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Vitamin D Appears to Cut Breast and Colorectal Cancer Risk **CME**

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February 12, 2007 — Researchers say that raising vitamin D levels may prevent up to half of all breast and two thirds of colorectal cancer cases in the United States. Based on the results of 2 separate studies, the investigators recommend a daily intake of 2000 IU of vitamin D₃ and, when possible, moderate sun exposure.

"The results are pretty straightforward," Karen Glanz, PhD, director of Emory University's Prevention Research Center at the Rollins School of Public Health in Atlanta, Georgia, said in a news release. However, changing behavior on the basis of these studies may be premature, she noted. The analyses found an association between vitamin D levels and lowered risk, not a definite link, Dr. Glanz said, but adding vitamin D to the diet or taking a supplement would probably not do much harm and there could be a benefit.

During an interview with Medscape, lead author Cedric Garland, DrPH, of the University of California at San Diego, agreed that future consensus is needed, but he recommended no delay in raising vitamin D levels. "We shouldn't hold up implementation," he said. "Inadequate photosynthesis or oral intake of vitamin D is associated with high incidence and mortality rates of breast cancer."

Published in the January 30 Article in Press issue of the *Journal of Steroid Biochemistry and Molecular Biology*, the researchers pooled dose-response data from 2 previous studies — the Harvard Nurses Health Study and the St. George's Hospital Study. They found that patients with the highest blood levels of 25-hydroxyvitamin D had the lowest risk for breast cancer.

Dr. Garland and his team divided the more than 1700 records in the studies into 5 groups from the lowest blood levels of 25-hydroxyvitamin D (< 13 ng/mL) to the highest (approximately 52 ng/mL). These data also included whether the patient had developed cancer.

The investigators found that patients with serum 25-hydroxyvitamin D of approximately 52 ng/mL had a 50% lower risk for breast cancer than those with serum measuring less than 13 ng/mL. This level corresponds to a vitamin D intake of 4000 IU per day, which exceeds the National Academy of Sciences upper limit of 2000 IU per day. "Leading researchers are building a case to have this level increased," Dr. Garland told Medscape, "but in the meantime, we are recommending a daily intake of 2000 IU."

The group is also calling for an additional 10 to 15 minutes of daily sun exposure when appropriate — an amount estimated to be equivalent to an oral intake of 3000 IU of vitamin D₃.

But What About the Risk for Skin Cancer?

As previously reported by Medscape, the American Academy of Dermatology has voiced concern about the vitamin D literature prescribing the health benefits of sunlight. "While many health issues are complex and involve multiple factors, we know that ultraviolet light is the primary cause of skin cancer, and avoiding excessive exposure to the sun and other forms of ultraviolet radiation is the solution," Clay Cockerell, MD, president of the academy said in a news release.

During an interview with Medscape, Dr. Garland emphasized that his group is advocating prudence and moderation, including the use of a

broad-brimmed hat. "I think most physicians will see this as a well-controlled and reasonable approach," he added.

The article points out that sun exposure is inadvisable for patients with primary photosensitivity disorders, people taking photosensitizing medications, and anyone with a personal or close family history of skin cancer or actinic keratosis.

Evidence Stacking in Favor of Vitamin D

Dr. Garland was also a coauthor of a second study examining the effect of vitamin D levels on colon cancer risk. Published in the February issue of the *American Journal of Preventive Medicine*, the researchers conducted a meta-analysis of 5 studies examining serum 25-hydroxyvitamin in colorectal cancer.

The investigators combined the findings of the 5 studies using standard methods for pooled analysis. There were 535 cases and 913 controls or 1448 participants in total. The researchers divided the results into quintiles with median 25-hydroxyvitamin values of 6, 16, 22, 27, and 37 ng/mL.

Previous studies had shown that lower blood levels of vitamin D did not protect against colorectal cancer, but in the current study, the researchers came to a different conclusion. "Through this meta-analysis we found that raising the serum level of 25-hydroxyvitamin D to 34 ng/mL would reduce the incidence rates of colorectal cancer by half," lead author Edward Gorham, MPH, PhD, a research epidemiologist with the Naval Health Research Center in San Diego told reporters. "We project a two-thirds reduction in incidence with serum levels of 46 ng/mL."

The amount of dietary vitamin D needed to reach the serum levels that appear to be protective against colorectal cancer — 1000 to 2000 IU per day — would not pose any risk, Dr. Gorham said. "The Institute of Medicine has set a 'No Adverse Effect Level' of 2000 IU per day for vitamin D intake, so this recommendation would be safe for most people."

J Steroid Biochem Mol Biol. Published online January 30, 2007.

Am J Prev Med. 2007;32:210-216.

