

See Dr. Susman's editorial "Diving for PURLs" PAGE 878

Double-dose vitamin D lowers cancer risk in women over 55

Practice changer

Increasing the dose of vitamin D₃ from the current standard of 400–600 IU per day to 1000 IU per day lowers future risk of cancer in women older than age 55 who do not get adequate vitamin D from sun exposure or diet.¹

Strength of recommendation (SOR)

A: Well done randomized controlled trial²

Lappe JM, Travers-Gustafson D, Davies KM et al. Vitamin D supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007; 85:1586–1591.

ILLUSTRATIVE CASE

A healthy 60-year-old Chicago woman who takes 1500 mg calcium and a multi vitamin daily tells you she has read that extra vitamins prevent cancer. She is particularly concerned about cancer because of her strong family history. Should you recommend that she take any additional vitamins to reduce her risk of cancer?

BACKGROUND

Will this trial pass the test of time? We think so

Wouldn't it be nice if we could recommend something as simple and safe as a daily vitamin to reduce the risk of cancer? Until now, we have had no definitive evi-

dence to support such a recommendation. The Lappe et al trial, however, concluded that improving calcium and vitamin D nutritional status substantially reduces all-cancer risk in postmenopausal women.¹ Will this single, relatively small study pass the test of time and be confirmed by future clinical trials? We think so.

- The estimated relative risk reduction was dramatic (0.232) and the 95% confidence interval was 0.09 to 0.60, meaning that the true relative risk reduction has a 95% probability of being in the range of 40% to 91%. The *P* value of <.005 suggests that the probability of this finding occurring by chance alone is less than 1 in 200.

- Our critical appraisal found no significant flaws in this randomized controlled trial.

- Vitamin D is known to have cancer protective effects at the cellular level.

- Prior population based studies support the association between vitamin D and cancer prevention.

For these reasons—and the fact that 1000 IU vitamin D is very safe for most patients—we find this single RCT convincing as a practice changer. For us, the potential benefit outweighs the potential harm.

United States Preventive Services Task Force. A 2003 report on “routine vitamin supplementation to prevent cancer and cardiovascular disease” cited insufficient evidence to recommend the use of supplemental vitamins A, C, E, multivitamins with folic acid, or antioxidants to prevent

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FAST TRACK

1000 IU vitamin D daily is safe for most patients. Potential benefit outweighs potential harm

PURLs methodology

The criteria and findings leading to the selection of this study as a Priority Update from the Research Literature can be accessed at www.jfponline.com/purls.

TABLE

3 ways to get vitamin D: Food, sun, and supplements⁹

	SOURCE	AMOUNT
Food	1 cup of fortified milk	100 IU vitamin D ₃
	One serving (3.5 oz) of oily fish (salmon, tuna, sardines, mackerel or herring)	200 to 300 IU vitamin D
Sun (ultraviolet B radiation)	Expose face, arms, hands, or back for 10 to 15 minutes (without sunscreen) at least twice a week during summer months or in warm climates	3000 IU vitamin D ₃ per exposure
Supplements	Vitamin D ₃	1000 IU/day
	Vitamin D ₂	50,000 IU every 2 to 4 weeks

cancer or cardiovascular disease; vitamin D is not mentioned.³

Institute of Medicine. In 2005, the IOM suggested an Adequate Intake (AI) of vitamin D of 400 IU for women from 51 to 70 years of age, and 600 IU for women over 70 years of age, to maintain bone health and normal calcium metabolism in healthy women. The IOM cited epidemiologic studies showing an inverse association between either increased sun exposure or higher vitamin D levels and decreased risk of cancer, and included the caveat that it was premature to recommend taking vitamin D for cancer prevention until well-designed trials prove that vitamin D is protective against cancer.⁴

Electronic knowledge resources that are evidence-based and frequently updated did not recommend vitamin D for cancer prevention on the dates we searched.⁵⁻⁸

CLINICAL CONTEXT**■ Food, sun, supplements may not deter deficiency**

Few people get enough vitamin D to match the dosage that reduced cancer incidence in this trial. In fact, inadequate vitamin D intake, even to meet current standards, is surprisingly common—even in people who are apparently conscious of their nutritional needs. A Boston hospital found that 32% of healthy students, physicians, and resident physicians were vitamin-D deficient, despite drinking a glass of milk

daily, taking a daily multivitamin, and eating salmon at least once a week.⁹ An estimated 1 billion people worldwide have vitamin D deficiency or insufficiency.⁹

Many factors affect vitamin D levels (TABLE).⁹ Foods that contain vitamin D₃ include fortified milk (100 IU per cup) and oily fish, including salmon, tuna, sardines, mackerel, and herring (200–300 IU per 3.5-oz serving). Sun exposure for 10 to 15 minutes (without sunscreen) at least twice a week to the face, arms, hands, or back is considered sufficient to provide adequate vitamin D during summer or in warm climates.

