Vitamin D: Cancer Prevention’s Sunny Future?

By Samantha Beres

Could preventing cancer be as easy as taking a vitamin D supplement? For decades, studies have suggested that sunlight and vitamin D decrease the risk of some cancers. In the past few years, there has been a crescendo in the research, including results from the first randomized, controlled trial to show that vitamin D can lower cancer risk.

The Canadian Cancer Society thinks that vitamins might be one way to prevent some cancers. In June 2007, the national organization recommended that adults living in Canada consider taking vitamin D supplements of 1,000 international units (IU) a day in the fall and winter. Those at high risk of low vitamin D levels should take it year round. The move was a break from the Canadian government’s daily intake recommendation of 200–600 IU, which is aligned with the U.S. Institute of Medicine’s adequate intakes.

Then, in October, the Canadian Cancer Society wrote a letter to North American research granting agencies, including the National Institutes of Health, lobbying for a large-scale clinical trial that tests at least 1,000 IU of vitamin D. The goal: to figure out what dose prevents cancer.

Although making a recommendation and asking for more research at the same time may seem contradictory, Heather Chappell, senior manager of cancer control policy for the Canadian Cancer Society, said that this approach struck a balance between two health issues. One is geographic location—90% of vitamin D comes from the sun when ultraviolet rays convert a precursor in the skin to vitamin D, but during fall and winter at higher latitudes, no vitamin D synthesis occurs. Findings from a conference on vitamin D and health, sponsored by the cancer society and the National Cancer Institute of Canada, concluded that overall vitamin D levels may be low in the general population and that “vitamin D may have beneficial effects on some types of cancer.” The other issue is reminding Canadians to protect themselves from the sun. Tanning salons in Canada were advertising indoor tanning as a venue to get your vitamin D, which most scientists consider dangerous because of the skin cancer risk.

“Taking a supplement is a safer alternative for Canadians than indoor tanning,” Chappell said. “That recommendation is only based on what we know to date.”

What the society does know is based on a combination of the conference findings (which brought together 14 national health organizations) and a review of about 60 studies, mostly observational, Chappell said. But making recommendations before there have been many randomized, controlled trials concerns some researchers. Several research conferences and organizations have looked at the many questions that still need to be answered about vitamin D and cancer risk.

“When you find something in observational studies, the interventions are rarely, rarely as positive or as powerful as the observations,” said Wake Forest University professor Gary Schwartz, Ph.D., who has been examining the vitamin D link to prostate cancer for two decades. “It is an open question whether vitamin D supplementation will reduce the risk of cancer. The questions are how much vitamin D, when, and what cancer.”

Ecologic, epidemiologic, and laboratory studies have provided evidence linking higher vitamin D exposures to lower risk of colon, breast, and prostate cancers. But a U.S. National Cancer Institute conference in May 2007 determined that there are many gaps in the research. The conference was spurred by the “sunshine vitamin” getting a lot of attention in the lay press, for which pace picked up after results from a randomized trial were published.

**Trial Shows Lowered Risk**

The Canadian Cancer Society recommendation, below the safe upper limit of 2,000 IU (in Canada and the U.S.), came right after the first randomized, controlled clinical trial to show that vitamin D reduces cancer risk.

In the 4-year double-blind study, 1,179 women were assigned to take daily dosages of 1,400–1,500 mg of calcium plus 1,100 IU of vitamin D, calcium alone, or a placebo. The subjects were aged 55 and older, postmenopausal, and free from known cancer for at least 10 years before entering the study. The researchers from Creighton University in Omaha, Neb., found that women taking the vitamin D-calcium combination had a 60%–77% reduced risk of cancers compared with that in the placebo group. (After researchers removed new cancer cases that developed in the first year, the percentage was 77%.) The calcium alone did not substantially reduce the risk of cancer—the decreased risk was about 47% compared with that in the placebo group. After researchers removed cancer cases in the first year, the risk for the calcium-only group stayed basically the same, whereas the vitamin D group decreased risk by an additional 17%. The total number of cancer cases during the 4 years of the study was 50–20 in the placebo group, 17 in the calcium-only group, and 13 in the combination vitamin D group.
Some researchers have criticized the study’s importance for cancer prevention—its primary outcome was bone health; cancer was secondary. Others think that the size of the trial was too small to be a definitive proof of cancer prevention.

But Joan M. Lappe, Ph.D., a professor of nursing and medicine at Creighton who led the trial, said that size is why this study is so interesting. “Our study was striking because we found this reduction in what was, compared with other cancer trials, relatively small,” she said.

Jean Wactawski-Wende, Ph.D., at the University of Buffalo is concerned about the few cancer cases. “While the results of the trial are intriguing, only two cases of colorectal cancer occurred. The number of cases is far too small to make a statement about colorectal cancer prevention,” she said.

