

Perspective

See related article by Richie et al., p. 796

**Selenium and Prostate Cancer Prevention:
What Next—If Anything?**

Merrill J. Christensen

Abstract

Chemopreventive effects of the essential trace element selenium against prostate cancer have been shown in preclinical models and human observational studies, but results from clinical trials have been disappointing. It appears that there is a threshold selenium (Se) status below which improvement will decrease prostate cancer risk, but above which supplemental Se may be deleterious. Different forms of selenium have different effects, and genetic and other factors modify selenium's chemopreventive potential. Identification of men most likely to benefit from Se status improvement could have significant public health benefits. *Cancer Prev Res*; 7(8); 781–5. ©2014 AACR.

Diet-based cancer-preventive agents are attractive due to their pleiotropic effects in multiple pathways and their lower toxicity compared with pharmaceutical agents (1). Recent meta-analyses of observational studies suggest that high selenium (Se) concentrations in plasma, serum, or toenails may be associated with reduced risk for prostate cancer (2–4). These analyses are consistent with results in several preclinical models (reviewed in ref. 5). In these models, Se has been shown to modify antioxidant protection, immunity, DNA repair, apoptosis, angiogenesis, and other processes involved in carcinogenesis. However, clinical trials of supplemental Se for prostate cancer prevention have produced mixed results (6–10).

Table 1 summarizes results from four clinical trials of Se compounds. Attention has focused primarily on the Nutritional Prevention of Cancer Trial (NPCT), whose complete results were published in 2003 (6), and the Selenium and Vitamin E Cancer Prevention Trial (SELECT), the final report of which appeared in 2011 (7). The shortcomings of each study have previously been discussed. In brief, the NPCT was designed to test the efficacy of high-Se yeast against recurrence of nonmelanoma skin cancer in 1,312 subjects. Results were negative. However, in secondary analyses a dramatic protective effect was seen against prostate cancer, with a risk reduction of 86% among men in the lowest tertile of baseline plasma Se. These results should be viewed with caution, considering that analyses were based on a total of only 64 cases of prostate cancer, that secondary analyses are at higher risk of false positives due to multiple

testing, and that subjects receiving the placebo had a much higher rate of biopsy (35 vs. 14%) than did Se-supplemented subjects. After correction for differences in biopsy rates, the protective effect of Se remained significant, but less so, in men in the lowest tertile of baseline Se. In SELECT, prostate cancer was the primary endpoint. Supplemental Se provided no protection. The most common criticisms of SELECT include a highly Se-replete cohort at baseline and an ineffective chemical form of Se (selenomethione, SeMet) used as a supplement. Acknowledging the limitations of each trial, reviewers point to certain consistencies seen in these and other studies summarized in Table 1. Supplementation of Se seemed to be effective only when given to men (i) of lesser Se status, (ii) with initial PSA < 4 µg/L, and (iii) as Se-yeast.

Data from these and observational studies suggest that there is a plateau or threshold Se status below which increasing Se intake may be protective, but above which supplemental Se will provide no additional benefit, and may be detrimental. Investigators have used multiple methods to calculate plasma and toenail Se concentrations associated with maximum chemoprevention. Using the experimentally derived conversion factor of Waters and colleagues (11) to equate toenail Se with plasma or serum Se concentration, these calculated threshold values varied between 122 and 133 µg Se/L plasma or serum, equivalent to 0.82 to 0.89 µg Se/g toenail (3, 6, 11–13). As seen in Table 1, the tertile cutoffs in the NPCT were all at or below the threshold, whereas the four treatment groups in SELECT all had median values well above it. The threshold theory was strengthened by two recent reports. In the first, Geybels and colleagues (14) showed a strongly protective effect of higher Se status in a cohort whose baseline quartile cutoffs for toenail Se were all well below the calculated toenail Se threshold. In contrast, the equally recent report of Kristal and colleagues (10) showed no effect of supplemental SeMet in SELECT trial subjects of which all toenail Se cutoffs were above the threshold except for that of the lowest quintile.

