in many of these organs and cells. Once 1,25(OH)<sub>2</sub>D carries out its autocrine function within the cell, it then induces its own destruction by markedly increasing the expression of the 25-hydroxyvitamin D-24 hydroxylase (CYP24R; 24-OHase) (11,33).

### Clinical Uses of the Antiproliferative Activity of 1,25(OH)<sub>2</sub>D<sub>3</sub> and Analogs

Epidermal cells have a VDR, and their proliferation is inhibited by 1,25(OH)<sub>2</sub>D<sub>3</sub> (2,11). This observation led to the concept that 1,25(OH)<sub>2</sub>D<sub>3</sub> could be used to treat the hyperproliferative skin disorder psoriasis. Topical application of 1,25(OH)<sub>2</sub>D<sub>3</sub> was found to be very effective for treating psoriasis with no untoward toxicity (42). 1,25(OH)<sub>2</sub>D<sub>3</sub> and several of its analogs are now one of the first-line treatments for psoriasis (11).

The observation that 1,25(OH)<sub>2</sub>D<sub>3</sub> was effective in inducing leukemic cells to differentiate *in vitro* led to a clinical trial in which patients with preleukemia were given 1,25(OH)<sub>2</sub>D<sub>3</sub>. Initially, patients responded favorably to the treatment but over time developed severe toxicity, including hypercalcemia, and ultimately died from their aggressive leukemia (43).

1,25(OH)<sub>2</sub>D<sub>3</sub> has been given to men with metastatic prostate cancer. When given daily, it caused significant hypercalcemia, thus limiting its usefulness (44); however, when men were treated with docetaxel and 45 mg of 1,25(OH)<sub>2</sub>D<sub>3</sub> three times a week, there seemed to be improvement in overall survival without toxicity (44).

Numerous analogs of 1,25(OH)<sub>2</sub>D<sub>3</sub> have been made, some of which have potent antiproliferative activity while having minimum calcemic activity (12,33). In animal models, some of these analogs, including novel analogs that have two side arms known as gemini analogs, have been found to be very effective in inhibiting colon tumor growth in mice while having minimum calcemic activity (33). To date, no active analogs of vitamin D have been proved to be efficacious for the treatment of any human cancer by themselves.

### Role of Vitamin D Nutrition in Tumor Promotion and Progression

There is overwhelming scientific evidence suggesting that maintenance of an adequate vitamin D status is important for the prevention of a wide variety of deadly cancers (7–11). Woo *et al.* (45) reported that men who had metastatic prostate cancer and received 2000 IU/d vitamin D had as much as a 50% reduction in prostate-specific antigen levels after 21 mo. Tangpricha *et al.* (46) investigated the role of vitamin D sufficiency and deficiency on colon tumor growth. They observed that

mice that were injected with mouse colon cancer cells (MC-26) and were vitamin D sufficient had a 40% decrease in the growth of their tumors compared with mice that were treated in an identical manner but were vitamin D deficient. Lappe *et al.* (47) observed that women who ingested 1400 to 1500 mg/d calcium and 1100 IU/d vitamin D<sub>3</sub> for 4 yr reduced their risk for developing cancer by 60%. When the analysis was confined to cancers that were diagnosed after 12 mo, the risk was reduced by 77% (47) (Figure 3). These data are also supported by the observation that women in the Women's Health Initiative who were vitamin D deficient [25(OH)D <12 ng] had a 253% increase risk for developing colorectal cancer during the 8 yr of the study compared with women who were vitamin D sufficient at the beginning of the study (48).

### Strategies for How Cancer Cells Resist the Antiproliferative Activity of 1,25(OH)<sub>2</sub>D<sub>3</sub>

One simple strategy for a cancer cell to decrease the effectiveness of 1,25(OH)<sub>2</sub>D<sub>3</sub>'s antiproliferative activity is to increase its destruction by enhancing the expression of 24-OHase. 24-OHase causes hydroxylations on the 1,25(OH)<sub>2</sub>D side arm, resulting in cleavage at carbon 23 forming the water-soluble inactive calcitropic acid. Human prostate cancer cells that have robust expression of 24-OHase either are nonresponsive or have minimum response to the antiproliferative activity of 1,25(OH)<sub>2</sub>D<sub>3</sub>. (49)

Another clever strategy that malignant cells have developed to mitigate 1,25(OH)<sub>2</sub>D<sub>3</sub>'s antiproliferative and prodifferentiation activities is to express the transcription factor SNAIL. SNAIL is a zinc-finger transcription factor that is involved in cell movement and exists in both invertebrates and vertebrates.

