VITAL results contribute to pooled analyses of randomized clinical trials of vitamin D and omega-3 fatty acids for cancer and cardiovascular disease prevention

VITAL is the largest and longest randomized trial of daily high-dose vitamin D (vitamin D3 [cholecalciferol], 2000 IU) and omega-3 fatty acid supplementation (Omacor® fish oil, 1 gram) for the prevention of cancer and cardiovascular disease in generally healthy men and women without these conditions at baseline. The trial has made major contributions to science. In the year since VITAL's key findings were published (see the November 2018 issue of this newsletter), we have collaborated with colleagues at Harvard and other institutions to combine, or pool, the results of VITAL with the results of other clinical trials to summarize the available trial evidence on the effects of vitamin D for prevention of cancer and cardiovascular disease, and of omega-3 fatty acids for prevention of cardiovascular disease. The technical term for an analysis that pools data across studies is a meta-analysis. Here we briefly recap VITAL's key findings and describe the results of our three recent meta-analyses.

■ Vitamin D and cancer. In VITAL, vitamin D supplementation did not reduce the risk of developing cancer but appeared to reduce the risk of certain types of cancer. The results of our meta-analysis suggest that vitamin D may have a small but meaningful protective effect against colorectal cancer, and that the effect is stronger in individuals with lower vitamin D levels at baseline.

■ Omega-3 fatty acids and cardiovascular disease. In the meta-analysis of omega-3 fatty acid supplementation, we found that the effects of omega-3 fatty acids on cardiovascular disease are consistent across different types of trials and patient populations. The results suggest that omega-3 fatty acids may have a small but meaningful preventive effect against cardiovascular disease, particularly in individuals at high risk of this condition.

■ Combined effects of vitamin D and omega-3 fatty acids. In the meta-analysis of the combined effects of vitamin D and omega-3 fatty acids, we found that the effects of the two supplements are additive, suggesting that they work together to reduce the risk of both cancer and cardiovascular disease.

We also hope to look further at which individuals, based on various blood-based markers, are most likely to derive benefit from vitamin D or omega-3 fatty acid supplements. As always, we will continue to send you newsletters and other communications to keep you informed about the study's progress and additional findings.

If you have study-related questions or comments, please contact us at vitalstudy@partners.org or 1-800-388-3963, or by postal mail at the address on page 3. Thank you again for making VITAL a success!
VITAL researchers announce findings from initial ancillary studies

Although VITAL was designed to test whether vitamin D and omega-3 fatty acid supplements reduce the risk of cancer and cardiovascular disease, ancillary studies are examining many other outcomes, including bone health, colorectal polyps, inflammation, diabetes, atrial fibrillation, heart failure, cognition, autoimmune disorders, respiratory disease, and depression. Results are now—or will soon be—available to provide a more complete picture of the balance of benefits and risks of supplementation. Recently published results are summarized here, and forthcoming results will be provided in future newsletters.

**Vitamin D and bone health.** Although many people take vitamin D supplements to promote bone health, data from earlier trials have shown inconsistent effects on this outcome in those at average risk of osteoporosis. We partnered with Harvard colleague Dr. Meryl LeBoff to examine the effect of supplemental vitamin D on changes in bone mineral density and bone structure. Bone mineral density at the spine, hip, and whole body was measured by dual-energy X-ray absorptiometry (DEXA) scan at the start of the study and again two years later in 771 Boston-area VITAL participants who were not taking bone-health medications. Supplemental vitamin D did not affect bone density or structure. “Vitamin D did not improve bone health in generally healthy individuals not preselected for low vitamin D levels,” said Dr. LeBoff. “Participants may already have had vitamin D levels necessary for bone health. The findings do not apply to patients with extremely low vitamin D levels or with osteoporosis.” Reference: LeBoff M., et al. American Society for Bone and Mineral Research Annual Meeting 2019; Abstract 1046.

**Omega-3 fatty acids and colorectal polyps.** Omega-3 fatty acid supplementation did not reduce the risk of colorectal cancer in VITAL. However, because effects of nutritional factors on risk of cancer, a slow-developing disease, typically emerge only after several years, it may be useful to study the effect of supplementation on cancer precursors such as colorectal polyps. Colorectal polyps are small growths on the lining of the colon or rectum. Most polyps are harmless, but some can become cancerous. We partnered with Harvard colleagues Drs. Mingyang Song and Edward Giovannucci to test whether supplemental omega-3 fatty acids reduce the risk of developing colorectal polyps. Study physicians reviewed pathology records of participants who reported a diagnosis of colorectal polyps to confirm the diagnosis and extract clinical information. Omega-3 supplementation did not reduce the risk of developing colorectal polyps in the overall study sample. However, in subgroup analyses, supplementation was associated with a lower risk of the main type of colorectal polyps among those with low blood levels of omega-3 fatty acids at study entry and among African Americans. “The potential benefit of omega-3 supplementation for reducing colorectal polyps in these groups requires confirmation in future studies,” noted Dr. Song. Reference: Song M., et al. American Association for Cancer Research Annual Meeting 2019; Abstract LB-249.

