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REPORT

Vitamin D

Cancer Prevention and Other New Uses

By Russell Martin

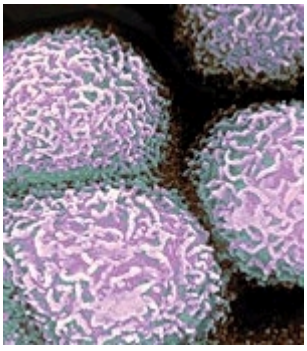
The past year has produced stunning research findings concerning vitamin D's potential role in preventing and perhaps even treating cancer.

Scientists are examining the use of vitamin D to reduce the risk of no fewer than 17 different types of cancer, ranging from colon, breast, and prostate cancers to ovarian, esophageal, renal, and bladder cancers. Moreover, researchers believe vitamin D may even improve treatment outcomes in people already diagnosed with cancer. A recent review article estimated that 50,000-70,000 Americans die prematurely from cancer each year due to insufficient intake of vitamin D.[1]

Emerging research suggests that vitamin D also has applications in promoting bone strength, as well as in mitigating autoimmune conditions such as multiple sclerosis, type I diabetes, and rheumatoid arthritis. Other potential benefits include promoting dental and skin health, and helping to prevent stroke, metabolic syndrome, and musculoskeletal pain.

New research indicates that vitamin D acts through several mechanisms to help fight cancer. Studies suggest that the active form of vitamin D may help to promote cell differentiation and support apoptosis (programmed cell death), as well as help to prevent metastases and angiogenesis.[2] Vitamin D's role in supporting calcium absorption may also contribute to its ability to fight cancer, since calcium has been shown to decrease proliferation and induce differentiation in epithelial cells.[1]

COMBATING COLORECTAL CANCER



Scanning electron micrograph of human colon carcinoma, magnified 15,000 times.

Vitamin D's effects in reducing cancer risk have been studied most extensively in colorectal cancer, the second leading cause of cancer death in the US.[3] A study in 2005 investigated the relationship between vitamin D intake, serum vitamin D levels, and colorectal cancer risk. Individuals with vitamin D intake of 1000 IU or more daily or with serum vitamin D (25-hydroxyvitamin D) levels of 33 nanograms per milliliter (ng/mL) experienced a 50% lower risk of colorectal cancer. A daily dose of 1000 IU of vitamin D is half the safe upper limit established by the National Academy of Sciences. According to the study authors, prompt public health action is needed to increase daily intake of vitamin D to 1000 IU and to raise serum levels of 25-hydroxyvitamin D. For some individuals, modest sunlight exposure may help achieve these optimal levels.[4]

An epidemiological review conducted in 2005 at Harvard Medical School corroborated vitamin D's protective effects against colorectal cancer and noted that typical dietary intake of 200-400 IU per day is probably too low to confer appreciable benefits. The Harvard study noted that a person's vitamin D status at the time of cancer diagnosis and treatment may influence survival.[5]

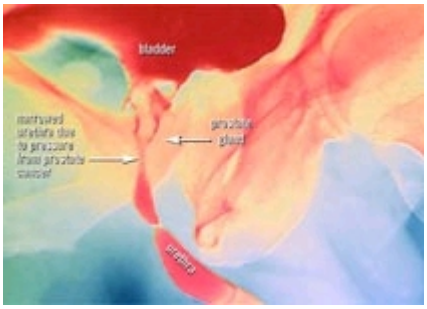
In the recent Polyp Prevention Trial, investigators analyzed several dietary factors in relation to the recurrence of adenomatous polyps in the colon.[6] Adenomatous polyps are considered pre-malignant and may therefore be a harbinger of colon cancer. Low intake of calcium and vitamin D was associated with increased risk of recurrence of the pre-malignant polyps. Optimal vitamin D and calcium status may thus be an important preventive strategy against colon cancer.

