



Prostate Cancer Risk Reduction Achievable Through Selenium Supplementation: Looking Back to Move Forward

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Prostate cancer is the product of dysregulated homeostasis within the aging prostate and a major cause of cancer-related mortality in men world-wide. In 1996, investigators of the Nutritional Prevention of Cancer (NPC) trial reported that daily supplementation with the essential trace mineral selenium significantly reduced prostate cancer incidence [1]. The notion that dietary selenium supplementation could provide a safe, practical approach to achieving prostate cancer risk reduction accelerated the exploration of selenium's anticancer mechanisms and justified the design of further clinical studies, including SELECT — the largest prostate cancer prevention trial ever conducted [2].

Today, nearly a quarter of a century after the results of the NPC trial, the intellectual debate continues concerning who will benefit from selenium supplementation, who might be harmed, and what role dose and form of selenium may play. Instead of passively subscribing to opinions borrowed from a recent meta-analysis of se-

lenium and human cancer risk [3], our aim is to present a perspective so that readers might gain a closer appreciation of how our collective understanding of selenium and prostate cancer has been actively shaped since the initial NPC trial results that stimulated subsequent contributory work. By offering health professionals this evolutionary look at the selenium-prostate cancer connection, we reinforce an intellectual framework that should help to guide current and future understandings of the impact of selenium on prostate cancer risk reduction. Using the initial results of the NPC trial as a starting point, we examine the extent to which results of subsequent studies — even the seemingly contradictory results of SELECT — can be productively integrated with the novel result of the original study. We contend that the value of a deeper appreciation of this intellectual progression is that it can refocus our present energies on a critical, unmet goal: Identifying those men for whom selenium supplementation may lower prostate cancer risk.

An Evolutionary Look at the Selenium-Prostate Cancer Connection (Figure 1).

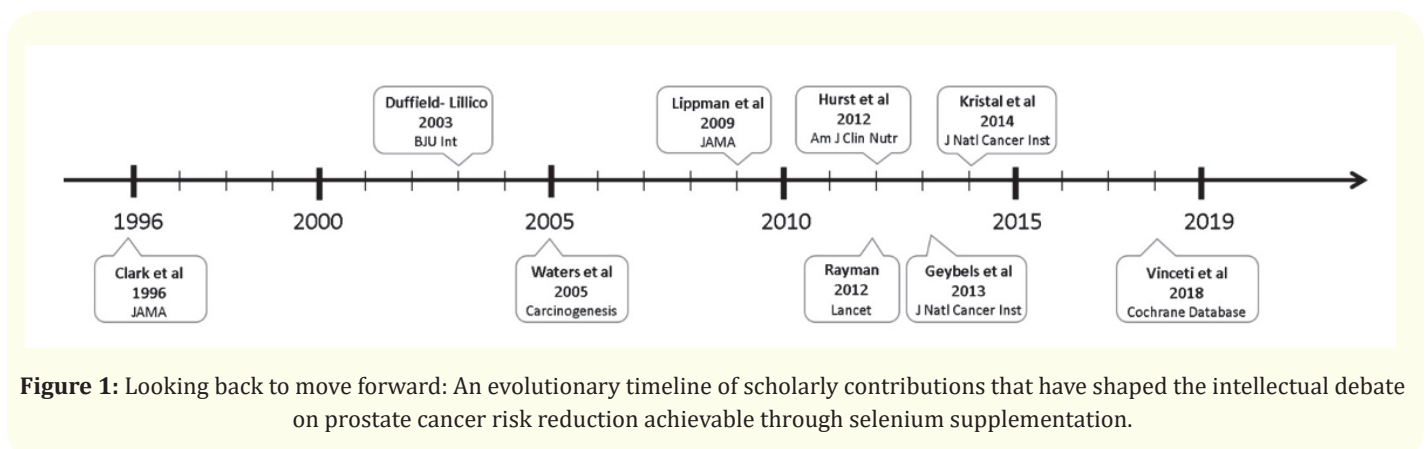


Figure 1: Looking back to move forward: An evolutionary timeline of scholarly contributions that have shaped the intellectual debate on prostate cancer risk reduction achievable through selenium supplementation.

