Re: Calcium Plus Vitamin D Supplementation and the Risk of Breast Cancer

In a recent issue of the Journal, Chlebowski et al. (1) presented the association between supplementation with vitamin D plus calcium and breast cancer based on the impressive Women’s Health Initiative (WHI) clinical trial. The overall result showed, as in a previous study from WHI with colorectal cancer as endpoint (2), no protective effects of the supplementation. Both the authors and the accompanying editorial (3) suggest that the administrated dose of vitamin D (400 IU) might have been too low to show a protective effect.

The potential negative health effects of low vitamin D serum levels have recently received considerable interest, and large supplemental doses of vitamin D to the general population are advocated by many scientists. We are, however, concerned that the discussion on potential negative effects of vitamin D supplementation (besides those of toxicity) is very limited.

In both cancer studies from WHI, the results show trends toward potential harmful effects of total high vitamin D intake; in the breast cancer study a statistically significant interaction between baseline intake of vitamin D and the intervention was seen ($P = .003$), such that women with intakes of vitamin D less than 200 IU at baseline had beneficial effects of the intervention, but those with baseline intakes greater than 600 IU and an additional supplementation of 400 IU through the intervention had increased risk of breast cancer (hazard ratio = 1.34, 95% confidence interval = 1.01 to 1.78). In the study with colorectal cancer as endpoint (2), a similar tendency was seen with baseline serum levels of vitamin D, such that estimates relating intervention to cancer incidence were below 1.00 for those with lowest baseline serum levels, whereas the estimates were above 1.00 for those with the highest baseline serum vitamin D levels. In the colorectal study neither the estimates nor the test for interaction ($P = .54$) were even close to reach statistical significance, but a negative effect of supplementation among those with highest baseline levels of serum vitamin D cannot be excluded. The WHI have also indicated that vitamin D supplementation may increase the risk of colorectal cancer among women using estrogen therapy (4).

The results from WHI are further complemented by another study recently published in the Journal (5), showing rather strong increased risks of prostate cancer, especially the more advanced stages, among men with high serum levels of vitamin D. We argue the need for caution before recommending that the population take high doses of vitamin D supplements. We agree that many interesting studies indicate promising effects of vitamin D regarding public health, but the past has shown us (with the history of β-carotene and lung cancer as the scariest lesson) that observational studies on micronutrient blood levels cannot always be extrapolated to positive effects of high-dose supplementation. Furthermore, it is rather interesting that both high physical activity and low body mass index seem to be strongly associated with high vitamin D blood levels (1,5). Could confounding by these two important health measures be an important part of the explanation for the preventive effects observed in some studies regarding vitamin D?

ANJA OLSEN
RIKKE EGEBERG
ANNE TJØNNELAND

References