PROTECTING THE PROSTATE

Recent clinical trials suggest that vitamin D and its analogs promise to be important therapies for prostate cancer.[7] Experimental evidence indicates that the active form of vitamin D promotes differentiation and inhibits proliferation, invasiveness, and metastasis of human prostate cancer cells.[8,9]

In a study conducted last year, investigators examined the relationship between sun exposure and prostate cancer. Comparing

450 men with advanced prostate cancer with 450 unaffected men, they found that those with a high level of sun exposure had a 50% lower prostate cancer risk than men with low sun exposure. The researchers believe sunlight helped protect the men against prostate cancer by promoting vitamin D synthesis. Because of the association between sun exposure and certain skin cancers, however, the scientists noted, “increasing vitamin D intake from diet and supplements may be the safest solution to achieve adequate levels of vitamin D.”[9]



Colored urogram of the pelvis of a 60-year-old man with prostate gland cancer.

The prostate is below the bladder and should be clear, but due to the presence of a tumor it appears cloudy. The urethra shows narrowing caused by the pressure from the tumor.

Another study in 2005 demonstrated a therapeutic role for vitamin D in prostate cancer. Sixteen men who had previously been treated for prostate cancer supplemented with 2000 IU daily of vitamin D. The investigators then monitored prostate-specific antigen (PSA) levels for over two years. PSA is a marker of prostate cancer recurrence or progression. In nine patients, PSA levels decreased or remained unchanged after vitamin D supplementation began. In patients with rising PSA levels, supplementation with vitamin D3 significantly lengthened the PSA doubling time, by an average of 75%. (The rate at which PSA increases or doubles is correlated with disease prognosis, with longer PSA doubling times associated with better outcomes.) These findings indicate that vitamin D may help to slow or prevent disease recurrence or progression in patients who have been treated for prostate cancer.[10]

Vitamin D has also been reported to benefit patients whose prostate cancer has metastasized to the bones. This patient population commonly develops vitamin D deficiency. Supplementing these individuals with vitamin D was found to reduce pain, boost muscle strength, and improve overall quality of life.[11]

BENEFITS FOR BREAST HEALTH

Several lines of evidence suggest vitamin D may help reduce the incidence of breast cancer. A prospective study published in 2005 examined the relationship of plasma vitamin D metabolites to breast cancer risk in a cohort of women enrolled in the Nurses’ Health Study. Blood samples were collected from study participants from 1989 to 1990 and analyzed for the vitamin D metabolites 25-hydroxyvitamin D and 1, 25-dihydroxyvitamin D. The study participants were followed until 1996. The researchers then compared blood samples from women who developed breast cancer with samples from cancer-free control subjects. High levels of both vitamin D metabolites were associated with a non-significantly lower risk of breast cancer. For both metabolites, the association was stronger in women aged 60 and older.[12]

In another line of study last year, investigators looked at the relationship between dietary vitamin D and calcium intake and breast density as measured by mammography.[13]

Mammographic density is considered a strong risk factor for breast cancer.[14] Dietary intake of vitamin D and calcium was assessed in a group of women, aged 40-60, who had screening mammograms. Women who had a combined daily intake of 100 IU or more of vitamin D combined with 750 mg or more of calcium demonstrated decreased breast density compared to women with lower intakes of the two nutrients. This suggests that adequate consumption of vitamin D and calcium may reduce breast cancer risk by influencing breast tissue architecture.[13]

IMPROVING LUNG CANCER SURVIVAL

Vitamin D may help people with lung cancer to live longer, according to a study released in 2005. The most common cause of cancer death in American men and women, lung cancer can be challenging to treat effectively. The report found that men with early-stage non-small cell lung cancer who had higher vitamin D indices (based on dietary intake and exposure to sunlight) had improved recurrence-free survival rates compared to men with lower vitamin D intake and sun exposure.[15] Another study conducted in 2005 demonstrated that the active form of vitamin D inhibited lung cancer metastasis in an animal model of the disease.[16] These findings suggest that implementing vitamin D therapy may be critical to improving survival rates for lung cancer patients.

Additional scientific evidence suggests that optimal vitamin D status may be associated with reduced risk of many other forms of cancer. These include cancers of the bladder, esophagus, stomach, ovary, uterus, cervix, pancreas, larynx, oral cavity, and gall bladder, as well as Hodgkin’s and non-Hodgkin’s lymphomas.[1]

In addition to its effects against numerous cancers, vitamin D holds promise in preventing and alleviating autoimmune conditions and in optimizing the health of the gums, bones, and muscles.