Learning Objectives for This Educational Activity

Upon completion of this activity, participants will be able to:

- Describe the potential benefits of vitamin D intake to reduce the risk for breast cancer.
- Identify the recommended intake of vitamin D to protect against colorectal cancer.

Clinical Context

Higher levels of metabolites of vitamin D have been associated with lower risks for cancer in some observational research, although data regarding the effectiveness of vitamin D supplementation and cancer prevention has not all been positive. In a study of the Women's Health Initiative cohort by Wactawski-Wende and colleagues, which appeared in the February 16, 2006, issue of the *The New England Journal of Medicine*, supplementation with vitamin D at a dose of 200 IU twice daily failed to reduce rates of colon cancer compared with placebo.

The dose of vitamin D in the Women's Health Initiative was modest, and subjects were followed up for a mean of only 7 years. It is not clear if there is a threshold for serum 25-hydroxyvitamin D levels, the best serum marker of vitamin D levels, in reducing the risk for cancer. Two current analyses address this issue.

Study Highlights

- **Vitamin D and Prevention of Breast Cancer: Pooled Analysis**
 - Researchers searched PubMed for articles published between 1966 and 2006 that related quantile of serum 25-hydroxyvitamin D level to the risk for breast cancer.
 - The authors created a summary odds ratio for the development of breast cancer for each quintile of serum 25-hydroxyvitamin D.
 - 2 studies involving 1783 patients were included in the analysis. One study found an inverse relationship between levels of serum 25-hydroxyvitamin D levels and the risk for breast cancer, whereas the other study found no relationship. Again, study methods in the 2 studies were fairly homogeneous.
 - Serum 25-hydroxyvitamin D levels were divided into quintiles of 6, 18, 29, 37, and 48 ng/mL. Again, there was a negative linear relationship between levels of serum 25-hydroxyvitamin D and the risk for breast cancer, with odds ratios of 1.00 (referent group in the lowest quintile of serum 25-hydroxyvitamin D), 0.90, 0.70, 0.70, and 0.50 for increasing quintiles of serum 25-hydroxyvitamin D concentration.
 - Compared with a serum 25-hydroxyvitamin D level less than 10 ng/mL, a level of 50 ng/mL reduced the risk for breast cancer by 50%. This level of serum 25-hydroxyvitamin D would require an average intake of 4000 IU of vitamin D per day, although the authors note that intake of 2000 IU per day combined with sun exposure of approximately 12 minutes per day with 50% of the skin exposed could also help patients achieve a serum 25-hydroxyvitamin D level of 50 ng/mL.
- **Optimal Vitamin D Status for Colorectal Cancer Prevention**
 - Researchers searched PubMed for articles that related quantile of serum 25-hydroxyvitamin D level to the risk for colorectal cancer. 5 studies published between 1966 and 2005 met inclusion criteria.
 - The authors created a summary odds ratio for the development of colorectal cancer for each quintile of serum 25-hydroxyvitamin D.
 - All included studies were case-control analyses with follow-up between 2 and 25 years. 3 studies reported a reduction in the risk for colorectal cancer with higher levels of serum 25-hydroxyvitamin D level, although 2 studies failed to demonstrate a significant protective effect of serum 25-hydroxyvitamin D level. However, the authors of the current study state that the methods of the 5 studies were fairly homogeneous.
 - There was a linear trend toward reduced risk for colorectal cancer as levels of serum 25-hydroxyvitamin D increased. The odds ratios for colorectal cancer for each increasing quintile of serum 25-hydroxyvitamin D level were 1.00 (referent group), 0.82, 0.66,

0.59, and 0.46.

- Compared with a serum 25-hydroxyvitamin D level less than 12 ng/mL, a level of at least 33 ng/mL or more was associated with a 50% reduction in the risk for incident colorectal cancer.
- Despite the fact that women are more likely to use vitamin D supplementation vs men, there was no report of a difference between sexes regarding the protective effect of levels of serum 25-hydroxyvitamin D.
- The authors conclude that vitamin D intake of 1000 to 2000 IU per day would confer an appropriate balance between protection against colorectal cancer and adverse events related to hypervitaminosis.

Pearls for Practice

- The current review suggests that the risk for breast cancer may be reduced by 50% through consumption of 4000 IU/day of vitamin D. Alternatively, individuals may consume 2000 IU of vitamin D per day and spend approximately 12 minutes per day in the sun.
- The current review suggests a linear, negative relationship between levels of serum 25-hydroxyvitamin D and the risk for colorectal cancer. Based on these data, vitamin D intake at an average of 1000 to 2000 IU per day should provide significant protection against colorectal cancer.

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This article is intended for primary care clinicians, oncologists, gastroenterologists, endocrinologists, and other specialists who care for patients at risk for colon and breast cancer.

Goal

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