Selenium, Vitamin E and Prostate Cancer

The Selenium and Vitamin E Cancer Prevention Trial (SELECT), a randomized, controlled trial in 35,533 men aged 50 years or older from the United States, Canada, and Puerto Rico, was discontinued before the expected end date when analyses showed no significant association between prostate cancer risk and supplementation with 200 µg /day selenium (from L-selenomethonine) with or without 400 international units (IU)/day of synthetic vitamin E (from *all rac*-α-tocopheryl acetate) (1).

The recent follow-up study (2) and subsequent analysis (3)of the baseline selenium status and the effects of selenium and vitamin E supplementation on prostate cancer based on data from the SELECT study found that selenium supplementation did not benefit men with low selenium status but increased the risk of high-grade prostate cancer among men with high selenium status; and that vitamin E increased the risk of prostate cancer among men with low selenium status (3).

This study should not be considered in isolation, but as one in a series of studies looking at selenium and vitamin E in prostate cancer. Currently the results of these studies appear to be in conflict. Rather than see this data as simply conflicting, some commentators believe that the puzzle has different pieces and we need further studies to elucidate a more complete picture (4).

One question every scientist asks when faced with unexpected results, such as those delivered by the SELECT trial is "*are the results biologically plausible?*"

In an attempt to answer this question we need to consider the doses of the active agents. Interestingly, the SELECT trial protocol paper (5) noted that prior to SELECT there had been only one study that had evaluated the combination of selenium and vitamin E in a cancer prevention study. This trial undertaken in Linxian in China demonstrated that selenium (50µg), α-tocopherol (30mg) and β-carotene (15mg) per day decreased total general mortality and total cancer mortality (6). Instead of replicating these low doses of selenium and vitamin E the SELECT study group chose for a number of reasons to increase the doses from 50µg of selenium to 200µg and 45IU of vitamin E to 400IU. In an editorial that accompanied the recent SELECT trial publication the authors conjectured that the high dose of α-tocopherol given may severely depress the effects of gamma-tocopherol, a vitamin E homologue, and its preventive activity in prostate cancer and that this may be critical in low selenium status individuals (7). They also noted that vitamin E reduces highly reactive peroxyradicals to intermediate less reactive hydroperoxides which in turn are reduced to benign lipid alcohols by a selenium dependent enzyme. In a low selenium state these hydroperoxides would build up and may contribute to cancer causation. While these observations remain conjectures until demonstrated under experimental conditions they do provide biologically plausible models to be tested.

The interplay between selenium, α-tocopherol and gamma-tocopherol is complex and has not been clearly elucidated. One study undertaken in 10,456 male residents of Washington County, MD, USA demonstrated that risk of prostate cancer declined but not in a linear fashion with increasing concentrations of alpha-tocopherol which suggests other factors at

play (8). In the same study they demonstrated that men who had the highest level of gamma-tocopherol had a five-fold reduction in prostate cancer compared with men who had the lowest concentration. The association with selenium was not statistically significant. However, the group found statistically significant protective associations for high levels of selenium and alpha-tocopherol only when gamma-tocopherol concentrations were high.

In contrast, another study raised concern of the link between high circulating levels of gamma-tocopherol and an increased risk of high-grade prostate cancer (9). This group noted that of the 11 other cohort studies examining the association between gamma-tocopherol and prostate cancer risk, three observed a reduced risk of prostate cancer incidence among men with higher circulating levels and 8 observed no association. This was the first study to look at the relationship between alpha and gamma-tocopherol and high-grade prostate cancer. Unfortunately the group did not measure selenium levels.

Apparently gamma-tocopherol levels were measured in the SELECT study, but we are as yet unaware of any analysis that includes them. This data may shed further light on the dynamic interplay between these nutrients and may assist in better understanding the results of the SELECT study.

The SELECT study has raised concerns about possible harmful effects from high dose selenium and vitamin E supplements. Until we have a better understanding of the role of selenium and vitamin E in prostate cancer the precautionary principle would suggest that men over 50 and any man over 40 with a family history of prostate cancer should avoid selenium and vitamin E supplementation at doses that exceed recommended dietary intakes if not prescribed by a health professional.

References

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