THE SUNSHINE DEBATE

Because vitamin D is fat soluble, it can be stored in the adipose tissue of the body, presumably for long-term access. Much debate on vitamin D has focused on the need for dietary supplementation versus the body's endogenous (internal) manufacture of the vitamin from sunlight exposure.

For those living in climates with greatly reduced angles of sunlight (the northern and southern parts of the globe) or where sunlight itself is rare, the need for supplementation is unchallenged. The human body is designed to obtain vitamin D from exposure to sunlight, with only brief exposure providing roughly 80-90% of the body's vitamin D stores.17 Exposure of the entire body to sunlight may produce approximately 10,000 IU of vitamin D a day.18 To prevent the accumulation of toxic levels of vitamin D, the body naturally limits the amount of vitamin D it synthesizes from sunlight.[19]

For years, health advocates have suggested that sun exposure may contribute to cancer risk and sunscreen should be used for all sun exposure greater than 15 minutes. New evidence suggests, however, that vitamin D can in fact protect against several forms of cancer. While sunscreen may help protect against the deadliest skin cancer—melanoma—its effect of limiting vitamin D production could lead to a greater incidence of other cancers.20 That does not mean that sunscreens should not be used, as they can significantly protect against premature skin aging (and skin cancers). What this does tell us, however, is that in one way or another, it is critical that we obtain optimal levels of vitamin D.

Cancer occurs more frequently in dark-skinned people, the obese, and regions with limited exposure to ultraviolet B radiation from sunlight. Each of these factors is associated with low blood levels of vitamin D. Furthermore, cancer survival rates are lower when the diagnosis occurs in months of lower sunlight levels, suggesting a protective role of vitamin D. Studies suggest that vitamin D protects against numerous forms of cancer, including widely prevalent cancers such as those affecting the colon, prostate, breast, and lung.[1,20]

PREVENTING MULTIPLE SCLEROSIS

Multiple sclerosis is an immune-mediated inflammatory and neurodegenerative condition of the central nervous system. Its symptoms include weakness, visual problems, and impaired coordination. Although its causes remain unknown, scientists suspect that multiple sclerosis may represent an autoimmune condition.

Investigators have established a strong link between multiple sclerosis incidence and geographic location, noting that areas with abundant sun exposure or plentiful dietary fish intake experience reduced risk. Multiple sclerosis occurs more often in people who lived in northern areas of Europe and North America during childhood, and less often in people who live closer to the equator.[23] Individuals appear to retain the level of risk associated with the area in which they lived until age 15, even if they moved to a different area later in life.[23] In Switzerland, multiple sclerosis rates are higher at low altitudes and lower at high altitudes, where UV light is more intense. In Norway, multiple sclerosis rates are higher inland, but much lower near the coast, where vitamin D3-rich fish is consumed regularly.[24] Vitamin D, obtained through both sun exposure and diet, may be the factor responsible for the link between geography and multiple sclerosis risk.

Evidence suggests that vitamin D supplementation may decrease the lifetime risk of multiple sclerosis in women. Experimental data suggest the white matter of the brain that multiple sclerosis affects contains vitamin D receptors, and inadequate vitamin D during early development may predispose these cells to an early demise.[25]

Researchers have noted that administering the active form of vitamin D—1,25-dihydroxyvitamin D—to animals can completely protect them against an experimentally induced form of multiple sclerosis.[24] According to the investigators, the active form of vitamin D may act as a selective immune system regulator that works to inhibit autoimmune disease.

Later research indicated that 1,25-dihydroxyvitamin D also helped to reduce multiple sclerosis disease activity in mice with an experimentally induced model of the disease.[26] Based on this animal data, Dutch researchers postulated that multiple sclerosis patients may similarly benefit from optimal serum concentrations of vitamin D. Optimal vitamin D levels might not only help achieve immune-mediated suppression of disease activity, but also help decrease complications related to multiple sclerosis, such as muscle weakness, osteoporosis, and bone fractures.[26]

VITAMIN D BASICS

Technically, vitamin D is not a true vitamin. Since sun exposure can stimulate its synthesis in the body, it is not necessarily required in the diet, except in certain circumstances. Furthermore, its structure and mechanism of action more closely resemble those of a hormone than those of a vitamin.