Many patients need supplements to reach the levels provided by 1000 IU daily, especially in colder climates. Most over-the-counter supplements containing vitamin D alone contain 400 to 1000 IU vitamin D₃. Prescription vitamin D₂ capsules contain 50,000 IU.⁹ Vitamin D is available as vitamin D₂ and D₃:

- **Vitamin D₂** is usually labeled vitamin D or calciferol. Vitamin D₂ is only 30% as effective as vitamin D₃ (doses should be adjusted accordingly).
- **Vitamin D₃** is labeled vitamin D₃ or cholecalciferol.

STUDY SUMMARY**■ Cancer was a secondary outcome**

This trial was well designed and executed, with impressive findings. The primary outcomes were related to skeletal status

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Improving vitamin D nutritional status substantially reduces the all-cancer risk in post-menopausal women

and calcium economy. Cancer incidence was one of the secondary outcomes.

This population-based study was randomized, double-blinded, and placebo-controlled, with concealed allocation. The researchers enrolled 1180 women older than 55 years of age, with no known cancer, and with adequate mental and physical health to allow an expected 4 years of participation in the trial. The trial was conducted in rural Nebraska. Eighty-six percent of the participants completed the study. Participants were randomly assigned to 3 groups:

- **Placebo** (calcium placebo plus vitamin D placebo, n=266)
- **Calcium-only** (1400 mg calcium citrate or 1500 mg calcium carbonate plus vitamin D placebo, n=416)
- **Calcium + D** (1000 IU [25 mcg] vitamin D plus calcium [as above], n=403)

Every 6 months, adherence was assessed by bottle weight. Mean adherence (taking $\geq 80\%$ of assigned doses) was 85.7% for vitamin D and 74.4% for calcium. Serum samples were analyzed for 25(OH)D at baseline and then yearly.¹

Key results

Fifty women developed non-skin cancer during the study: 13 in the first year, and 37 during the second to fourth years. Excluding cancer diagnosed in the first year (it was assumed that these cancers were present, though undiagnosed, at entry), the relative risk reduction (RRR) for the calcium + D group was 0.232 (confidence interval [CI], 0.09–0.60; $P < .005$), and the RRR for the calcium-only group was 0.587 (95% CI, 0.29–1.21; $P = .147$) compared with the placebo group.

Number needed to treat (NNT) to prevent 1 case of cancer for the calcium + D group is 21, with an absolute risk reduction of 0.048, or approximately 5%.

Risk reduction. Using baseline 25(OH)D concentration as the predictor variable and cancer as the outcome variable in logistic regression, Lappe et al predicted a 35% reduced cancer risk for

every 25 nmol/L (10 ng/mL) increase in serum 25(OH)D.¹

WHAT'S NEW?

■ First RCT to show reduced cancer incidence

This is the first randomized-controlled clinical trial to show that vitamin D reduces cancer risk. (It is important to note that one prior randomized controlled trial¹⁰ found no impact on cancer incidence; however, that trial used a vitamin D₃ dose of 400 IU, which is lower than the 1000 IU dose used by Lappe et al.)

Vitamin D curbs carcinogenic potential.

The new findings build on prior basic research, which established the pathophysiologic process by which vitamin D may prevent cancer in humans. Vitamin D receptors are found not only in the small intestines, bones, and kidneys, but also in most other tissues, including skin, colon, prostate, breast, and brain. The interaction of 1,25(OH)₂D with vitamin D receptors induces terminal differentiation and apoptosis and inhibits cellular growth, angiogenesis, and metastatic potential.¹⁰

Other studies suggest vitamin D plays a part. Previous population-based studies also suggested an association between vitamin D and reduced cancer incidence.

