Breast Cancer Risk Warrants High-Dose Vit. D

BY ERIK GOLDMAN

FROM THE SOCIETY FOR INTEGRATIVE ONCOLOGY INTERNATIONAL CONFERENCE

NEW YORK – High-dose vitamin D supplementation has potential to reduce risk of primary breast cancer as well as breast cancer recurrence, with minimal risk of toxicity, according to researchers and clinicians at the conference.

The meeting was held just 2 weeks before the Institute of Medicine published its consensus statement suggesting that daily intake beyond 600 IU has little value and that high-dose vitamin D might be dangerous. Data presented at the SIO conference indicate that women with serum levels under 20 ng/mL are at significantly increased risk for breast cancer, that raising levels to 50 ng/mL could mitigate that risk, and that oral doses up to 10,000 IU/day are safe for adult women.

Although many questions about vitamin D in cancer prevention and treatment remain unanswered, speakers at the conference were largely in agreement that the recommended daily allowance of 400 IU/day, which had been in place for many years, has little scientific basis.

The IOM's new recommendation of 600 IU for adults – including postmenopausal women – is considerably lower than the doses some nutrition-oriented oncologists are recommending for cancer prevention, and also much lower than the doses being studied in ongoing cancer prevention trials.

The notion that vitamin D may help prevent breast cancer emerged from epidemiologic and case-control studies; these types of studies were largely discounted by the IOM committee.

Some of the strongest recent data come from the Long Island Breast Cancer Study Project, which involved 1,026 women diagnosed between 1996 and 1997, and 1,075 matched controls. Vitamin D deficiency, defined as a serum level under 20 ng/mL, had a roughly 30% prevalence in both groups, reported Dr. Katherine Crew, an epidemiologist at Columbia University, New York, and the study's lead investigator.

However, the women with blood levels of 40 ng/mL or greater had 40% lower odds of breast cancer, compared with those with serum levels of 20 ng/mL or lower. Women with serum levels of 20-29 ng/mL – a level Dr. Crew defined as low but not technically deficient – showed a 16% risk reduction, compared with those who were frankly deficient. She noted that the data were adjusted for age, race, parity, family history of breast cancer, and other key variables (Cancer Prev. Res. Phila. 2009;2:598-604).

"Higher levels of 25-hydroxyvitamin D confer lower risk of breast cancer," Dr. Crew said. "This was consistent for both estrogen receptor (ER)–positive and ER-negative breast cancer, which is important because we really don't have effective chemotherapy for ER-negative breast cancer."

She acknowledged the limitations inherent in a case-control study like this, and urged caution in drawing definitive conclusions. Still, she said that the correlations are significant and should not be ignored.

In a later interview, Dr. Crew said she had read the IOM report and believed that "they took a conservative approach in terms of making broad recommendations on vitamin D for the general public." Those recommendations may not be relevant for specific subpopulations at risk for specific disorders.

Several other studies suggest that increasing vitamin D intake can reduce breast cancer risk. For example, the Women's Health Initiative's 2007 report, while showing no significant breast cancer risk reduction from vitamin D at the standard dose of 400 IU/day, did show a 20% reduction in incidence among the women who took additional vitamin D on their own, beyond the officially sanctioned 400 IU/day. The biggest reduction was in ER-negative cancers. Dr. Crew noted that these findings are significant but have been largely overlooked.

Another study of 1,179 postmenopausal women showed that those taking 1,100 IU/day of vitamin D plus calcium (1,500 mg/day) had less than one-third the incidence of breast cancer that those taking

placebo had (2% versus 6.8%). A third subgroup, taking calcium alone, also had fewer breast cancers but the reduction was not as great (3.6% versus 6.8%) (Am. J. Clin. Nutr. 2007;85:1586-91).

Serum level – not daily intake – is the key variable, experts at the meeting emphasized. According to the best available data, breast cancer odds ratios begin to drop significantly as serum vitamin D levels get over 50 ng/mL (J. Steroid Biochem. Mol. Biol. 2007;103:708-11). Several speakers suggested that 40-60 ng/mL is the target range and that supplementation should be individually tailored to help patients achieve those levels.

How much vitamin D must a woman take to reach those levels? A lot more than the 600 IU recommended in the new IOM guidelines. Depending on the baseline blood levels, supplementation on the order of 2,000-4,000 IU/day is what some clinicians are recommending. This is far higher than the IOM's new recommendation, but still within range of the new upper limit.

The notion that vitamin D may help prevent breast cancer emerged from epidemiologic and case-control studies, but such studies were largely discounted by the IOM committee.

The most worrisome potential adverse effects of excessive vitamin D are hypercalcemia, bone demineralization, nephrocalcinosis, and cardiac arrhythmias. However, these conditions don't really arise until serum levels get above 150 ng/mL, Dr. Crew said, a level that would require high amounts of vitamin D supplementation over a long period.

A study done in 2004 looked at daily doses of 10,000 IU for up to 5 months, and found no evidence of toxicity (J. Steroid Biochem. Mol. Biol. 2004;89-90:575-9).

Researchers at Columbia are in the midst of a trial assessing the effect of cholecalciferol (vitamin D_3) at 20,000 IU and 30,000 IU/week, in vitamin D–deficient pre- and postmenopausal women at high risk of breast cancer. The women will be treated for a full year. The study will ultimately involve 80 participants, and investigators are tracking a number of breast-specific outcomes including tissue changes on biopsy, changes in breast fibrodensity, and cancer markers in urine and serum.

The weekly doses in this study translate to roughly 2,800 IU and 4,300 IU/day, which are quite a bit higher than the IOM's new recommendation. In an interview, Dr. Crew said the doses do fall close to the IOM's new safe upper limits, but her group has no plan to change the protocol in light of the IOM report.

"For new participants that we're screening, there has been some hesitation from a few women, but others are still willing to participate," she noted.

According to Julie Campbell, a research fellow involved in the study, 20 premenopausal and 14 postmenopausal women have completed the yearlong intervention, with no evidence of any adverse effects at either dose level. "There have been no cases of hypercalcemia so far, and only one woman has shown high urine calcium levels," she said.

The high-dose supplementation did produce fairly rapid increases in serum levels. Among the premenopausal women, mean levels had reached the 50- to 60-ng/mL range within 3 months. The 30,000-IU/week doses resulted in a larger increase than did the 20,000-IU/week doses. But even at these high doses, none of the subjects so far have shown potentially toxic serum levels in the range of 150 ng/mL and higher.

Many of the correlations found between vitamin D level and breast cancer risk have also been observed in studies of colorectal cancer, said Dr. Roberd M. Bostick, professor of epidemiology at Emory University, Atlanta.

A dose-response trial is underway involving 272 patients with sporadic colorectal adenoma. The four-arm, placebo-controlled study will assess tissue changes and biomarkers after 6 months of vitamin D supplementation at 1,000, 2,000, and 4,000 IU/day, Dr. Bostick said at the meeting.

Although the IOM report cites the potential dangers of high-dose vitamin D, it is important to realize that "they still raised the RDA from 400 to 600 IU daily and the upper safety limit was doubled from 2,000 IU to 4,000 IU daily. This is still progress in terms of being able to raise people's serum 25-hydroxyvitamin D to sufficient levels," Dr. Crew said in an interview.

The researchers did not report any financial conflicts. ■