Vitamin D occurs in nature in two main forms: vitamin D2, or ergocalciferol, and vitamin D3, or cholecalciferol. While vitamin D2 is obtained from plant sources, vitamin D3 can either be obtained through animal sources or synthesized in the skin when its precursor molecule absorbs light energy from ultraviolet B rays. Vitamin D can refer to either D2 or D3. In the liver, both are

converted into 25-hydroxyvitamin D, the primary circulating form of vitamin D. Conversion into its active form, 1,25-dihydroxyvitamin D, occurs in the kidney. Pharmaceutical drug forms of vitamin D include calcitriol, doxercalciferol, and calcipotriene.[21]

Vitamin D's most crucial role is regulating calcium and phosphorus concentrations in the serum. Vitamin D assists with absorption of these two minerals in the small intestine. When dietary intake of calcium is below optimal levels, vitamin D3 along with parathyroid hormone will move calcium from storage in the bone into the serum, where the body as a whole can use it.[22]

Because Vitamin D is found naturally in relatively few foods, supplementation in certain products, particularly milk, has become a main avenue for obtaining the vitamin. Foods that contain vitamin D include fatty fish such as tuna, sardines, herring, and mackerel, as well as eggs from hens that have been supplemented with vitamin D.[21]

EFFECTS ON TYPE I DIABETES

Some scientists believe that type I diabetes may be an autoimmune condition in which insulin-producing pancreatic beta cells are destroyed. Evidence from animal experiments and human observational studies suggests that vitamin D may help prevent type I diabetes, perhaps by acting as an immune system modulator.[27]

Researchers demonstrated that the pancreatic beta cells of mice contain receptors for 1,25-dihydroxyvitamin D. When they administered this active form of vitamin D to mice early in life, the animals demonstrated a reduced incidence of type I diabetes. However, when 1,25-dihydroxyvitamin D was administered later in the life span of mice, diabetes incidence was not affected. Vitamin D appears to limit the expression of certain cytokines, which may prevent the autoimmune attack on pancreatic cells that can lead to diabetes.[28]

Human studies likewise suggest that vitamin D may have a protective effect against type I diabetes. In a large-scale investigation, more than 12,000 pregnant women in Finland enrolled in a trial studying the relationship between vitamin D intake and type I diabetes in infants. After one year, children who supplemented with the suggested study dose of vitamin D (2000 IU per day) had a much lower risk of type I diabetes than children who did not supplement.[29]

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LOWERING GINGIVITIS RISK

High blood levels of a vitamin D metabolite are associated with a decreased risk of the gum disease gingivitis, according to a recent report from the American Journal of Clinical Nutrition. Researchers at Boston University analyzed data from 6,700 nonsmokers, aged 13-90+, from the National Health and Nutrition Examination Survey.[30]

The investigators analyzed blood levels of 25-hydroxyvitamin D and assessed the participants' gums for the presence of gingivitis, an inflammatory condition marked by redness and tendency to bleed. Participants with the highest blood levels of 25-hydroxyvitamin D were the least likely to display signs of gingivitis. In fact, the association between vitamin D levels and gingivitis incidence appeared to be linear over the entire range of blood levels. This association was similar even in relation to other factors such as gender, ethnic groups, and age.[30]

The scientists noted that vitamin D may reduce susceptibility to gingivitis by exerting anti-inflammatory effects, and postulated that gingivitis may provide a useful clinical model for further investigation into the anti-inflammatory effects of vitamin D.[30]

PROMOTING BONE HEALTH

One of vitamin D's greatest contributions to health is promoting strong, healthy bones. Vitamin D deficiency is associated with skeletal diseases characterized by weak bones, such as rickets in children and osteomalacia and osteoporosis in adults.[22]

Vitamin D combined with calcium supplementation is widely known to help decrease postmenopausal bone loss and prevent osteoporosis.[31,32] Furthermore, vitamin D combined with calcium can help decrease the risk of hip and non-vertebral fractures.[32]

Osteoporosis prevention may optimally begin early in life. In a retrospective study, investigators compared prepubescent females who received oral vitamin D in infancy to those who did not. Girls who received vitamin D had significantly increased bone mineral density compared to those who did not receive the vitamin.[33]

While commonly thought of as a female disease, osteoporosis affects men as well. Osteoporosis and associated fractures are increasingly prevalent in men, and mortality rates following major fractures are higher in men than in women.[34] As with women, osteoporosis prevention in men should begin in youth and continue in adulthood, using vitamin D, calcium supplementation, and physical activity. Bone density screening may be an important tool in assessing osteoporosis risk.