Clark *et al* (1996) [1]

The Nutritional Prevention of Cancer (NPC) trial was a randomized clinical trial designed to test the efficacy of daily selenium supplementation, as 200 µg of high selenium yeast, in preventing non-melanoma skin cancer among residents of the eastern United States, a region characterized by low selenium content in soil. Initial analysis of secondary endpoints revealed that daily selenium supplementation was associated with a striking reduction in prostate cancer incidence by 63% (RR, 95% CI = 0.37, 0.18-0.71). These results clinically validated a substantial body of experimental evidence that selenium can exert anticancer effects in animal and cellular models [4,5]. The study provoked a new understanding and a new set of research priorities. In addition to seeking confirmatory support from additional trials, further work would be needed to identify the subset of men who would benefit from selenium supplementation.

Duffield-Lillico *et al* (2003) [6]

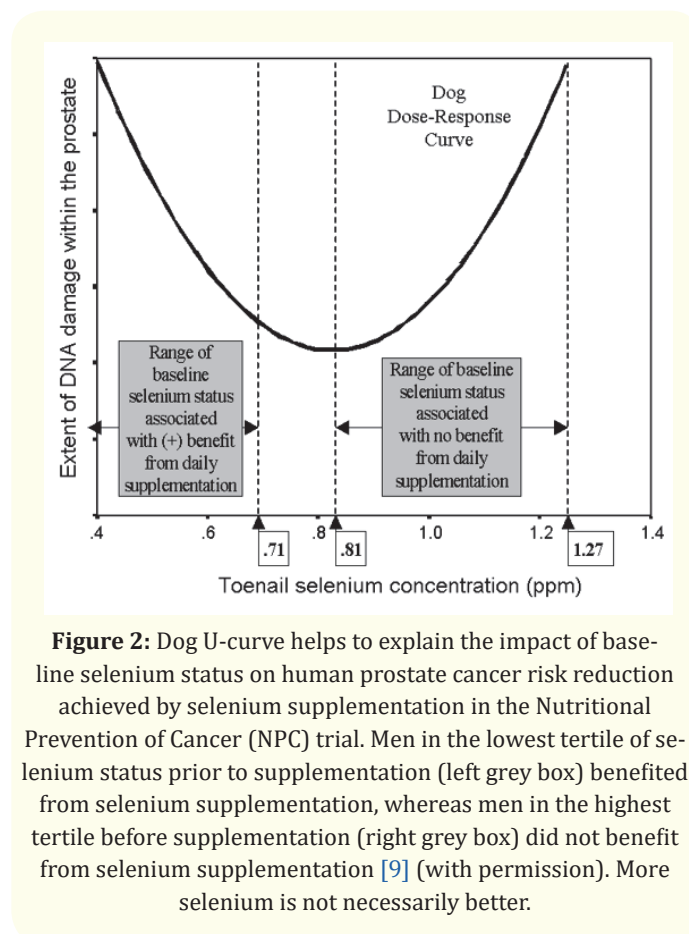
With this report, investigators turned considerable attention to the potential importance of baseline selenium status as a predictor of the benefits achieved by selenium supplementation. Using data from men in the NPC trial, it was shown that the prostate cancer protective effect of selenium was confined to men with lower baseline plasma selenium concentration (<123 µg/L). Men with the lowest selenium status prior to supplementation (<106 µg/L plasma Se, equivalent to < .71 ppm toenail Se) had a significant 86% reduction in prostate cancer risk in response to selenium supplementation. In contrast, men with the highest selenium status prior to supplementation did not experience a reduction in prostate cancer risk with selenium supplementation. Instead, these men had an alarming 88% increase in overall cancer incidence [7].

From this 2003 analysis, it was concluded that additional dietary selenium would potentially benefit only the subgroup of the population that had low selenium status; additional selenium intake would not be expected to reduce disease incidence in subjects with higher selenium levels. The same conclusion was reached by Willett and colleagues 20 years earlier in their interpretation of the first prospective cohort study on selenium and cancer risk in humans [8].

