Despite aggressive treatment and screening efforts, breast cancer remains the second leading cause of cancer-related deaths among women in the United States (1). Because of the large number of women dying from this disease and the toxicity of breast cancer treatments, recent efforts have focused on identifying effective cancer preventive agents. These efforts have led to the development of antiestrogen agents, such as tamoxifen and raloxifene, which prevent approximately 50% of invasive breast cancers in women who are at high risk for breast cancer. However, the use of these agents for breast cancer prevention has been limited by their toxicity.

A large amount of evidence exists to indicate that vitamin D may be a particularly promising cancer preventive agent. Vitamin D is a fat-soluble vitamin that is essential for bone formation and calcium homeostasis. The potential link between vitamin D levels and reduced cancer incidence was suggested by results from epidemiological studies by Garland et al., Giovannucci, and others (2–5) and by recent data suggesting a strong association between low vitamin D levels and increased colon cancer risk (6). Several case-control and cohort studies support an inverse relationship between vitamin D intake and breast cancer incidence (7–11); however, other studies show either no association or an association with increased breast cancer risk (10,12–14). In addition, recent studies found that vitamin D deficiency was linked to poor outcomes in patients with early breast cancer (15).

It is against this backdrop that Chlebowski et al. (16) report the results of a randomized controlled clinical trial evaluating the breast cancer preventive effect of vitamin D and calcium supplementation. This study, which was compiled from the calcium plus vitamin D (CaD) arm of the Women’s Health Initiative (WHI), randomly assigned 36,282 postmenopausal women to receive daily doses of either 1000 mg calcium with 400 IU vitamin D3 supplementation or placebo and were followed up for an average of 7 years. To maximize participation and size, the WHI trial had overlapping groups, including a dietary modification (DM) group, a hormone therapy (HT) group, and a CaD group, which was added in the second year of the study. As a result, 69% of women in the calcium with vitamin D trial were also part of the DM group, 54% were part of the HT group, and 14% had participated in both the DM and the HT trials (17). Furthermore, in this trial, personal use of calcium and vitamin D was permitted in both the supplementation and the placebo groups.

Chlebowski et al. should be congratulated for successfully completing such a large and sophisticated trial. The well-designed and well-executed randomized, double-blinded, placebo-controlled trial with a nested case–control study is unrivaled in its scope and complexity. This current study tested the hypothesis that 1000 mg/day calcium plus 400 IU vitamin D3 supplementation would reduce the risk of breast cancer among postmenopausal women. Breast cancer incidence was a prospectively planned secondary endpoint in the WHI study. This trial had a large number of racially diverse women who maintained relatively good adherence to the study protocol. Despite the meticulous design, careful control, and adequate adherence, Chlebowski et al. report that calcium and vitamin D supplementation did not reduce the incidence of breast cancer.

Previous groups (17,18) have reported the results of the other components of the WHI study. In these studies, there was a small but statistically significant increase in hip bone density, suggesting the possibility of a clinically relevant effect of CaD supplementation. Analysis of this WHI data also demonstrated that there was no decrease in hip bone fractures or colorectal cancer incidence, which were the other primary and secondary endpoints of the trial (17,18). These results, along with the results presented in this issue (16), suggest that women who received the CaD in this trial did not experience the predicted benefits of calcium and vitamin D supplementation—a reduction in bone fractures, colon cancer, and breast cancer.

Should these negative results discourage the use of calcium and vitamin D in future breast cancer prevention studies? Not necessarily. Although Chlebowski et al. (16) did not find a statistically significant association between calcium and vitamin D supplementation and reduced incidence of breast cancer, there could be several important confounders at play. The first confounder is that of variable baseline vitamin D levels. The authors measured the baseline level of plasma 25-hydroxyvitamin D and compared this level with self-reported vitamin D intake. There was a large overlap of baseline self-reported vitamin D intake across the plasma 25-hydroxyvitamin D quintiles, suggesting that factors besides intake (such as sunlight exposure, body mass index, metabolism, physical activity, and genetic factors) have a stronger influence on plasma 25-hydroxyvitamin D than just intake quantity alone.

