

# Calcium + Vitamin D: Surprises From Long-term Follow-up

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Hello. This is Dr. JoAnn Manson, Professor of Medicine at Brigham and Women's Hospital and Harvard Medical School in Boston, Massachusetts. I want to talk about an update of the long-term follow-up of the calcium and vitamin D supplementation trial in the Women's Health Initiative.

A report by Jane Cauley and colleagues<sup>[1]</sup> was published last month in the *Journal of Women's Health*. I encourage you to take a look at the details of the study, because it includes interesting new findings. Today, I will touch on a few of the key points.

In this large trial, more than 36,000 postmenopausal women aged 50-79 years were randomly assigned to treatment with a combination of calcium carbonate at a dose of 1000 mg elemental calcium plus vitamin D<sub>3</sub> 400 IU daily, or placebo. Women received treatment for an average of 7 years. This follow-up took place an average of 5 years after intervention, for a total follow-up of about 12 years.

The overall outcomes for hip fracture in the intention-to-treat analysis were neutral; the trial showed no significant reduction in hip fracture among the active treatment group. However, the analyses that were limited to adherent women who were taking at least 80% of their study pills compared with the women who were taking at least 80% of their placebo pills showed a statistically significant 29% reduction in the risk for hip fracture.

In addition, with the follow-up now at 12 years, a significant 13% reduction in vertebral fracture emerged in the active treatment group, even in the intention- to-treat analyses. And already reported was the significant improvement in bone mineral density of the hip for those receiving active treatment vs placebo, as measured by DXA (dual-energy X-ray absorptiometry).

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## 3 Areas of Support for Supplements

We now have 3 lines of evidence of benefit for calcium plus vitamin D supplementation: the reduction in hip fracture seen among adherent women, the reduction in vertebral fracture in the intention-to-treat analyses, and the improvement or better results for bone mineral density with active treatment compared with placebo and also in the intention-to-treat analyses. Overall, there is increasing evidence that calcium plus vitamin D supplementation does have benefits for bone health.

Also shown in the new report is that with longer-term follow-up, a statistically significant reduction in in situ breast cancer emerged -- a 13% reduction overall. The authors reported no reduction in invasive breast cancer, but it will be of interest to see whether such a reduction does emerge with longer follow-up.

In terms of all cancers, among the women who had low baseline intake of vitamin D, there was a statistically significant 9% reduction in total cancer with supplementation, and also a marginally significant 9% reduction in all-cause mortality. No reduction in colorectal cancer was seen in the trial.

For the cardiovascular endpoints, such as heart disease, stroke, and total cardiovascular events, there was no evidence of benefit or risk. Thus, this was a neutral result for cardiovascular outcomes, which is notable given the controversy about whether calcium may increase the risk for cardiovascular events.

The overall findings appear to be favorable for calcium and vitamin D supplements compared with placebo. We certainly need additional trials of higher-dose vitamin D supplementation beyond 400 IU daily. The Institute of Medicine now recommends that women older than 50 years have at least 1200 mg of calcium per day from a combination of diet and supplements if needed, and 600-800 IU of vitamin D. Perhaps randomized trials of higher-dose vitamin D supplements will show that higher-dose supplementation can provide greater benefits.

Thank you very much for your attention. This is JoAnn Manson.

#### **References**

1. Cauley JA, Chlebowski RT, Wactawski-Wende J, et al. Calcium plus vitamin D supplementation and health outcomes 5 years after active intervention ended: the Women's Health Initiative. *J Womens Health (Larchmt)*. 2013;22:915-929.