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RESEARCH HIGHLIGHT

Heart healthy=prostate healthy: SELECT, the symbolic end of preventing prostate cancer *via* heart unhealthy and over anti-oxidation mechanisms?

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The Selenium and Vitamin E Cancer Prevention Trial (SELECT) randomized over 35 000 men into four groups: high-dose vitamin E (400 IU day^{-1}), high-dose selenium (200 mcg day^{-1}), combination of vitamin E and selenium, or placebo.[1] The brief time period to reach full recruitment was unprecedented; thus, it seemed that participants and health-care professionals were equally eager to test the hypothesis that high-dose antioxidant supplementation could prevent prostate cancer. However, the trial was terminated early, after a median of 5.5 years due to a lack of efficacy, although at the time a non-significant (P=0.06) increased risk of prostate cancer in the vitamin E arm, and type 2 diabetes in the selenium group (P=0.16) were observed.

Yet, to the credit of the SELECT research group, participant follow-up continued (54 464 added person-years), which provided a more lucid understanding of any further health impact after the cessation of these dietary supplements.[2] And, what was revealed recently in this follow-up period was a concern. A significant (P=0.008; hazard ratio (HR)=1.17) increased risk of prostate cancer was found in the vitamin E group, but not in the selenium or combination intervention arm. Perhaps, even more concerning is that the risk of Gleason 7 or higher disease was greater for the three intervention arms compared to placebo, but did not reach statistical significance in any group. The HR and P value for Gleason 7 and higher disease compared to placebo was 1.16 (P=0.20), 1.21 (P=0.11) and 1.23 (P=0.08) for vitamin E, selenium and the combination. Furthermore, the increased risk of prostate cancer with vitamin E began to emerge after only 3 years, and was found to be consistent for low- and high-grade disease types.

The negative results from this trial cannot be explained by bias or increased biopsy rates, but suggest that the interventions themselves are the issue, and the confidence intervals have only continued to narrow over time.[2] Other findings from secondary end points that included other cancers and cardiovascular events did not find statistical differences compared to placebo with this additional analysis. Perhaps this is one small piece of good news in light of such negativity from ingesting what many would have perceived as benign over the counter agents.

Are any of the SELECT results a surprise when reviewing the history of these and other nutritional interventions? It could easily be argued that not only were the results somewhat expected, but they could have been even more disconcerting over time if the interventions were continued. And, even if any of these interventions would have prevented prostate cancer, it is highly questionable whether they would have still provided a tangible clinical advance in medicine. Why? The potential problem that plagued high-dose vitamin E and selenium supplements from past clinical trials was the lack or even negative impact on the number 1 cause of death in men and women, cardiovascular disease.[3,4] Even a past potential increased risk of all-cause mortality had been a concern with high-dose vitamin E supplementation.[5]

One could argue that the synthetic vitamin E supplements utilized in the SELECT trial were the reason for negative findings (also known as 'natural *vs.* non-natural' debate), but this cannot be the case, because several past trials of 'natural' vitamin E derived supplements in high-dose showed no overall impact,[4,6] or a significant increased risk of specific cardiovascular events such as heart failure.[6] So, it is doubtful that the form of vitamin E would have provided alternative results.

One might also argue that the intake frequency (i.e., daily use) of vitamin E led to the negative finding and intermittent dosing would have provided a better benefit-to-risk ratio. This also appears to be an anemic argument because another large randomized trial of vitamin E and prostate cancer risk in healthy men, the Physicians Health Study II, found no impact of 400 IU of vitamin E every other day compared to placebo,[7] but a significant increased risk of hemorrhagic stroke was observed.[8] And, as a side note, one also has to ponder why two independent large trials, conducted primarily in the United States of America, on high-dose vitamin E supplements and prostate cancer prevention were conducted simultaneously at such an enormous financial cost? Why not conduct one trial and save a plethora of resources, time, enthusiastic volunteers and money for another unique chemoprevention trial?

Some might argue that the vitamin E dosage might have been the issue, and this has some potential merit. For example, a common citation or justification for SELECT was the Alpha-Tocopherol, Beta-Carotene (ATBC) trial, which demonstrated a 35% risk reduction of prostate cancer risk with vitamin E from a secondary end point, but the dosage utilized in this trial was only 50 IU (approximately 8 times lower compared to SELECT) and a higher rate of hemorrhagic stroke was also found.[9] Additionally, men in ATBC were chronic 36 years on average smokers, and continuous tobacco users are notorious for multiple nutrient deficiencies, not just vitamin E.[10] Less than 10% of SELECT participants were smokers,[2] which leaves one to ponder the outcome of this trial had a lower scientifically

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more justifiable dose been utilized. Why the belief that more is better? Isn't this one stereotype applied to some patients that utilize a multitude of non-evidence-based dietary supplements? Healthy and primarily non-smoking or former smoking men (85% of the participants) from a unique randomized trial utilizing far lower doses of vitamin E (30 IU) and other supplements demonstrated not only the potential for notable benefit for prevention, but also harm for men with higher baseline prostate-specific antigen levels.[11,12] Regardless, controversial issues have existed with antioxidants at a variety of concentrations in healthy non-smokers.