A second potential confounder is the high level of calcium and vitamin D self-supplementation (up to 1000 mg of calcium and 1000 IU of vitamin D) that was allowed during the study. This “outside of study” supplementation led to 15% of placebo patients “dropping in” to the active treatment component of the study.
Such “outside of study” supplementation, sometimes at levels more than twice the trial dose, may have diminished the observed difference in breast cancer incidence between the placebo and CaD arms.

Another very important issue is the dose of vitamin D given in this trial. Recent reports suggest that higher doses of vitamin D (1000–2000 IU/day) may be required to prevent cancer (19). It is possible that doses sufficient to prevent osteoporosis are not sufficient to prevent cancer. The results of this trial suggest that a dose of 400 IU of vitamin D could be insufficient to prevent breast cancer (16) or colon cancer (17).

Another important aspect of this trial is the age of the study population. The women in the WHI trial were postmenopausal and aged 50–79 years. Previous epidemiological studies (8,10,14,20) have not shown a clear association between vitamin D intake and breast cancer in postmenopausal women (relative risks [RRs] = 0.55 to 1.3); however, results from epidemiological studies of premenopausal women (10,14) suggest that vitamin D intake may prevent breast cancer in these women (RRs = 0.65 to 0.89). Furthermore, given long latency of breast cancer, many of the postmenopausal women in the WHI trial may have already developed premalignant breast lesions or cryptic breast cancers at the time of study enrollment. If vitamin D is effective as a cancer preventive agent only before breast cells become cancerous, then the vitamin D taken by women with existing, undetected breast cancers would not prevent the progression of these cryptic cancers. Indeed, the results reported by Chlebowski et al. show that 140 women developed cancer within the first year of the trial; these women may have had in situ noninvasive breast cancers or small, undetected invasive breast cancers before the trial began. In addition, 26% of women who developed breast cancer during the trial were diagnosed with cancer within 2 years of trial initiation. It is interesting that the cumulative hazard lines begin to separate between the supplemented and placebo groups in the last 2 years of the trial (although this difference is not statistically significant). This result suggests that vitamin D plus calcium supplementation is effective only at early stages of breast carcinogenesis. To investigate this hypothesis, it would be particularly useful to determine whether these lines further separate with continued follow-up.

Should we then abandon further study of vitamin D as a breast cancer prevention agent? Given the extensive preclinical data showing a cancer preventative effect of vitamin D (21,22), to do so may be premature. We should first attempt to answer several questions not answered by the current study. Could vitamin D have a different cancer preventive effect on premenopausal vs postmenopausal women? Should vitamin D be used earlier in the course of breast carcinogenesis, ie, at a younger age? Did concomitant HT, which may increase the risk of developing breast cancer, affect the results of the study? Did DM with a low-fat, high fruit and vegetable diet vs no DM affect the response to vitamin D and calcium? Is 400 IU of supplemented vitamin D too low of a dose to prevent breast and colon cancer?

These questions should drive the design of future vitamin D cancer prevention trials. It is particularly important that future trials evaluate higher doses of vitamin D. With such a high percentage of pre- and postmenopausal women taking vitamin D and calcium supplements, future trials will likely need to compare “standard dose” supplements with “high dose” supplements. In addition, future trials may need to be carefully controlled for diet, sunlight exposure, HT, and physical activity. Finally, such trials may require earlier initiation and longer duration. Given the long latency of breast cancer, longer follow-up times may be needed to evaluate the effect of vitamin D on breast cancer incidence.

Because preclinical, epidemiological, and clinical trial results of vitamin D supplementation are conflicting, additional studies will be needed to determine whether vitamin D plus calcium will prevent breast cancer. However, this article by Chlebowski et al. offers an important first step in addressing this issue. Future clinical trials should address the above questions to help determine whether higher doses of vitamin D supplements will be cancer preventive. The potential health benefits of vitamin D and calcium may yet still have a bright future.

References


