Vitamin D is getting its moment in the sun, and news of its potential health benefits has some scientists wondering if warning people away from solar rays is doing more harm than good. Are we inviting some diseases—including common cancers—to avoid skin cancers?

The list of maladies linked with vitamin D insufficiency is growing far beyond rickets and other bone diseases. Epidemiologic studies suggest that higher intake of vitamin D protects against multiple sclerosis and rheumatoid arthritis. A study from Finland showed that vitamin D supplementation in infancy is associated with a reduced risk for type 1 diabetes. Clinical studies have linked low serum vitamin D levels with hypertension.

“There’s more to this vitamin D story,” said Ronald Lieberman, M.D., program director of the Prostate and Urologic Cancer Research Group in the National Cancer Institute’s Division of Cancer Prevention. “It is fascinating as a molecule. It’s been shown to be antiproliferative, proapoptotic, antiangiogenic. In prostate cancer, its effects appear to be on the cell cycle, stopping growth by upregulating [the tumor suppressor] p21.”

He is quick to add, “Yet we don’t have a bit of data that I could show you to say it will work as a preventative.” Most of the evidence is from ecologic, epidemiologic, and laboratory studies of cancers of the prostate, breast, colon, and pancreas. For now, the available studies in patients are treatment trials suggesting that vitamin D may heighten the effects of chemotherapy or radiation. There have been few studies of vitamin D as a cancer chemopreventive.

**From Vitamin to Hormone**

The active form of vitamin D is a hormone called calcitriol or 1 alpha, 25-dihydroxyvitamin D [1alpha,25(OH)2 D]. Most vitamin D is made when ultraviolet B light hits a precursor molecule in the skin. The new intermediate, 25-hydroxyvitamin D [25(OH)D], travels through the blood to the kidneys, where it turns into the active hormone that regulates calcium levels.

The kidneys do not have a monopoly on calcitriol production, according to recent studies. Cells from the breast, prostate, and pancreas manufacture their own supply of the hormone—if enough 25(OH)D is around. “These cells have receptors for the hormone, and they make the active form as they need it to control growth and proliferation,” said epidemiologist Gary Schwartz, Ph.D., of Wake Forest University, who first proposed the vitamin D prostate cancer link in 1990.

In March 2004, Martin Hewison, Ph.D., at the University of Birmingham, United Kingdom, reported that breast cells manufacture the hormone from the precursor as part of their natural immune response to a tumor. His group showed how vitamin D is activated to calcitriol in the breast.

**Prostate Cancer Higher in Blacks—and Scandinavians**

“The connection that’s been difficult to make has been that sunlight exposure could explain some of the important geographic and racial differences in cancer rates,” said Schwartz. Fifteen years ago, he noticed that the people most likely to die from prostate cancer were African Americans, followed by Scandinavians. People living in northern latitudes, where the angle of the sun is insufficient to generate vitamin D through the skin, are commonly vitamin D deficient, as are blacks. The melanin in densely pigmented skin absorbs UV light and retards the ability of sunlight to stimulate vitamin D production. In a 2002 study from the National Health and Nutrition Examination Survey, 42% of African American women had low circulating 25(OH)D levels, compared with 4% of white women.

Dartmouth Medical School’s John A. Baron, M.D., was surprised to see the geographic connection when he studied calcium supplementation to reduce risk for colorectal cancer. In the multicenter, phase III randomized Calcium Polyp Prevention Study, 1,200 mg of calcium per day over 4 years significantly reduced risk for adenomas compared with placebo. Baron noticed, however, that the most beneficial effects occurred in sunny locations. When his team measured 25(OH)D levels, they saw that calcium’s protective effect was restricted to participants in the upper half of circulating 25(OH)D levels.

The excitement about vitamin D has moved beyond the vitamin D community, said Baron, who is about to begin his first vitamin D supplementation study. “I’m very optimistic—as optimistic as you can be in this business. After watching the beta-carotene story, you need a grain of salt. But I am optimistic, and others are too.”

