

Study: Vitamin D Supplements and Prevention of Cardiovascular Disease and Cancer. *N Engl J Med*; published online November 10, 2018.

Study Design: The Vitamin D and Omega-3 Trial (VITAL) was a randomized, double-blind, placebo-controlled trial, with a two-by-two factorial design, that assessed the benefits and risks of supplementation with vitamin D₃ (at a dose of 2,000 IU per day) and n-3 fatty acids (1 g per day as a fish oil capsule containing 840 mg of n-3 fatty acids, including 460 mg of eicosapentaenoic acid and 380 mg of docosahexaenoic acid) in the primary prevention of cardiovascular disease and cancer. The study population was men 50 years of age or older and women 55 years of age or older in the United States. Eligible participants were required to agree to limit the use of vitamin D from all supplemental sources, including multivitamins, to 800 IU per day and to complete a 3-month placebo run-in phase.

The primary endpoints were major cardiovascular events (composite of myocardial infarction, stroke, and death from cardiovascular causes) and invasive cancer of any type. Secondary cardiovascular endpoints were major cardiovascular events plus coronary revascularization (percutaneous coronary intervention [PCI] or coronary-artery bypass grafting [CABG]) and individual components of the primary endpoint. For cancer, secondary endpoints were colorectal, breast, and prostate cancers during the trial period and death from cancer.

Results: The study included 25,871 participants, with a mean age of 67.1 years. The median follow-up period was 5.3 years. There were no significant differences in the incidence of invasive cancer between the vitamin D and placebo groups (hazard ratio [HR] 0.96; 95% confidence interval [CI], 0.88 to 1.06). Additionally, no significant differences between the two groups were observed in the incidence of breast, prostate, or colorectal cancer, or death from cancer. Post-hoc analyses of the rate of death from cancer suggested a possible benefit after excluding early follow-up data (i.e., excluding the first two years of follow up). Preliminary analyses of cancer stage at diagnosis showed slightly fewer advanced cancers, metastatic cancers, or both among patients assigned to vitamin D than among those assigned to placebo, but differences were not significant. In subgroup analyses, normal-weight participants who received vitamin D had a lower incidence than those who received placebo. This effect was not observed in overweight or obese participants.

With respect to the other primary endpoint, no significant difference was observed in the incidence of major cardiovascular events between the vitamin D and placebo groups (HR 0.97; 95% CI, 0.85 to 1.12). Vitamin D supplementation also did not affect the risk of secondary cardiovascular endpoints. There was no significant effect modification according to randomization to the n-3 fatty acid intervention. Effects did not vary according to baseline serum 25-hydroxyvitamin D [25(OH)D] levels.

Regarding safety, there were no significant differences between the vitamin D and placebo groups with respect to incident diagnoses of hypercalcemia, kidney stones, or gastrointestinal symptoms.

Authors' Conclusions: "In summary, daily supplementation with high-dose vitamin D for 5 years among initially healthy adults in the United States did not reduce the incidence of cancer or major cardiovascular events."

CRN's Comments: This was a well-designed and executed clinical trial. Strengths of the trial included a cohort that was diverse with respect to race, ethnic group, and geography; a high follow-up and adherence rate; and rigorously adjudicated endpoints. Additionally, blood samples were obtained at baseline from 65.5% of study participants. Among the 15,787 participants who had blood samples that could be analyzed, the mean (\pm SD) serum total 25(OH)D level at baseline was 30.8 \pm 10.0 ng/mL (77 nmol/L); 12.7% had levels below 20 ng/mL (50 nmol/L), and 32.2% had levels from 20 to less than 30 ng/mL (50

to <75 nmol/L). In the 1,644 participants with repeat measurements after 1 year, mean 25(OH) D levels increased by 40% in the vitamin D group and changed minimally in the placebo group.

Although vitamin D supplementation did not significantly affect cancer incidence or death from cancer, post-hoc analysis showed a suggested benefit of decreased rate of total deaths from cancer after exclusion of early follow-up data. This is consistent with previous clinical trials, observational studies, and pre-clinical research. Additionally, subgroup analyses showing a potential benefit of vitamin D supplementation on cancer risk in normal-weight participants are supported by mechanistic research. However, the authors caution that the post-hoc and subgroup analyses “should be considered hypothesis-generating, in the context of the negative findings for the primary outcome measures and given that they are not adjusted for multiple comparisons.”

This trial was limited in that the duration of the intervention and follow-up period may not have been long enough to detect differences, particularly for cancer endpoints. Furthermore, the dose was low and the patient population was sufficient in Vitamin D. A dose of 2,000 IU is moderate to low and the patient population had median serum 25-hydroxy-vitamin D levels in participants was 30.8 ng per milliliter (ng/mL) at baseline. According to the National Institutes of Health Office of Dietary Supplements, normal levels of vitamin D are 20 ng/mL – 50 ng/mL.