

Calcium plus vitamin D did not prevent hip fracture or colorectal cancer in postmenopausal women

Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med*. 2006;354:669-83.

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;354:684-96.

Clinical impact ratings: GIM/FP/GP ★★★★★☆ Geriatrics ★★★★★☆ GIM/FP/GP ★★★★★☆ Gastroenterology ★★★★★☆
Oncology ★★★★★☆

QUESTION

In postmenopausal women, does supplementation with calcium and vitamin D reduce risks for fractures and colorectal cancer?

METHODS

Design: Randomized placebo-controlled trial (Women's Health Initiative [WHI] calcium with vitamin D trial).

Allocation: Unclear allocation concealment.*

Blinding: Blinded (clinicians, participants, and outcome assessors).*

Follow-up period: Mean 7 years.

Setting: 40 centers in the United States.

Participants: 36 282 healthy postmenopausal women 50 to 79 years of age (mean age 62 y) who were also enrolled in the WHI Dietary Modification and Hormone Therapy (HT) trials. Exclusion criteria included expected survival < 3 years, hypercalcemia, kidney stones, corticosteroid use, and calcitriol use.

Intervention: Calcium carbonate, 500 mg, and vitamin D₃, 200 IU (*n* = 18 176), or placebo (*n* = 18 106), twice daily with meals. Personal use of calcium (up to 1000 mg/d),

vitamin D (up to 1000 IU/d), bisphosphonates, and calcitonin was allowed. 52% of women were taking HT at baseline.

Outcomes: Hip, wrist, vertebral, and total fractures; bone mineral density (BMD) (in a subgroup of 2431 women); colorectal cancer; death; and adverse effects.

Patient follow-up: 99% (intention-to-treat analysis).

MAIN RESULTS

Adherence ($\geq 80\%$ of study medication taken) was about 60% in both groups throughout the study period. Women who received calcium plus vitamin D or placebo did not differ for hip, wrist, vertebral, or total fractures (Table). Calcium plus vitamin D reduced risk for hip fracture in subgroups of women who complied with the medication regimen, were ≥ 60 years of age, had no history of falls in the year before enrollment, and were randomized to active HT in the WHI HT trial (Table). At year 6, calcium plus vitamin D increased mean BMD by 0.9% at the hip but did not affect BMD at the spine or total body. Groups did not differ for invasive

colorectal cancer overall (Table). No benefit was seen in compliant women or any subgroup by baseline characteristics. Groups did not differ for type, location, histologic characteristics, grade, stage, or size of colorectal tumor. Calcium plus vitamin D increased risk for kidney stones (Table) but not gastrointestinal symptoms. Groups did not differ for all-cause mortality (Table).

CONCLUSION

In healthy postmenopausal women, supplementation with calcium and vitamin D did not reduce risks for fractures or colorectal cancer.

Sources of funding: National Heart, Lung and Blood Institute; National Center for Research Resources; GlaxoSmithKline.

For correspondence: Dr. R.D. Jackson, Ohio State University, Columbus, OH, USA. E-mail jackson.20@osu.edu. Dr. J. Wactawski-Wende, University at Buffalo, Buffalo, NY, USA. E-mail jww@buffalo.edu. ■

*See Glossary.

(continued on page 5)

(continued from page 4)

Calcium plus vitamin D vs placebo to prevent fractures and colorectal cancer in postmenopausal women at mean 7 years†

Outcomes (subgroup)	Annualized event rates		RRR (95% CI)	NNT (CI)
	Calcium + vitamin D	Placebo		
Hip fracture	0.14%	0.16%	12% (–8.0 to 28)	Not significant
Vertebral fracture	0.14%	0.15%	10% (–10 to 26)	Not significant
Total fractures	1.6%	1.7%	4.0% (–2.0 to 8.9)	Not significant
Hip fracture (compliant)	0.10%	0.14%	29% (3.0 to 48)	2465 (1489 to 23 826)
Hip fracture (≥ 60 y)	0.19%	0.24%	21% (2.0 to 36)	1986 (1159 to 20 858)
Hip fracture (no previous falls)	0.11%	0.15%	26% (2.0 to 44)	2566 (1516 to 33 358)
Hip fracture (randomized to HT)	0.10%	0.17%	42% (7.0 to 63)	1402 (934 to 8410)
Death	0.58%	0.63%	9.0% (–1.0 to 17)	Not significant
			RRI (CI)	NNH (CI)
Wrist fracture	0.44%	0.44%	1.0% (–10 to 14)	Not significant
Colorectal cancer	0.13%	0.12%	8.0% (–14 to 34)	Not significant
Kidney stones	0.35%	0.30%	17% (2.0 to 34)	284 (143 to 2407)

†HT = hormone therapy. Other abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from hazard ratios in article.

COMMENTARY

These 2 reports from the large WHI randomized controlled trials do not support the widely held belief that calcium plus vitamin D supplementation prevents fractures and colorectal cancer. Does this settle the issue? We are taught that results of clinical trials are the standard for questions of effectiveness. But even with unimpeachable methods, “negative” trials of dietary supplements can still be misleading because of the many possibilities for false-negative conclusions, for both the women in the trials and others who might be offered the supplements.

Regarding fractures, although the results were not statistically significant, they suggest a small protective effect. Treated women had 12% fewer hip fractures, the type of fracture associated with the highest morbidity and mortality. The 95% confidence interval is consistent with as many as 28% fewer fractures at one extreme and 8% more fractures at the other, with most of the likely values in the protective range. Effectiveness was supported by the pattern of results in subgroups and by other outcomes. Protective effects for hip fracture were larger (and statistically significant) in women who actually took the assigned treatments, were older, and were not falling. Also, bone density in the hip was increased in the group offered calcium plus vitamin D. Therefore, effectiveness is probably present, but not large.

There are many reasons why this particular trial, for all its strengths, might have underestimated potential benefit for other kinds of women. Women in the trial were at low risk; many had already had the intervention by taking substantial amounts of calcium and vitamin D, and more than half were taking HT. By the end of the trial, most participants had not reached the age at which fractures are common. The dose of vitamin D was relatively small, below the level (700 to 800 IU/d) that other trials have shown to be effective (1). Many women in the intervention group (40%) did not take the recommended supplements.

As for colorectal cancer prevention, this trial, although state-of-the-art, was not a robust test of the hypothesis that calcium plus vitamin D supplementation is protective over the long term. Average follow-up was only 7 years, whereas most cases of colorectal cancer develop in ≥ 10 years. The trial did show that the combination of calcium and vitamin D was not effective in preventing colorectal cancer within several years, but there is not much reason to believe it would act so quickly.

As a practical matter, clinicians are in much the same position as they were before these trials were published. They should act as if calcium and vitamin D supplements contribute in a small way to the prevention of postmenopausal fractures, even in low-risk women and in the short term, but at the cost of a small increase in risk for kidney stones. Effects may be larger with higher doses of vitamin D and in older women or those who are already having fractures. Powerful drugs (HT, bisphosphonates, calcitonin, parathyroid hormone, and others) are available for high-risk women, and their effects dwarf those of calcium with vitamin D alone. Regarding cancer prevention, clinicians might, in the absence of strong evidence or recommendations in clinical practice guidelines, choose to include calcium in a program of prevention of colorectal cancer, in concert with other such protective factors as exercise, diet, and smoking cessation. But a protective effect, if it occurs at all, can be expected only after many years. Meanwhile, screening is effective.

*Robert H. Fletcher, MD, MSc
Professor Emeritus, Harvard Medical School
Boston, Massachusetts, USA*

Reference

1. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA*. 2005;293:2257-64.