**Treatment First**

One piece of evidence that supports a role for vitamin D in cancer prevention comes from treatment trials, said NCI’s Lieberman. Tomasz Beer, M.D., at Oregon Health Sciences University, showed in a phase II trial that more than 80% of advanced prostate cancer patients experienced a 50% drop in their prostate-specific antigen (PSA) levels when given high-dose calcitriol with the taxane docetaxel. In studies of taxanes alone, 42% of patients showed a similar PSA response. “To me, it’s another piece of the puzzle that vitamin D is active in prostate cancer,” Lieberman said.

NCI is supporting studies in a pre-prostatectomy model that Lieberman calls the closest thing to chemoprevention. During the time between diagnosis of localized prostate cancer and surgery to remove the

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**Dr. Gary Schwartz**

Ph.D., of Wake Forest University, who first proposed the vitamin D prostate cancer link in 1990.
prostate, novel agents, including vitamin D, are being tested. The researchers can compare tissue biopsied before treatment with the entire gland following treatment and surgery. A study at the University of Wisconsin of a form of the vitamin D prohormone called doxercalciferol (trade name Hectorol) is in a phase II clinical trial that is halfway through accrual. The hope, said Lieberman, is that evaluation of this and other agents may lead to the next generation of phase III chemoprevention trials for prostate cancer.

That next generation will likely involve analogs of vitamin D because giving calcitriol directly can cause life-threatening hypercalcemia. Synthetic analogs are designed to enhance cancer regulatory effects without the calcium side effects. None so far are completely without the calcium effect. Several analogs, some already on the market for other diseases, are being studied in human cell lines and treatment studies.

The breast cancer story is interesting too, but not as far along as prostate cancer. JoEllen Welsh, Ph.D., at the University of Notre Dame, is studying human cell lines, nude mouse models, and a vitamin D receptor knockout mouse to look at the effects of vitamin D on growth and survival in normal mammary glands and breast cancer.

“Clearly, in vitro and animal models of vitamin D and synthetic analogs can inhibit growth and induce regression of tumors,” she said. In breast cancer, however, “there are no really good clinical trials of these compounds yet. There have been a few small-scale trials in Europe, but they have two problems: They choose patients with advanced disease, and the vitamin D analogs being tested have some side effects.”

Welsh maintains that lifelong exposure to vitamin D is what is important for breast cancer. “The breast has so many developmental periods. We don’t know if vitamin D exposure and intake during adolescence is important. What about pregnancy and lactation? During aging too, the mammary gland undergoes developmental changes. We need to know a lot more about vitamin

In Baron’s new study, 2,000 people with a history of adenomas will be randomly assigned to receive either calcium supplements or vitamin D supplements, both, or placebo. The vitamin D is 1,000 IU per day—higher than the 400 IU found in most multivitamins. “We don’t really know the dose needed for an anticancer effect,” Baron admitted. The expectation is that it is higher than that for bone health, but no one knows how much higher.

Michael F. Holick, M.D., Ph.D., of Boston University School of Medicine, an outspoken advocate of vitamin D’s merits, is willing to make a recommendation. He states that, in the absence of sunlight exposure, a minimum of 1,000 IU per day is required to maintain a healthy concentration of 25(OH)D in the blood. That’s a lot of milk—10 cups a day. The U.K.’s Hewison suggests more widespread fortification of foods.

Most of the scientists interviewed were quick to point out that a mere 15 minutes of sun exposure—three times a week—before slathering on the sunscreen, would do enough to boost vitamin D levels.

The American Academy of Dermatology is not moved. A July 2003 press release stated, “It is dangerous to mislead the public into thinking that sunlight is a safe and effective ‘cure’ for other health conditions.” AAD president Raymond L. Cornelison Jr., M.D., suggested that people take a multivitamin or drink a few glasses of vitamin D–fortified milk every day, adding, “the dangers of exposing oneself to carcinogenic UV light from the sun, even for a few minutes, are firmly established.”

“Is vitamin D insufficiency common? Yes. Is it likely a contributing factor to prostate, breast, colon, and maybe some other cancers? Yes,” said Schwartz. “Am I saying ‘get thee to a skin tannery’? No.”

“I’m not sure how the sun-versus-supplement issue will play out,” said Baron, whose study will include a questionnaire on sun exposure. Welsh added, “It’s still too early to know the right thing to do.”

—Cori Vanchieri