Waters *et al* (2005) [9]

The NPC trial findings were sufficient to put forth a new hypothesis: Selenium significantly regulates the extent of genotoxic damage within the aging prostate and the relationship between dietary selenium intake and DNA damage is non-linear, i.e. more selenium is not necessarily better. To test this hypothesis, we conducted a randomized feeding trial in which elderly beagle dogs (physiologically equivalent to 62-69 year old men) received nutritionally adequate or supranutritional levels of selenium. We found that the relationship between selenium status and prostatic DNA damage

was U-shaped in dogs, the only non-human species that naturally develops prostate cancer during aging. Next, we tested the translational significance of the dog U-curve. This analysis showed that the dog U-curve predicted the results of men in the NPC trial — both the benefit observed in men with lowest baseline selenium, and the undesired effect in men with highest baseline selenium status (Figure 2). Later, the dog U-curve would provide a plausible explanation for the unanticipated increase in prostate cancer incidence among men in SELECT who had the highest baseline selenium status and received selenium supplementation. These findings advanced a new conceptual framework: U-shaped thinking [10].



Lippman *et al* (2009) [2]

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) randomized 35,533 men living in North America to receive vitamin E (400 IU alpha-tocopherol) or selenium (200 µg selenomethionine), both vitamin E and selenium, or placebo. Seven years after its inception, SELECT was halted because there was no convincing evidence that the interventions significantly reduced the number of incident prostate cancers. This report of the absence of benefit following selenium supplementation was disappointing, but not altogether unexpected, considering the relatively high baseline selenium status (average, 135 µg/L plasma Se) of the study participants, representative of men living in the United States.

In the eyes of some, the results of SELECT dashed earlier optimism raised by the NPC results. However, interpreted through the lens of U-shaped thinking, it would not be expected that an evaluation of the selenium-replete population of men in SELECT could either validate or refute the benefits of selenium supplementation documented in men with low baseline selenium status in the NPC trial. Indeed, in a written reply published in *JAMA* in 2009, SELECT investigators clearly stated: “The design of SELECT does not address [this] contention ... regarding a potential benefit of selenium in men with low plasma levels of selenium” [11]. Instead, the investigators stated that the intent of SELECT was to determine whether daily selenium supplementation could decrease prostate cancer risk in men whose baseline selenium distribution was representative of the U.S. population [11].

But for men living outside of the United States, lower selenium status commonly prevails, which would be expected to limit the applicability of the results of SELECT to populations around the globe. Figure 3 shows that the critical hypothesis that men with low selenium status can achieve cancer risk reduction through daily selenium supplementation could be tested by enrolling the average man living in many countries in the world — because their selenium status places them in the low suboptimal range. Clearly, this situation does not hold true for the population of men living

in Canada or the United States, where SELECT was conducted. And looking forward, based upon recent modeling of climate-soil interaction — a major factor influencing the retention of selenium and other trace minerals in soil — it is predicted that more than 60% of croplands worldwide will lose selenium, indicating that the frequent occurrence of insufficient selenium intake in humans is expected to increase [12].

Hurst *et al* (2012) [13]

As disappointment with the null results of SELECT grew, so too was there growing frustration regarding the apparent failure to situate the results of SELECT in a context of dose-response. Hurst and colleagues [13] reported a dose-response meta-analysis examining the relationship between selenium status and prostate cancer risk in case-control and nested case controlled studies. Twelve studies contributing a total of 13,254 participants and more than 5000 cases of prostate cancer were included. The relationship between toenail selenium and prostate cancer was U-shaped. Analysis of toenail selenium data indicated a 71% reduction of prostate cancer (RR, 95% CI = 0.29, 0.14 - 0.61) in the range of 0.85 to 0.94 ppm Se. The analysis showed that average baseline selenium status in SELECT participants prior to supplementation was already in this risk-reduction range, suggesting that increasing plasma selenium concentration to 250 µg/L (achieved in SELECT) would confer no additional prostate cancer protection. In addition to providing a credible explanation for the failure of SELECT, the optimal selenium status for prostate cancer risk reduction based upon toenail selenium levels in this analysis (0.85 - 0.94 ppm) showed close agreement with the proposed optimal selenium range based on the dog U-curve (0.80 - 0.92 ppm) [see reference 14 for further discussion].