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Table 1. Summary of clinical trials of selenium for prostate cancer prevention

	Baseline plasma/serum Se ($\mu\text{g/L}$)	Baseline PSA ($\mu\text{g/L}$)	Form of Se	Daily supplement	Adjusted HR Se vs. placebo	Reference
NPCT	Tertiles (n) ≤ 106.4 (317) 106.8–123.3 (305) > 123.2 (305) Overall median: 113	≤ 4 (624) > 4 (70)	Selenized yeast (Se-yeast)	200 μg	Plasma Se tertiles ≤ 106.4 : <u>0.14</u> 106.8–123.3: <u>0.33</u> > 123.2 : <u>1.14</u> PSA ≤ 4 : <u>0.33</u> > 4 : <u>0.95</u>	Duffield-Lillico et al. (6)
SELECT	Medians of 4 treatment groups: 137.6, 135.9, 135.0, 136.4; Overall median: 135	Selection criterion ≤ 4	L-seleno-methionine (Se-Met)	200 μg	SeMet: <u>1.09</u> SeMet + Vti E: <u>1.05</u>	Klein et al. (7)
Phase III trial in men with HGPIN	Medians (n) Se (46): 138.1 Placebo (51): 135.2	< 4 (40%) 4–10 (60%)	Se-Met	200 μg	RR: <u>0.97</u>	Marshall et al. (8)
Phase III trial in high-risk men	Means of 3 treatment groups: 124.5, 126.6, 127.2; Overall mean: 126.1	Selection criterion > 4	Se-yeast	200 or 400 μg	200 μg : <u>0.94</u> 400 μg : <u>0.90</u>	Algotar et al. (9)
	Baseline Toenail Se ($\mu\text{g/g}$)					
SELECT	Quintile cutoffs: 0.758, 0.832, 0.901, and 1.003 Overall mean: 0.89	Selection criterion ≤ 4	L-seleno-methionine (Se-Met)	200 μg	Se+Vitamin E, in quintiles 4 and 5 combined: <u>2.24</u>	Kristal et al. (10)

NOTE: Underlined values indicate the adjusted HR, comparing Se with placebo. Bold and italicized values indicate statistically significant hazard ratios ($P < 0.01$).

Use of "selenium" in describing these and other studies implies that "selenium" is a single entity or that all chemical forms of Se are of equal efficacy. However, there is a wealth of preclinical data demonstrating that different chemical forms of Se have different effects. In cultured prostate cancer cells, different Se compounds target different molecular mechanisms to inhibit proliferation and viability (15, 16). In rodent models of prostate cancer, various Se species likewise show varying degrees of efficacy (reviewed in ref. 5). Li and colleagues (17) showed in a xenograft model of prostate cancer that supplemental Se-methylselenocysteine (MSC) and methylseleninic acid (MSA) were equally effective at inhibiting tumor growth, but that MSC promoted apoptosis, whereas MSA significantly decreased angiogenesis. Supplemental selenite and SeMet did not affect tumor growth. Some of the most compelling data demonstrating differential effects of Se forms come from the work of Zhang and colleagues (18). In their proteomic analysis of prostate proteins from mice supplemented with the same four forms of Se, they discovered for each Se compound a unique set of proteins regulated only by that compound. Clearly, different forms of Se have different effects.

The limitations of NPCT and SELECT raise questions such as "Would SeMet have worked in the NPCT? Would Se-yeast have been effective in SELECT? What if prostate cancer had

been the primary endpoint in NPCT?" In this issue of the journal, Richie and colleagues (19) report the results of their work which begins to address these questions. Theirs is the first clinical trial to directly compare the effects of Se-yeast, the supplement given in the NPCT that showed Se protection (6), and SeMet, the form of Se used in SELECT, which did not (7). In their study, the primary endpoint was reduction in biomarkers of oxidative stress relevant in prostate cancer. Of the three supplemented groups—low-dose Se-yeast (200 μg Se), high-dose Se-yeast (285 μg Se), and SeMet (200 μg Se)—only subjects receiving high-dose Se-yeast showed statistically significant decreases. Consistent with the threshold theory, high-dose Se-yeast had beneficial effects in men in the lowest tertile of baseline plasma Se (mean 115 μg Se/L; slightly below the threshold) but not in subjects in the second and third tertiles with starting mean Se values of 136 and 152 μg Se/L, respectively.

The high-dose Se-yeast supplement that provided 200 μg Se as SeMet—the same dose of SeMet used in SELECT—along with additional Se in other forms resulted in a statistically significant benefit. This may be due to provision of different chemical forms of Se in addition to SeMet, or simply provision of more total Se. Low Se-yeast subjects received the same blend of chemical forms as did the high Se-yeast recipients, only at lower concentrations that were

ineffective. These results suggest the possibility that there may be a minimum dose of supplemental Se required for benefit, either as total Se or as a specific form or forms, which was not reached in this study by giving 200 μg Se as Se-yeast or SeMet. It is critical to determine the minimally effective dose and form of Se compounds required for efficacy to minimize the likelihood of toxicity associated with excessive supplementation or very high Se status.