Lin et al, as part of the Women's Health Study, found that higher intake of calcium and vitamin D was associated with a lower risk of breast cancer in premenopausal but not in postmenopausal women. The highest dosage quintile was >548 IU; therefore, many if not most women likely ingested an inadequate dose of vitamin D to reduce risk of cancer.¹¹

The Health Professionals Follow-up Study, which followed a cohort of 47,800 men, from 1986 until 2000, found that low levels of vitamin D were associated with increased incidence of cancer and mortality.¹²

In the only other randomized controlled trial of vitamin D and cancer (also part of the Women's Health Initiative), Wactawski-Wende et al found no

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To implement all USPSTF-recommended preventive health services would take 7.4 hours per day

difference in the risk of colorectal cancer between women taking calcium and vitamin D and women taking placebo, over an average of 7 years of follow-up. However, the vitamin D dose was only 400 IU daily, the dosage recommended for general health and bone health.¹³

CAVEATS

■ Consider toxicity unlikely

Although excess vitamin D intake, leading to a serum level of 25-hydroxyvitamin D (25[OH]D) >150 ng/mL, can cause toxicity, the IOM has set the tolerable upper intake level of vitamin D (a fat-soluble vitamin stored in the liver) at 2000 IU (50 mcg) for adults and children older than 1 year. Moreover, studies have shown that adults can tolerate doses as high as 10,000 IU per day.⁴

Symptoms of toxicity include nausea, vomiting, poor appetite, constipation, weakness, and weight loss as well as signs and symptoms of hypercalcemia, including mental status changes, renal failure, and arrhythmias.⁴

Diseases and drugs that affect serum levels. Patients with mild to moderate renal failure or chronic granulomatous diseases, such as sarcoidosis, are at higher risk of developing vitamin D toxicity. Patients with malabsorption syndromes, mild or moderate hepatic failure, or who take certain medications, like anticonvulsants or glucocorticoids, that increase vitamin D metabolism may need higher doses of vitamin D.⁹

The good sun. Exposure to sunlight never leads to vitamin D toxicity, as UV radiation destroys any excess vitamin D that is produced.¹⁰

CHALLENGES TO IMPLEMENTATION

■ A matter of time

The primary challenge is likely to be the competing demands and limited resources inherent in delivering all preventive health services in the primary care setting. By one estimate, implementing

all preventive health services recommended by the US Preventive Services Task Force would require 7.4 hours per day, leaving little if any time to address the acute and chronic care needs of each individual patient.¹⁴ ■

PURLS methodology

This study was selected and evaluated using FPIN's Priority Updates from the Research Literature Surveillance System methodology. The criteria and findings leading to the selection of this study as a PURL can be accessed at www.jfponline.com/purls.

References

- Lappe JM, Travers-Gustafson D, Davies KM, et al. Vitamin D supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007; 85:1586-15-91.
- Ebell MH, Siwek J, Weiss BD et al. Strength of recommendation taxonomy (SORT): A patient-centered approach to grading evidence in the medical literature. *J Fam Pract* 2004; 53:111-120
- US Preventive Services Task Force Web site. Routine vitamin supplementation to prevent cancer and cardiovascular disease: recommendations and rationale. June 2003. Available at: www.ahrq.gov/clinic/3rduspstf/vitamins/vitaminsrr.htm. Accessed on October 15, 2007.
- National Institutes of Health, Office of Dietary Supplements. Dietary Supplement Fact Sheet: Vitamin D. 2005. Available at: ods.od.nih.gov/factsheets/vitamind.asp. Accessed on October 15, 2007.
- Fletcher RH, Fairfield KM. Vitamin supplementation in disease prevention. UpToDate [database online]. Updated January 8, 2007. Available at: www.uptodateonline.com. Accessed on June 25, 2007.
- Becker KL. Vitamin D intake and supplementation. Dynamed [database online]. Updated June 28, 2007. Available at www.dynamicmedical.com. Accessed on July 5, 2007.
- Rosen, HN. Vitamin D therapy in osteoporosis. UpToDate [database online]. Updated February 21, 2007. Available at www.uptodate.com. Accessed on July 11, 2007.
- Vitamin D. PepidPCP [database online]. Available at www.pepidonline.com. Accessed on August 6, 2007.
- Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357:266-281.
- Holick M. Vitamin D: its role in cancer prevention and treatment. *Progress in Biophysics and Molecular Biology* 2006; 92:49-59.
- Lin J, Manson JE, Lee I, et al. Intakes of calcium and vitamin D and breast cancer risk in women. *Arch Intern Med* 2007; 167:1050-1059.
- Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst* 2006; 98:451-459.
- Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* 2006; 354:684-696.
- Yarnall KSH, Pollak KI, Ostbye T, et al. Primary care: is there enough time for prevention? *Am J Public Health* 2003; 93:635-641.

FAST TRACK

Exposure to sun never leads to vitamin D toxicity