Rayman (2012) [15]

Broader acceptance for adopting the idea of long-term selenium supplementation as a strategy for cancer risk reduction would benefit from a deeper understanding of the impact of selenium on a broader range of health outcomes. An expert review published in *Lancet* provided a much needed perspective on the effects of selenium on an array of non-cancer dimensions of human health, such as thyroid function, immune function including antiviral resistance, neuroprotection, fertility and reproduction, cardiovascular disease, and type 2 diabetes mellitus. After this close examination placing selenium nutrition in a context of overall health, the author concluded: “The crucial factor that needs to be emphasized with regard to the health effects of selenium is the inextricable U-shaped link with status; whereas additional selenium intake may benefit people with low status, those with adequate-to-high status might be affected adversely and should not take selenium supplements” [15]. Based on these considerations, the author suggested a beneficial range to optimize health of 130 to 150 µg/L — a level of plasma selenium already attained by the average man in SELECT *prior to selenium supplementation*.

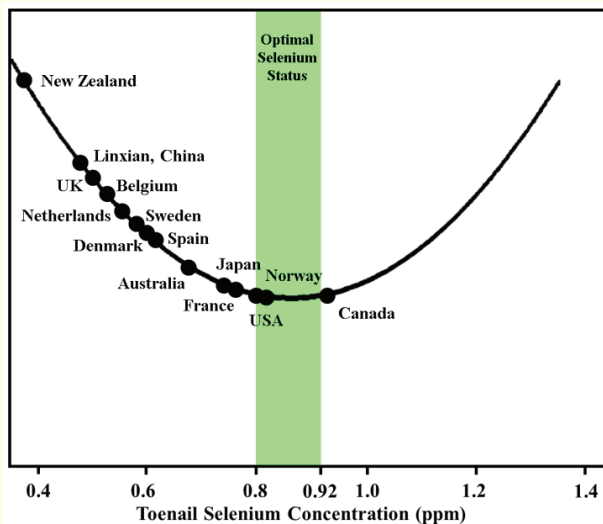


Figure 3: Average selenium status of men living in 13 countries: Implications for cancer prevention trial design. The average man living in many countries (USA and Canada are exceptions), has a selenium status that falls well below the optimal level for prostate cancer risk reduction predicted by the dog U-curve (shown as shaded rectangle), suggesting they might benefit from selenium supplementation. For each country, solid circles represent published data on the selenium status of 40-65 year-old men (for details, see ref 10)(with permission). Toenail selenium concentration of 0.8 - 0.92 ppm corresponds to plasma selenium concentration of 119 - 137 µg/L [9].

Geybels *et al* (2013) [16]

The concept of U-shaped thinking predicts that reports of linear dose-responses between selenium levels and disease outcomes in populations are expected, especially in countries with low selenium status. To this point, an observational cohort study of 58,279 men in the Netherlands showed an inverse linear association between toenail selenium levels and prostate cancer risk. In this study, there was a statistically significant 63% reduction in advanced prostate cancer risk in men within the highest quintile of selenium status compared to men in the lowest quintile. Based upon these results, more selenium would appear at first glance to be better for prostate cancer risk reduction. However, the dog U-curve provides the necessary integration, comfortably placing in context the reported linear dose-response of men living in the Netherlands — all of the men in the study population fit precisely within the downswing of the U-curve (see reference 10 for further explanation). Clearly, to resolve the question of who will benefit from supplementation, selenium status matters.