What about selenium supplementation? The impact of high-dose selenium supplements on heart and overall health from past clinical trials was arguably as concerning as past vitamin E data,[13] and included a potential significant increased risk of type-2 diabetes and non-melanoma skin cancer recurrence.[14,15] Interestingly, this increased risk of skin cancer recurrence was the final conclusion surrounding the primary end point analysis of the landmark randomized selenium supplement trial (nutritional prevention of cancer) which was utilized to help justify initiating SELECT itself.[14,16] Why attempt to prevent prostate cancer with high-dose interventions that may actually increase the risk of other primary causes or even the number 1 cause of morbidity and mortality in men, regardless of its potential for a favorable impact on prostate cancer? Past primary prevention trials are mirror reflections of the current health status of populations and the prostate cancer prevention trial and SELECT morbidity and mortality rates from cardiovascular events, regardless of the group assignment,[1,17] continue to demonstrate the ideal prostate cancer chemoprevention agent needs to potentially reduce the risk of cancer and heart disease simultaneously. This would represent an advance in medicine and not a lateral movement at best.

One could absolutely argue that the SELECT researchers were never capable of launching a sterile clinical trial, without it being contaminated by the time of randomization, because of a novel phenomenon that was not in their control that I'd like to call the 'over anti-oxidation of the US population'. For example, baseline serum selenium status in SELECT was a dramatic 22 points higher (135 ng ml^{-1} *vs.* 113 ng ml^{-1}) compared to notable trials from the 1990s in the United States of America,[1] which essentially equates to a population of men that are no longer deficient in this antioxidant before even ingesting a selenium pill! In otherwords, in the United States of America and in multiple countries around the world, this author has been observing countless multiple nutrients being added to a diversity of foods, beverages and supplements such as multivitamins at an uncontrolled rate over the past decade as preliminary research highlights some potential benefits in various observational studies. Is this good for marketing and business? Arguably so, but is this good for science and safety? This is highly questionable. Thus, by the time any nutritional deficiency trial is designed and initiated over several years, the depleted participants being tested will now be replete with the product(s) being tested even before the trial officially commences. This was the untold story and one primary lesson of the SELECT trial in my opinion. This will represent a challenge to any further nutrient trial in the Western world, and it is my belief, for example, that multiple future supplement or nutritional interventional trials, including vitamin D for example, will also suffer from the same SELECT trial over anti-oxidation controversy and fate.

Finally, it should be of interest to the reader that it has now become difficult to ignore three heart healthy interventions that arguably appear to be more promising than any costly interventions that might selectively and precisely prevent prostate cancer. Aspirin, cholesterol-lowering (statins) medications and metformin, all continue to garner attention for being cost-effective, generic, generally safe and heart healthy in the appropriate population (middle aged and older men).[18–20] These interventions also have unique mechanisms of action that potentially reduce the number 1 cause of morbidity and mortality in men and women. Perhaps, it is time to realize that after an era of subscribing to a philosophy of 'more is better', it is now time to believe that 'less is more' and heart health is tantamount to prostate health. Arguably, not just pills but virtually every single heart healthy lifestyle change (tobacco cessation, weight loss, exercise, diet, blood pressure/cholesterol reduction, *etc.*) has demonstrated some potential to prevent common cancers, such as prostate carcinoma. Yet, what if heart healthy interventions or lifestyle changes ultimately do not prevent prostate cancer from a notable future randomized trial? Then, it is time to facetiously apologize that attempting to reduce the number 1 cause of morbidity and mortality in men and women in the worse-case scenario is really not such a bad worse-case scenario.

1 Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM *et al*. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2009; **301**: 39–51.
2 Klein EA, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS *et al*. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2011; **306**: 1549–56.
3 Eidelman RS, Hollar D, Hebert PR, Lamas GA, Hennekens CH. Randomized trials of vitamin E in the treatment and prevention of cardiovascular disease. *Arch Intern Med* 2004; **164**: 1552–6.
4 Lee IM, Cook NR, Gaziano JM, Gordon D, Ridker PM *et al*. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 2005; **294**: 56–65.
5 Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ *et al*. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005; **142**: 37–46.
6 Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue J *et al*. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA* 2005; **293**: 1338–47.
7 Gaziano JM, Glynn RJ, Christen WG, Kurth T, Belanger C *et al*. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA* 2009; **301**: 52–62.
8 Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C *et al*. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA* 2008; **300**: 2123–33.
9 The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 1994; **330**: 1029–35.
10 Lodge JK. Vitamin E bioavailability in humans. *J Plant Physiol* 2005; **162**: 790–6.
11 Hercberg S, Galan P, Preziosi P, Bertrais S, Mennen L *et al*. The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med* 2004; **164**: 2335–42.
12 Meyer F, Galan P, Douville P, Bairati I, Kegle P *et al*. Antioxidant vitamin and mineral supplementation and prostate cancer prevention in the SU.VI.MAX trial. *Int J Cancer* 2005; **116**: 182–6.
13 Navas-Acien A, Bleys J, Guallar E. Selenium intake and cardiovascular risk: what is new? *Curr Opin Lipidol* 2008; **19**: 43–9.
14 Duffield-Lillico AJ, Slate EH, Reid ME, Turnbull BW, Wilkins PA *et al*. Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial. *J Natl Cancer Inst* 2003; **95**: 1477–81.
15 Stranges S, Marshall JR, Natarajan R, Donahue RP, Trevisan M *et al*. Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. *Ann Intern Med* 2007; **147**: 217–23.
16 Clark LC, Combs GF Jr, Turnbull BW, Slate EH, Chalker DK *et al*. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial. *JAMA* 1996; **276**: 1957–63.
17 Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ *et al*. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003; **349**: 215–24.
18 Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP *et al*. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomized trials. *Lancet* 2011; **377**: 31–41.
19 Solomon KR, Freeman MR. The complex interplay between cholesterol and prostate malignancy. *Urol Clin N Am* 2011; **38**: 243–59.
20 Jalving M, Gietema JA, Lefrandt JD, de Jong S, Reyners AK *et al*. Metformin: taking away the candy for cancer? *Eur J Cancer* 2010; **46**: 2369–80.