Wactawski-Wende led the only other randomized trial of vitamin D and cancer from the Women’s Health Initiative, which looked for an effect on the incidence of colorectal cancer in women aged 50–79 who were taking calcium and vitamin D. Of 36,282 subjects, approximately half received a daily dose of 400 IU of vitamin D, with 1,000 mg of calcium. The 7-year study found no benefits.

Lappe noted that 400 IU was not enough to raise serum vitamin D levels substantially—only about 2 ng/mL, compared with a 9.7-ng/mL increase in the first year of the Creighton study. “I think it’s important to realize we’re not giving megadoses of more than a person would require,” Lappe said. “The reason vitamin D can have such an effect is that many, many people are deficient in vitamin D.” Supplementing for many people, she added, simply brings the vitamin D levels to where they should be.

Wactawski-Wende agreed that the doses may have been low—when the study was designed in 1993, 400 IU was considered substantial. Another weakness of the study was that subjects did not take the supplements consistently. “Perhaps the duration of the study, 7 years, was not long enough,” she added. Colorectal cancer takes up to 20 years to develop. “Nonetheless, I think it’s too soon to know whether recommendations of higher-dose supplements will in fact reduce cancer.”

Both Wactawski-Wende and Cindy Davis, Ph.D., of NCI point out that there is no way to decouple the effects of vitamin D and calcium in either study. Davis would like to see the results of the Creighton trial confirmed in another study but doesn’t know what that study would look like. “That’s a very, very difficult question to answer because there are so many unanswered questions,” Davis said.

**Gaps in the Research**

Davis organized a conference held by the NCI and the National Institutes of Health’s Office of Dietary Supplements to critically evaluate the strength of the scientific evidence and point out the many gaps in vitamin D–cancer research.

One finding is a need for better ways to evaluate a person’s vitamin D intake and status. After vitamin D is synthesized in the skin, it is metabolized in the liver into 25-hydroxyvitamin D (25OH-D), the major circulating form of vitamin D and a marker of an individual’s vitamin D status. A challenge, though, is that not all people synthesize vitamin D from ultraviolet-B rays equally. The elderly and people with dark skin pigmentation need longer exposure to synthesize the same amount of vitamin D as younger or lighter-skinned people. Intake also varies depending on geographic location, sunscreen use, diet, and some medical conditions.

“It’s difficult to monitor sunlight exposure and it’s difficult to monitor dietary intake of vitamin D because the databases aren’t as complete as they should be,” Davis said. “Looking at serum levels of vitamin D takes into account dietary and sunlight exposure.”

Epidemiologic data presented at the conference showed an association between lower levels of 25OH-D and higher risks of colon, prostate, and breast cancers. But no optimal concentrations of 25OH-D have been established. “The 25OH-D levels have a half-life of 4–5 weeks. Many serum level studies take one measurement, which gives you just a snapshot of solar exposure, rather than a measure of lifetime solar exposure,” said Schwartz of Wake Forest, who gave a presentation on problems in epidemiologic studies of vitamin D and cancer. Because cancer can take decades to manifest, knowing when vitamin D levels are important is crucial to the research advancing, he said.

There is also some question whether 25OH-D is the best measure of tissue exposure to vitamin D. In the kidneys, 25OH-D is converted to 1,25(OH)2D, the active hormonal form of vitamin D that regulates serum calcium levels. Recent discoveries show that cells in many organs—including the prostate, breast, colon, and pancreas—can make that conversion locally. Moreover, the active hormone exerts anticancer effects locally.

There are many other research areas that need further examination. These include vitamin D’s role in modifying disease risk in a specific gene, how vitamin D metabolism is influenced by the diet, whether obese individuals have altered vitamin D metabolism and decreased concentrations of 25OH-D, and mouse models showing that increasing vitamin D and calcium levels inhibits colon tumor growth.

This long list underlines the complexity of vitamin D research, Davis said. “We really don’t know yet how everything is inter-related,” she said. “… I think that there is some evidence suggesting vitamin D is protective against cancer. What we don’t know yet is who will benefit, who will be placed at risk, what the optimal timing is, and does it vary depending on the cancer site?”

continued on page 297
The American Institute for Cancer Research has included vitamin D and colorectal cancer in an evidence-based review called *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. A panel of 21 scientists looked at 11 cohort studies and 17 case–control studies that investigated total vitamin D and/or dietary vitamin D and colorectal cancer. Four cohort studies investigated plasma or serum vitamin D levels. They concluded that “the evidence on vitamin D was inconsistent. There is limited evidence suggesting that foods containing vitamin D or better vitamin D status protect against colorectal cancer.”

This conclusion is unlikely to be the last word on vitamin D. But whether other agencies will take up the Canadian Cancer Society’s call for randomized trials—or change their recommendations for supplements, sun intake, or daily recommended intake—may depend on answers to some of these questions.

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