Unfortunately, "very high Se status" cannot yet be adequately defined. At present, reliable measures of Se status in Se-replete individuals have not been identified. The limitations of current biomarkers of Se status have recently been reviewed (20). These limitations significantly impact the interpretation of results from studies of Se and prostate cancer.

Metabolic effects of Se are mediated by selenoproteins, for which there are 25 genes in the human genome (21). These proteins are characterized by translational incorporation of Se into selenoproteins as selenocysteine, specifically directed by a UGA codon in their mRNAs (22). Both organic and inorganic Se compounds can supply Se necessary for synthesis of selenoproteins. There are two selenoproteins in plasma, namely GPX3, a member of the antioxidant glutathione peroxidase family, and SEPP1, the primary Se transport protein. Maximization of GPX3 activity in plasma was used as the basis for the current Recommended Dietary Allowance (RDA) of 55 μg Se/day (23). However, Xia and colleagues (24) have since shown that higher Se intake is required to maximize SEPP1 and recommended reconsideration of the RDA. When SEPP1, and therefore also GPX3, are maximized, these two selenoproteins together total 73 to 80 μg Se/L plasma (25, 26). Increasing Se intake beyond the level necessary to maximize plasma GPX3 and SEPP1 produces no further increase in those selenoproteins. However, total plasma Se may continue to rise due to increases in other forms of Se. Unlike the specific, regulated insertion of selenocysteine into selenoproteins, SeMet is not distinguished in metabolic pathways from methionine and enters the methionine pool for nonspecific incorporation into all body proteins (27). Selenium from SeMet is made available for selenoprotein synthesis by metabolism in the transulfation pathway followed by β -lyase cleavage. However, those reactions proceed independently of selenoprotein synthesis and are not known to be regulated by Se status. As a result of nonspecific incorporation of SeMet into plasma proteins, increasing intake of SeMet from natural food sources, from Se-yeast or similar supplements, or as a single chemical compound will continue to increase plasma Se levels above that associated with maximum selenoprotein synthesis, due to increased, nonspecific incorporation of SeMet into plasma proteins. This phenomenon is graphically depicted in Fig. 1, which is a summary of several reports of Se speciation in plasma of human subjects (25–34). The figure shows that as the concentration of total Se in plasma increases, the percentage of that total accounted for by selenoproteins is reduced, and the fraction of Se present in other forms, such as SeMet in plasma proteins, correspondingly rises.

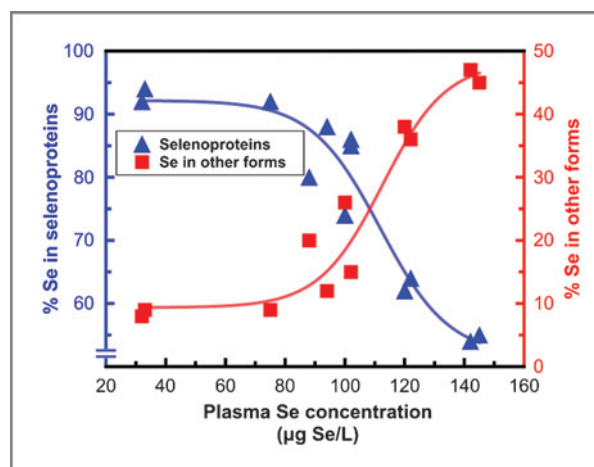


Figure 1. Relative contributions of selenoproteins and other forms of Se at different concentrations of total plasma Se.

Finally, a small portion of plasma Se is accounted for by other forms of the element, including unincorporated SeMet, Se-cystine, Se IV, Se VI, and additional low-molecular-weight uncharacterized forms of Se, either bound to proteins or as unbound metabolites (25, 35). To utilize plasma measurements to assess Se status in nondeficient individuals a more detailed quantitation of the various forms of Se present in plasma will be required.