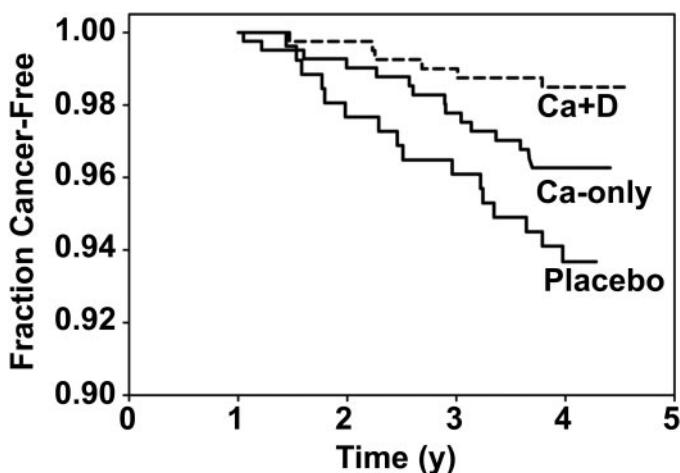


Figure 3. Kaplan-Meier survival curves (*i.e.*, free of cancer) for the three treatment groups randomly assigned in the cohort of women who were free of cancer at 1 yr of intervention ( $n = 1085$ ). Sample sizes are 266 for the placebo group, 416 for the calcium-only (Ca-only) group, and 403 for the calcium plus vitamin D (Ca+D) group. The survival at the end of study for the Ca+D group is significantly higher than that for the placebo group, by logistic regression. Reprinted with permission from Dr. Robert Heaney, 2007.

E-cadherin expression is important for cellular adhesion and differentiation (50). 1,25(OH)<sub>2</sub>D<sub>3</sub> enhances the expression of E-cadherin in VDR and human colon cancer cells. E-cadherin binds  $\beta$ -catenin, which prevents it from inducing nuclear activation of genes that are responsible for enhancing cellular proliferation.

1,25(OH)<sub>2</sub>D<sub>3</sub> also inhibits the Wnt/ $\beta$ -catenin pathway in colon cancer cells. The 1,25(OH)<sub>2</sub>D<sub>3</sub>-VDR complex binds  $\beta$ -catenin, preventing it from inducing proliferation. Palmer *et al.* (50) observed that when the human colon cancer cell line SW480-ADH was transfected with the SNAIL gene so that the cells overexpressed this transcriptional factor, it prevented the anti-proliferative and prodifferentiating activity of 1,25(OH)<sub>2</sub>D<sub>3</sub> (Figure 4). SNAIL 1, which induces epithelial-to-mesenchymal transition, was able to inhibit the expression not only of the VDR but also E-cadherin, both of which inhibit cellular proliferation. Thus, the ratio of VDR and SNAIL expression in cells may be critical for E-cadherin expression, which ultimately influences cellular growth and, thus, colon cancer progression.

### Conclusions

There is overwhelming scientific evidence suggesting that increased exposure to sunlight, which increases vitamin D<sub>3</sub> synthesis and a person's vitamin D status, can influence the risk for an outcome of many deadly cancers. A multitude of *in vitro* research, *in vivo* studies in mice, and the recent observation that 1100 IU of vitamin D<sub>3</sub> along with adequate calcium supplementation markedly reduces the risk for developing cancer all provide solid evidence to promote sensible sun exposure and encourage both children and adults to increase their vitamin D intake. It has been suggested that the reason that black men have a higher cancer risk and mortality compared with white men is because of their higher incidence of vitamin D deficiency (51). The recent observation by Abbas *et al.* (52) of a strong association with vitamin D deficiency and risk for breast cancer in a large case-control study of postmenopausal women adds to the overwhelming evidence that vitamin D deficiency is a major risk factor for this common cancer.

It is essentially impossible to obtain an adequate amount of vitamin D from dietary sources now that most experts agree that a minimum of 1000 IU/d vitamin D is required by both children and adults to maintain serum 25(OH)D levels of at least >20 ng/ml. For every 100 IU of vitamin D<sub>2</sub> or vitamin D<sub>3</sub>, serum 25(OH)D levels increase by 1 ng/ml (14,15). Thus, because most children and adults have blood levels of between 18 and 22 ng/ml, 1000 IU/d vitamin D is barely able to raise blood levels to what is now considered to be the preferred healthy level of >30 ng/ml (11,15). There is no need to be concerned about vitamin D intoxication from either exposure to sunlight or being exposed to sunlight and taking 1000 IU vitamin D supplementation (11). It is estimated that ingestion of >10,000 IU/d vitamin D for >6 mo increases risk for vitamin D intoxication (11).