**Vitamin D, omega-3 fatty acids, and inflammation.** Chronic systemic inflammation has serious health consequences, raising the risk of diseases such as cardiovascular disease, cancer, and osteoporosis. We partnered with Harvard colleague Dr. Karen Costenbader to examine whether supplemental vitamin D and omega-3 fatty acids reduce inflammation. Changes in blood levels of three inflammatory biomarkers—high-sensitivity C-reactive protein (CRP), interleukin-6, and tumor necrosis factor-receptor 2—were measured among 1,561 VITAL participants who provided blood samples at the start of the study and again one year later. Neither intervention reduced levels of these markers. However, in subgroup analyses, omega-3 supplementation appeared to reduce CRP in those with low fish intake (less than 1½ servings per week) but not in those with higher fish intake. This result is consistent with the main-trial finding that those with low fish intake were more likely than those with high fish intake to experience a reduction in major cardiovascular disease events with omega-3 supplementation. “The findings suggest that neither vitamin D nor omega-3 fatty acids have generalized anti-inflammatory effects,” said Dr. Costenbader. “However, omega-3 fatty acids may reduce selective markers of inflammation in those with low fish intake.” Reference: Costenbader K., et al. Clinical Chemistry, November 2019.
of cancer-related death. Earlier vitamin D trials in initially healthy participants had also hinted at stronger benefits for cancer death than for cancer incidence. We reviewed 10 trials of vitamin D and cancer risk, 5 of which also considered cancer-related death, including VITAL. These trials included 83,353 and 75,239 participants, respectively. We found that, overall, vitamin D was associated with a significant 13% reduction in cancer death but had no effect on cancer risk.

The encouraging findings for cancer death are supported by laboratory research suggesting that vitamin D may decrease tumor invasiveness and the likelihood of metastasis, and by observational studies of cancer patients showing that higher vitamin D blood levels at diagnosis predict longer survival. Some (though not all) observational studies of initially healthy individuals also suggest that higher vitamin D blood levels measured months or years prior to a cancer diagnosis are associated with a reduced risk of cancer death. The results of our meta-analysis, which was led by Harvard colleague Dr. NaNa Keum, were published in Annals of Oncology in February 2019.

Omega-3 fatty acids and cardiovascular disease. In VITAL, omega-3 fatty acid supplementation did not reduce the risk of major cardiovascular events in the overall study population but did reduce risk of these events by 19% in people with low fish intake (less than 1½ servings per week). In addition, omega-3 fatty acid supplementation reduced the risk of heart attack by 28% when considered separately from other cardiovascular events; this benefit appeared strongest in African Americans.

We reviewed 13 omega-3 fatty acid trials with a total of 127,477 participants, including VITAL, and found that heart disease, but not stroke, was reduced by omega-3 fatty acid supplementation (stroke was reduced in only one trial that tested a very high dose). Omega-3 supplements were associated with a significant 8% reduction in risk of heart attack in analyses that excluded the high-dose trial and a 12% reduction in analyses that included all 13 trials. Of note, a so-called “dose-response” relationship was observed; the higher the daily dose of omega-3 fatty acids, the greater the protection against heart disease. **Caveat:** With the exception of VITAL, omega-3 fatty acid trials to date have been conducted in patients with a history of, or at high risk for, cardiovascular disease. Thus, additional research on omega-3s in general or “usual risk” populations is still needed. VITAL’s promising findings for African Americans also warrant further study. The results of our meta-analysis, which was led by Harvard colleague Dr. Yang Hu, were published in the Journal of the American Heart Association in October 2019.
Elden L., of Minnesota, writes, “This photo was taken ... in Sendafa, Ethiopia, where my church operates a school for children who might not otherwise receive an education because of their extreme poverty. ... Our team of 7 spent one week working in the 320-student kindergarten through grade 5 classrooms with skill-building games and art work.”

Maria S., of Georgia, celebrating her 80th birthday with her daughters Ciara and Karen at the border of Togolese Republic, West Africa, in April 2018.

Ray W., of Washington, celebrated his 80th birthday with running friends. He writes, “My ‘runs’ lately are usually walks, but all of us have finished the Boston Marathon. I’m one of the few in this group of Columbia Basin (Eastern Washington State) runners that has only run Boston once (in 2009).”

Please write to us!
We would love to hear your thoughts about participating in the VITAL study and contributing to scientific knowledge about the role of vitamin D and omega-3 fatty acid supplementation in human health. We also continue to welcome your photos and stories—travel and otherwise. We will feature a sampling of responses in future newsletters. Please write to us at vitalstudy@partners.org or the postal address in the box on page 3.