It is impressive that multiple authors using multiple methods almost all calculated virtually the same plasma and toenail Se threshold concentration. The critical next step is to identify what is maximized in plasma and tissues at those concentrations that accounts for the maximum chemopreventive effect. As noted above, the two plasma selenoproteins, GPX3 and SEPP1, reportedly accounted for 73 to 80 μg Se/L when maximized in plasma of healthy, unsupplemented U.S. adults. In those same subjects, GPX3 and SEPP1 together accounted for 54% to 64% of total plasma Se (25–28). The remaining 36% to 46% was accounted for by "other" Se, as shown in Fig. 1. If plasma selenoproteins present at a concentration of 73 to 80 μg Se/L account for 54% to 64% of total plasma Se when maximized, the total plasma Se concentration associated with maximum selenoprotein expression and activity would be in the range 114 to 148 μg Se/L. This agrees well with the "threshold" values (122–133 μg Se/L), calculated using various models as described above, for plasma Se associated with maximum chemopreventive efficacy. These calculations suggest that the plasma/toenail threshold concentration is associated with maximum selenoprotein expression and that a plasma level of total Se less than 115 μg Se/L may be insufficient to maximize selenoprotein expression and would therefore limit the potentially protective effects of selenoenzyme antioxidant functions.

The observation that the threshold plasma Se concentration is associated with both maximal selenoprotein expression and maximum chemoprevention might suggest that protective effects of Se are due exclusively to selenoprotein

action. However, present understanding is limited about what other forms of Se are present in plasma, how their concentrations change with increasing/decreasing intake, and what roles they may play in cancer prevention. Irons and colleagues (36) demonstrated that selenoproteins and low-molecular-weight selenocompounds may both play a role in cancer risk reduction. In their study of colon cancer, transgenic mice with impaired selenoprotein synthesis had more aberrant colonic crypts than did wild-type mice. This clearly demonstrated a protective role of selenoproteins. At the same time, in both wild-type and transgenic mice, a supranutritional dietary supplement of 2.0 $\mu\text{g Se/kg}$ diet as sodium selenite provided greater protection than did a nutritionally adequate 0.1 $\mu\text{g Se/kg}$ diet, which maximized selenoprotein synthesis. This finding strongly suggests that other forms of Se in addition to selenoproteins may play a role in chemoprevention.

The data of Richie and colleagues are consistent with that of many others showing that the increase in plasma Se seen in study subjects was directly proportional to the amount of SeMet supplemented and incorporated nonspecifically into plasma proteins. In many foods, especially grains, SeMet is the major form of Se. However, there are other commonly consumed foods, particularly vegetables, in which the predominant Se compound is MSC or its γ -glutamyl conjugate (37). High consumption of these foods would provide the majority of their Se in a form that could maximize selenoprotein synthesis, when needed, but would not increase total plasma Se concentration in replete subjects by nonspecific incorporation into plasma proteins. Thus, following maximization of selenoproteins, such forms may be available to exert chemopreventive effects independent of selenoproteins. Indeed, MSC has been shown to have superior chemopreventive efficacy compared with SeMet or inorganic Se in various rodent models of prostate cancer (17, 38).

In National Health and Nutrition Survey (NHANES) 2003–2004 and in the SELECT trial, 22% to 25% of subjects had baseline plasma Se values < 123.2 $\mu\text{g/L}$ (39, 40). Thus, based on the limited data in Fig. 1, including results from

studies described above that were conducted in unsupplemented U.S. adults, it is possible that 20% of American men may have a Se status insufficient to maximize selenoprotein synthesis and maximize Se chemoprevention of prostate cancer. Considering the rapid rise of prostate cancer incidence with age and the steadily increasing age of the U.S. population, the possibility that something as simple as supplementing Se could reduce prostate cancer risk could have profound public health implications.

Additional data are needed to more precisely define the relationships between plasma (or toenail) Se concentration, selenoprotein synthesis, and correlative chemoprevention. Given the well-publicized risks of supplementing Se-replete men (41), correction of suboptimal Se status must proceed cautiously and carefully with attention to baseline Se status, quantity, and chemical form(s) of Se administered. Clearly, recommendations for intervention should not be based simply on mathematical extrapolations. Confirmation of suboptimal Se status predicted by total plasma Se should be provided by assay of SEPP1. Continued refinement and standardization of Se speciation methodology will aid in quantitating potentially protective small-molecular-weight Se compounds, and developing or discovering Se status indicators that will be informative in Se-replete men. The comparative functions and potential roles of different selenoproteins and other Se compounds in prostate cancer chemoprevention remain to be explored. Genetic influences and other modifiers of Se status indicators (25, 42) and Se chemoprevention must be quantified. These approaches will help in identifying men most likely to benefit from improvement in Se status for prostate cancer risk reduction and customize the most effective intervention for them.

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