For >40 yrs, there has been the unchallenged message that all humans should avoid direct sun exposure and always wear sun protection when outdoors (53). Indeed, it has been suggested that vitamin D deficiency is not a major health risk and that

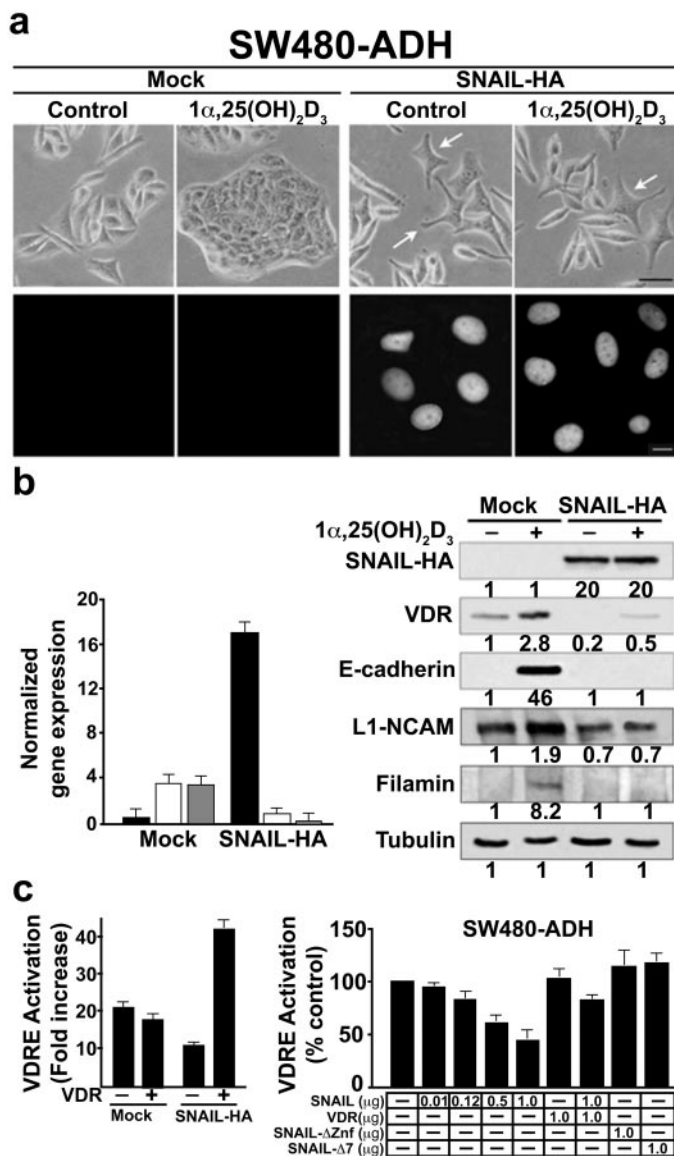


Figure 4. (Top) Micrographs of SNAIL-HA and mock-infected cells. Arrows indicate the phenotypic change induced by SNAIL. Bar = 50  $\mu$ m. (Bottom) Immunostaining of ectopic SNAIL expression using an antibody to HA. Bar = 10  $\mu$ m. (Left) Normalized SNAIL. Vitamin D receptor (VDR) and E-cadherin mRNA levels were measured by real-time reverse transcriptase-PCR. (Right) Protein expression was estimated by Western blot. Numbers refer to fold increase over untreated mock-infected cells. SNAIL inhibits the induction of L1-NCAM and filamin by 1,25(OH) $_2$ D $_3$ . Wild-type (left) but not mutant (right) SNAIL proteins inhibit VDR transcriptional activity (4XVDRE-tk-luciferase). Reprinted from reference (50), with permission.

linking vitamin D deficiency to medical illnesses is not well founded (53). The recommendation has been that you can get more than enough vitamin D from dietary sources (53). Very few foods naturally contain vitamin D, and most vitamin D-fortified foods contain only 100 IU of vitamin D in a serving, which is totally inadequate for satisfying the body's vitamin D

requirement (11). In Australia, where the sun-safe message has been strongly promoted, they now recognize that vitamin D deficiency has become a major health issue for both children and adults (11). As a result, the New Zealand Bone and Mineral Society in cooperation with the Australian College of Dermatologists and the Cancer Council for Australia have recommended a balance between avoiding the increased risk for skin cancer and achieving enough ultraviolet radiation to maintaining adequate vitamin D levels. This message has been endorsed by the Canadian Cancer Society, which now recommends that all Canadian adults ingest 2000/d IU vitamin D to decrease their risk for cancer. In addition, the Canadian Dermatologic Association, National Council on Skin Cancer Prevention (US), and the World Health Organization Collaborative Center for the Promotion of Sun Protection are recognizing the need to minimize the health risk associated with excessive ultraviolet B radiation exposure while maximizing the potential benefits of optimum vitamin D status, supplementation, and small amounts of sun exposure for obtaining adequate vitamin D.

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**Disclosures**

None.

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