VITAL Signs for Dietary Supplementation to Prevent Cancer and Heart Disease

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The use of dietary supplement products is common in the United States. The National Health and Nutrition Examination Survey, conducted from 1999 through 2012, showed that more than half the adults in the United States consumed dietary supplements.[1] In the past decade, the numbers of persons who supplemented their diets with fish oil increased by a factor of 10 and with vitamin D by a factor of 4.[1] But any long-term health benefits from these products remain in doubt. Hence, the results from the Vitamin D and Omega-3 Trial (VITAL), a randomized, double-blind, placebo-controlled trial (with a two-by-two factorial design) of vitamin D_3 (cholecalciferol, at a dose of 2000 IU per day) and marine n–3 fatty acids (also called omega-3 fatty acids, at a dose of 1 g per day) for the primary prevention of cancer and cardiovascular disease are both timely and relevant. Manson et al. now report in two *Journal* articles[2,3] that dietary supplementation with fish oil and vitamin D in this trial did not result in a lower incidence of invasive cancer or a prespecified combination of major cardiovascular events than that with placebo.

Compelling observational data have long existed that the consumption of fish is associated with protection from cardiovascular disease. However, evidence from trials that n–3 fatty acids may prevent coronary heart disease was not available until the open-label Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)–Prevenzione Trial in the late 1990s. Largely on the basis of that one trial (and supporting preclinical data), the American Heart Association issued a recommendation regarding the use of n–3 fatty acids for the secondary prevention of coronary heart disease.[4] That recommendation has since been updated after many large, randomized trials collectively showed no consistent effect of supplemental n–3 fatty acids to reduce the incidence of cardiovascular events in populations at high risk for coronary heart disease.[5] The only remaining use for n–3 fatty acids in the most recent American Heart Association statement is an opinion that the use of n–3 fatty acids is reasonable (not recommended) because it may prevent death from coronary heart disease in patients with a recent myocardial infarction, a statement made largely on the basis of a single meta-analysis.[6] Somewhat surprisingly, data from trials testing n–3 fatty acids on the primary prevention of cardiovascular disease in the general population were not available. VITAL has now filled this knowledge gap and convincingly shown that the use of n–3 fatty acids is not effective in preventing the combined end point of myocardial infarction, stroke, or death from cardiovascular causes in unselected patients. These data are generally consistent with those from the recent trial ASCEND (A Study of Cardiovascular Events in Diabetes), which showed that the use of n–3 fatty acids had no effect on the primary prevention of cardiovascular disease in patients with diabetes.[7]

Not unlike the results regarding marine n–3 fatty acids, there has been a host of observational data suggesting that lower levels of vitamin D are associated with a higher risk of cancer.[8] Such studies, in turn, highlighted the need for randomized, controlled trials. However, VITAL is not the first randomized trial to test whether vitamin D supplementation could prevent cardiovascular disease or cancer, although to our knowledge it is the largest and longest. The Vitamin D Assessment Study (VIDA) was a 3-year, randomized, placebo-controlled trial in New Zealand that involved 5110 persons who received supplementation with high-dose (100,000 IU) vitamin D monthly.[9] In that trial, there was no effect of vitamin D supplementation on the incidence of major cardiovascular events.[9] Similarly in a post hoc analysis from VIDA, the supplemental use of vitamin D had no effect on cancer outcomes.[10]

Despite those negative findings, there remains considerable uncertainty about cancer prevention with supplementary vitamin D because of several factors. First, active vitamin D consistently suppresses cell proliferation in vitro, and that could translate into potential in vivo anticancer efficacy.[11] Second, a recent meta-analysis showed a significant benefit with vitamin D with regard to cancer mortality.[12] In one randomized, placebo-

controlled trial of vitamin D, there was a signal for an anticancer benefit.[13] In that trial, 2000 IU of vitamin D and 1500 mg of calcium or placebo daily were administered to 2303 postmenopausal women. The risk of cancer of any type was 30% lower with the active interventions, although the confidence intervals included 1.0 and the result was not considered to be statistically significant.[13] As such, expectations were high that VITAL, which was powered to detect a 15% lower incidence of new cancers with the active treatment than with placebo and which included 10 times the number of participants as other trials, would provide a definitive answer.

VITAL enrolled 25,871 men and women and followed them for a median of 5.3 years. Adherence rates in the trial averaged 80% for both supplements and placebos. Manson et al. found no effect of vitamin D supplementation on a primary end point of invasive cancer of any type or on the secondary end points of site-specific cancers or death from cancer. Other aspects of this trial are noteworthy. First, the number of participants and the substantial proportion of black participants make this cohort a nationally representative sample. In that vein, the results of this trial should be directly generalizable to most patients. Second, although the median serum 25-hydroxyvitamin D level at baseline was 30.8 ng per milliliter, approximately 1 in 13 participants had a serum 25-hydroxyvitamin D level of less than 20 ng per milliliter at baseline. Even in that subgroup, vitamin D supplementation had no effect on the number of cases of invasive cancer of any type. Hence, across a wide range of serum vitamin D levels there was no health benefit from vitamin D supplementation.

Despite the negative findings regarding the primary end points in VITAL, the secondary end points will undoubtedly draw attention. It will be tempting to note the lower incidence of myocardial infarction and of death from myocardial infarction with n–3 fatty acids than with placebo and the lower mortality from cancer with vitamin D than with placebo and then to cite these findings as evidence that these supplements can benefit some patients in preventing coronary heart disease or cancer death. However, these "positive" results need to be interpreted with caution. First, there was no correction for multiple comparisons, as would be required to attenuate the chance that these are spurious results, owing, in part, to the number of secondary end points. Second, these putative effects have not been consistently observed across other large, randomized trials of n–3 fatty acids.[5,6] However, in one of the trials of vitamin D supplementation, post hoc analysis showed a lower incidence of cancer among women who received active supplements than among those who received placebo, excluding women who had withdrawn or in whom cancer had developed in the first year of the trial.[13] Finally, the medical literature is replete with exciting secondary end points that have failed when they were subsequently formally tested as primary end points in adequately powered randomized trials. Thus, in the absence of additional compelling data, it is prudent to conclude that the strategy of dietary supplementation with either n–3 fatty acids or vitamin D as protection against cardiovascular events or cancer suffers from deteriorating VITAL signs.

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