While early detection and monitoring of osteoporosis have advanced greatly, most osteoporosis patients are not treated for the cause of their fractures, nor are those who are at most risk being placed on preventive medical programs.[35] In light of the proven cost effectiveness of osteoporosis prevention using vitamin D, calcium, and weight-bearing exercise, this apparent disregard is highly alarming. Enormous sums of money are spent on osteoporosis-specific pharmaceutical drug development and marketing, yet millions of Americans do not receive adequate preventive treatment that costs literally cents a day.

ALLEVIATING MUSCULOSKELETAL PAIN

Low levels of vitamin D are associated with persistent, non-specific musculoskeletal pain, according to investigators at the University of Minnesota Medical School. Re-searchers conducted a cross-sectional study of 150 patients, aged 10-65, who presented to a primary care clinic over the course of two years with the complaint of persistent, non-specific musculoskeletal pain. Serum 25-hydroxyvitamin D levels were analyzed to assess vitamin D status.[36]

Ninety-three percent of the patients demonstrated deficient levels of vitamin D, and 28% were considered severely deficient. Five patients had vitamin D levels that were too low to detect. Particularly severe vitamin D deficiency was noted in young women, East African patients, and African-Americans.[36]

The research team concluded that all patients—regardless of gender or age—with chronic, non-specific musculoskeletal pain are at high risk of suffering from unrecognized vitamin D deficiency. Since osteomalacia is a known cause of chronic, generalized pain, doctors should screen all patients with such symptoms for vitamin D deficiency.[36] Vitamin D expert Dr. Michael Holick of Boston University has expressed a similar view, noting that vitamin D deficiency is often misdiagnosed as fibromyalgia.[37]

NEW APPLICATIONS FOR VITAMIN D

In recent months, scientists have discovered that vitamin D may have applications in preventing and managing numerous health conditions, including:

Rheumatoid arthritis. This inflammatory condition causes swelling, immobility, and joint pain. Recent reports indicate that vitamin D deficiency in adults is associated with an elevated risk of developing rheumatoid arthritis.[40]

Vitamin D may also be a crucial therapeutic tool for helping individuals receiving corticosteroid treatment for rheumatoid arthritis to maintain optimal bone mass.[41]

Hypertension. Investigators note that mounting evidence suggests that vitamin D deficiency may increase the risk of hypertension.[42] A recent study identified a possible mechanism by which vitamin D may support healthy blood pressure. Researchers at the University of Chicago found that analogs of vitamin D inhibit the expression of renin, a kidney-produced hormone involved in the pathogenesis of hypertension, in both laboratory and animal studies. This suggests that vitamin D could affect blood pressure by inhibiting renin, which helps regulate blood pressure.[43]

Skin disorders. Some investigators believe that based on the distribution of vitamin D receptors throughout the body, vitamin D may have potential therapeutic applications in managing numerous skin disorders, including actinic keratosis, seborrheic dermatitis, and photoaging.[44] One of the most troublesome and difficult-to-treat skin conditions is psoriasis, which is marked by patches of itchy, flaky skin. Both ultraviolet B radiation and topical application of the active form of vitamin D have been found to benefit patients who suffer from psoriasis. Scientists believe that vitamin D's antiproliferative and immune-regulating activities may be responsible for these benefits.[45,46]

Metabolic syndrome. A precursor to type II diabetes, metabolic syndrome is associated with an increased risk of heart disease. A recent study analyzing data from more than 10,000 participants found that increased dietary intake of vitamin D was associated with a decreased risk of developing metabolic syndrome. Calcium intake also exerted a protective effect against metabolic syndrome in this study of middle-aged and older women.[47]

