Vitamin D and Cancer: Uncertainty Persists; Research Continues

By Joanne Nicholas

About one-third of Americans are not getting enough vitamin D, according to a March report from the Centers for Disease Control and Prevention. That conclusion came about 6 months after the Institute of Medicine (IOM) issued new recommendations increasing the dietary reference intakes for vitamin D.

Notably absent from both reports were recommendations regarding vitamin D’s relationship to cancer.

For years, some studies have suggested that vitamin D intake is associated with reduced risk of cancer—particularly colorectal cancer but also breast, prostate, and pancreatic cancers. The findings have attracted media attention and raised hope that vitamin D supplements could ward off the disease. But other studies, including some large ones, have had conflicting results (see sidebar).

As a result, the IOM concluded that the evidence to date is too weak to make recommendations regarding vitamin D and cancer. “The role of vitamin D in both prevention and treatment of cancer remains a work in progress,” said IOM committee member JoAnn E. Manson, M.D., Dr.P.H., who cowrote a commentary on vitamin D and cancer in the New England Journal of Medicine in March. “We have seen this excitement before with beta-carotene, vitamin E, folate, and selenium,” said Manson, a professor at Harvard Medical School. “It is important that the enthusiasm not outpace the evidence as shown.”

Nevertheless, research on vitamin D and disease goes on. A look at the National Institutes of Health Clinical Trials website (http://clinicaltrials.gov) during the first week of May showed 1,326 trials assessing vitamin D’s effects on cancer, pregnant women, the elderly, African Americans, patients with HIV, prediabetes, heart disease, lupus, rheumatoid arthritis, cystic fibrosis, the obese, the mentally ill, and more.

The VITAL Trial

Amid the many studies under way is a newly launched, large multicenter trial called VITAL (Vitamin D and Omega-3 Trial), investigating whether high doses of vitamin D and the omega-3 fatty acids found in fish oil can reduce the risk of developing cancer, heart disease, and stroke. Primary outcomes are incidence of these diseases after 5 years.

VITAL is the first large-scale randomized trial designed to test vitamin D’s role in preventing cancer and cardiovascular disease, Manson said. The trial is testing a higher dose of vitamin D than most previous studies and is “large enough to provide conclusive results.”

In mid-2010, the trial began recruiting 20,000 U.S. men aged 60 years and over and women aged 65 and older, and enrollment will continue through 2011. The basically healthy participants, with no history of cancer or cardiovascular disease, will receive two pills per day in one of the following combinations: vitamin D3 and fish oil, vitamin D3 and fish oil placebo, vitamin D3, placebo and fish oil, or both placebos. (Vitamin D3 dose is 2,000 IU; fish oil dose is 1 g.) They will be monitored for 5 years and will be asked to complete an annual questionnaire about health, lifestyle habits, smoking, medication, and new medical diagnoses. Consent for medical record review will be requested to confirm health outcomes. (For more information about VITAL, see http://www.vitalstudy.org/.)

In addition to VITAL, several smaller trials are looking at specific questions related to vitamin D and cancer. Some are focusing on the vitamin in cancer patients. For example, at Memorial Sloan–Kettering Cancer Center in New York, researchers are investigating the effects, good or bad, that vitamin D levels have on stage IV colorectal cancer; a multicenter trial led by the University of Toronto and Mount Sinai Hospital in New York is investigating vitamin D’s effects on prostate cancer–associated lesions and on vitamin D metabolites in prostate tissue; and a study by Stanford University and the Department of Defense is assessing whether vitamin D levels affect the characteristics of a woman’s breast cancer at diagnosis and whether a short course of vitamin D in women with low levels changes the gene expression of their breast cancers.

Other key questions must also be addressed, said Steven K. Clinton, M.D., Ph.D., a professor in the division of medical oncology at Ohio State University in Columbus and a member of the IOM Committee. “For example, we need studies of how vitamin D impacts the efficacy of cancer therapy and its toxicity. In addition, many past studies do not differentiate between vitamin D alone and vitamin D plus calcium, so we need to examine the optimal intake of each nutrient independently.”

Design Flaw?

But additional studies may be definitive only if they are measuring vitamin D intake in...
Vitamin D Studies: No Final Answers Yet

Large studies on vitamin D and cancer in Japan, Europe, and the U.S. have had inconclusive, and sometimes conflicting, results:

- The Japan Public Health Center–Based Prospective Study of Plasma Vitamin D Levels and Colorectal Cancer Risk found that low plasma 25-hydroxyvitamin D \([25(OH)D]\) levels may be associated with later risk of rectal, but not colon, cancer (British Journal of Cancer, 2007).
- The European Prospective Investigation into Cancer and Nutrition Study (EPIC) included a study of prediagnostic vitamin D concentrations and the risk of developing colorectal cancer. Patients with the highest vitamin D levels had the lowest incidence of colon cancer (British Medical Journal, 2010).
- Another EPIC study found no association between serum vitamin D levels and the risk of prostate cancer (American Journal of Epidemiology, 2009).
- The Women’s Health Initiative (WHI) included the Calcium with Vitamin D (CaD) trial with 36,282 postmenopausal women aged 50–79 years. Calcium–vitamin D supplements had no detectable effect on the incidence of colorectal cancer (New England Journal of Medicine, 2006).
- Also in the WHI, calcium plus vitamin D supplementation for an average of 7 years did not reduce the incidence of invasive breast cancer compared with placebo (J. Natl. Cancer Inst., 2008).
- The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial included a case–control study that found no association between vitamin D status and risk of breast cancer (Cancer Epidemiology, Biomarkers, and Prevention, 2008).

the right populations. A commentary published in the *Journal of the American Medical Association* in April by Martha Clare Morris, Sc.D., and Christine C. Tangney, Ph.D., of Rush University Medical Center in Chicago, suggests that a design flaw in randomized trials of vitamin supplements may be responsible for many studies’ negative findings.

“Vitamin treatment may not be effective in these trials because nutrient intake among the participants is already at optimal levels,” Morris wrote in an e-mail. “Public health may be better served by initially conducting trials in individuals with insufficient levels of the vitamin studied and, if effective, to then test people with adequate levels.”

Morris said she is unaware of trials of vitamin D and cancer risk reduction that are restricting eligibility to people with low levels of the vitamin. But she believes that could be an important criterion for patient selection.

“I am in discussion with various experts across multiple fields on this topic,” Morris said, and she hopes to convene a conference “whose goal would be to come up with more appropriate approaches for examining nutritional relations with disease in both randomized trials and epidemiological studies and to make recommendations for how to establish best evidence in nutritional science.”