In the Selenium and Vitamin E Cancer Prevention Trial (SELECT) (1), neither 200 mcg/day of selenium (Se) from L-selenomethionine (SEM) nor 400 IU/day of all-racemic alpha-tocopheryl acetate (AT) provided benefit for the prevention of prostate cancer (PCa). In this issue of the Journal, Kristal et al. (2) report on the relationship between baseline toenail Se and the results of SELECT. Their intriguing results stimulate discussion on a variety of points.

One finding is that AT increased PCa risk in subjects with low baseline Se (2). This was unexpected because both AT and Se have antioxidant roles and one could reasonably expect the opposite—that supplemental AT could compensate for an antioxidant deficit resulting from low-Se status. However, supplementation with AT in SELECT was eight times the amount used in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group (3,4), which showed promise in the prevention of PCa. This high dose of AT severely suppresses serum gamma-tocopherol, the prevalent dietary form of vitamin E in the United States. Gamma-tocopherol exhibits potentially beneficial chemical and biological activities not shared by alpha-tocopherol that make it potentially an important compound for PCa prevention (5). As a result, high-dose AT could effectively diminish other critical tocopherol functions, which could be needed for subjects with low-Se status. Additionally, lipid radical inactivation is a two-step process: chemical reduction of highly reactive peroxyradicals by vitamin E to less reactive although inherently unstable hydroperoxides, followed by reduction of the hydroperoxides to more benign lipid alcohols by Se-dependent glutathione peroxidase 4 (GPx4). High-dose AT in combination with low-Se status could result in adverse accumulation of lipid hydroperoxides. Thus supplemental alpha tocopherol may paradoxically increase the need for GPx4 activity, an essential enzyme without redundancy (6).

To be relevant to the present context, such a scenario would require that GPx4 was at a submaximal activity in the low-Se subjects, implying a positive effect of SEM in the low-Se group, especially for those receiving high-dose AT. However, it is not surprising that no statistically significant finding for SEM in low-Se subjects was found considering the very large confidence bounds for the hazard ratio, and there would be far less power for a signal in the even smaller subset of low-Se subjects on the AT arm. Bundling quintiles together reduces the confidence interval but dilutes the low-Se population. This adverse AT effect on the low-Se placebo groups, combined with the low power to see an impact of SEM in low-Se subjects, leaves room for these or other interpretations. In any case, informative biological markers, including baseline tocopherol status and activities of the relevant selenoenzymes, would shed additional light on these latest results. The combination of low-Se status and either low gamma-tocopherol status or high alpha-tocopherol status may lead to increased cancer risk by mechanisms at the nexus between Se and vitamin E nutrition and should stimulate additional research and re-evaluation of past research.

Reconsidering the Nutritional Prevention of Cancer (NPC) Trial (7), to simply add 200 mcg of Se from 0.5 g of high-Se Brewer’s yeast into a diet of approximately 2500 g per day and have a statistically significant 65% reduction in PCa hazard, a statistically significant 39% reduction in all cancers, and a 21% decrease in the hazard for overall mortality (not statistically significant) is a stunning effect that one might only envision when the basic needs of many of the individuals weren’t being met: subacute Se deficiency.

It has been well established that the SELECT subjects had a higher baseline serum Se content, in the range of values where no benefit of SEM or even Se yeast would be expected (7,8,9). Kristal et al. (2) now provide additional evidence, noting that their lowest Se group cutoff was higher than the highest quintile cutoff for the recent work by Geybels et al. (9) on subjects in the Netherlands. Has the US population changed in Se status with the addition of selenized yeast to animal feed? Is subacute Se deficiency now rare in the United States? The enhanced risk of PCa for the high-Se group suggests adding SEM to an already replete population may have a negative impact on PCa, providing statistical significance to a previously observed trend (10).

SELECT, which used SEM, and NPC, which used Se yeast containing 16% SEM (11), both suggest low-Se status is at least a prerequisite for benefit. However, we do not know enough about other Se-related compounds, which may act quite differently to prevent cancer. In fact, SEM does not protect against chemically induced aberrant crypts, performing poorer than inorganic sources of Se even though the tissue Se content increases the most using SEM (12). Compare this to Se-enriched wheat and broccoli, which reduced chemically induced colon tumors in rats better than inorganic sources or low-Se broccoli (13,14). These benefits were also not associated with increases in liver glutathione peroxidase activity observed with selenomethionine. The major form of Se in high-Se wheat is SEM, and the major form of Se in enriched broccoli is Se methylselenocysteine, but neither one of these pure compounds was
effective in reducing these tumors. Similar results with Se-enriched broccoli were obtained with multiple intestinal neoplasia mice, which are considered a good genetic model to study the effects of dietary components on intestinal cancer (15). These animal studies suggest that the form of the Se does matter. Different Se forms are used differently in the body (eg, methylselenol), and even more intriguing, plants and yeast fed inorganic Se may create secondary compounds that could influence healthy people who consume them. The possibility remains that the positive outcome in NPC was due to these other secondary compounds or Se compounds other than SEM.

Finally, we need to revisit the question of evaluating the prevention of a single disease in healthy people, where competing risks may obscure reality (16). Even if a subset of subjects can be identified that would benefit from some form of Se or vitamin E supplementation, it must not be only a benefit to a single gland or based on one disease. This was highlighted in the Prostate Cancer Prevention Trial, (17) which reported nearly a 25% reduction in risk of PCa with finasteride but reported that the number of deaths observed on the finasteride arm was higher than on placebo and remains so many years later (18).

References

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