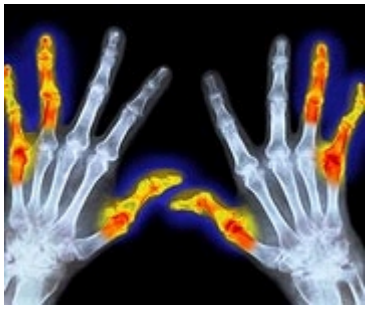
Averting stroke. A recent study examined how dietary intake and serum levels of vitamins and minerals influenced stroke risk in elderly subjects. More than 700 men and women were followed for up to 10 years. Low intake of vitamin D and low serum levels of its active form significantly predicted an increased risk for stroke, even after adjusting for factors such as age, gender, and smoking.[48]

Preventing tooth loss. Abundant intake of vitamin D is associated with a decreased risk of tooth loss, according to a recent study conducted in Japan. Researchers found that individuals in their seventies with relatively higher intakes of certain nutrients—including protein, vitamin D, and B vitamins—demonstrated a reduced incidence of missing teeth compared to people who consumed less of these nutrients.[49]

Supporting lung health. People with higher levels of vitamin D in the bloodstream demonstrate better lung function than their counterparts with lower vitamin D levels, according to a recent report. Researchers examined 14,000 participants and found that people with higher vitamin D levels could inhale and exhale substantially more air, as measured by forced vital capacity and forced expiratory volume. Though further studies are needed, these findings suggest that vitamin D might benefit smokers, asthmatics, and others with compromised respiratory function.[50]

PREVENTING FALLS IN THE ELDERLY

In elderly adults, falls occur frequently and are associated with significant morbidity and mortality.38 Research suggests that vitamin D may help prevent these dangerous falls.



Cross-sectional studies have shown that elderly adults with higher serum levels of vitamin D demonstrate a lower number of falls, as well as increased muscle strength.[39] One meta-analysis found that vitamin D supplementation helped reduce the risk of falling by more than 20%.[38] A randomized, controlled trial found that three months of supplementing with 1200 mg of calcium and 800 IU of vitamin D3 daily reduced the risk of falling by 49% in adults in a long-term geriatric care facility.[39]

SAFETY

Vitamin D is typically well tolerated in adults at doses up to 2000 IU daily, with some research indicating that even higher levels up to 10,000 IU daily may be used safely without adverse effects.[22,53] Excess vitamin D can lead to symptoms such as nausea, vomiting, poor appetite, constipation, and weakness.[22] Vitamin D is contraindicated in individuals with elevated blood calcium levels or hypercalcemia.[21] Individuals with kidney disease and people who use digoxin or other cardiac glycoside drugs should consult a physician before using supplemental vitamin D.[21]

CONCLUSION

Once considered little more than a compound that promotes healthy bones, vitamin D is now recognized as an important weapon in the fight against cancer. Its many other health-promoting effects include protecting muscle strength and modulating autoimmune disease. Optimizing vitamin D status through supplementation and prudent sun exposure should be a cornerstone of every health maintenance program.

NEW STUDY: OLDER ADULTS NEED MORE VITAMIN D

To maintain strong bones, older adults need more vitamin D than current guidelines recommend, according to a just-released report. While the Institute of Medicine suggests 400-600 IU of vitamin D daily, the American Medical Women's Association (AMWA) advises that all men and women over the age of 50 should consume 800-1000 IU of vitamin D each day.[51]

The AMWA noted that sunscreen, protective clothing, and lack of time spent outdoors may contribute to older adults' decreased synthesis of vitamin D. Fatty fish and fortified milk or juice may provide dietary sources of vitamin D, though supplemental sources may be the easiest way for Americans to boost their vitamin D consumption.[51]

While calcium has traditionally been considered the key to promoting bone strength, recent studies suggest vitamin D intake and exercise may be no less important in preventing osteoporosis.[51,52] In fact, a study published last year demonstrated that serum levels of vitamin D, rather than dietary calcium intake, was most intimately connected with optimal calcium balance in the body, as measured by serum parathyroid hormone.[52]

Patients should consult with their personal physicians to determine how much vitamin D best supports their unique health needs.

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