Kristal *et al* (2014) [17]

This long-awaited report of participants in SELECT revealed that baseline selenium status prior to supplementation did indeed influence the response to additional selenium. We learned that too much selenium could potentially *increase* prostate cancer risk. In men with the highest baseline selenium status (> .9 ppm toenail Se), daily selenium supplementation with 200 µg of selenomethionine was associated with a statistically significant 91% increase in the risk of high-grade prostate cancer. SELECT had limited power to detect the ability of selenium supplementation to benefit men with low selenium status. This is because more than 75% of men in SELECT had baseline selenium levels already in the high, suboptimal upswing of the dog U-curve. Not very many men had low selenium status. But when investigators did their best to use lower cut points (instead of standard quintiles), selenium supplementation was associated with a 21% reduction in prostate cancer in men with the lowest baseline selenium (< .7 ppm toenail Se), which approximated the baseline selenium status of the men in the NPC trial who achieved prostate cancer risk reduction following supplementation. Underpowered for this purpose, the observed trend toward protection did not reach statistical significance. After this detailed look, the lesson of SELECT had remained unchanged: Selenium does not prevent prostate cancer in selenium-replete men.

Vinceti *et al* (2018) [3]

In this Cochrane review, the results of 11 randomized clinical trials (RCTs) were evaluated. The investigators stated there was

insufficient evidence to support a cancer-preventive effect of selenium in humans. Five of these RCTs contributed to the conclusion that there was no beneficial effect of selenium supplementation on prostate cancer risk. Participants from the selenium-replete population of SELECT dominated the prostate cancer analysis, representing 90% of the 19,419 participants that contributed to the report. Baseline selenium status for these five contributing studies are worthy of inspection and are tabulated for the reader here (Table 1). Because of high baseline selenium status, and in one case higher dose of supplementation (400 µg per day) [19], post-supplementation plasma selenium levels ranged from 190 to 261 µg/L [1, 2,17-19], levels far exceeding the optimal range of plasma selenium for prostate cancer risk reduction estimated from dose-response meta-analysis (120 to 150 µg/L) [13]. None of the studies included in the analysis were designed or powered to refute or confirm the validity of the critical NPC-provoked hypothesis: Men with low selenium can achieve prostate cancer risk reduction through selenium supplementation.

Study	Country	Plasma Se Concentration (µg/L)
NPC Trial [6]	U.S.	115 (22)*
SELECT [2,17]	U.S., Canada, Puerto Rico	135 (23)#
SWOG S9917 [18]	U.S.	138 (62)#
NBT [19]	U.S., New Zealand	126 (26)*
ECOG 5597 [20]	U.S.	Not reported

Table 1: Baseline selenium status of men reported in the five randomized clinical trials relevant to prostate cancer included in the most recent Cochrane analysis of selenium and human cancer risk [3].

*: Values are mean (standard deviation); #: Values are median (interquartile range)

The Cochrane report concluded with an acknowledgement that some questions regarding selenium — such as whether supplementation might benefit cancer risk in individuals with low selenium status — have not been fully resolved. The authors of the report stated that the failure of randomized clinical trials using selenium to yield consistent beneficial effects suggests that new large-scale trials on the selenium-cancer connection are unlikely to be undertaken in the future. Should this opinion raise concern that the promising message of the NPC trial has been buried by the selenium-replete men of the massive SELECT?

Ralph Waldo Emerson (1846) [21]

In his poem “Fable”, Ralph Waldo Emerson describes a fictional conversation between a squirrel and a mountain. After being belittled by the mountain for his small stature, the squirrel replies:

“Talents differ; all is well and wisely put;
If I cannot carry forests on my back,
Neither can you crack a nut”.

The words depicting the interaction between these two characters eloquently captures our impressions of the intellectual progress surrounding selenium and prostate cancer and the wholly unsurprising conclusion of the Cochrane review. What can be expected of a conclusion generated by an analysis in which NPC results and SELECT results are combined mathematically? As illustrated in Figure 4, the number of men receiving selenium or placebo in the selenium-replete SELECT study population dwarfed by more than 18-fold the number of participants in the NPC trial.

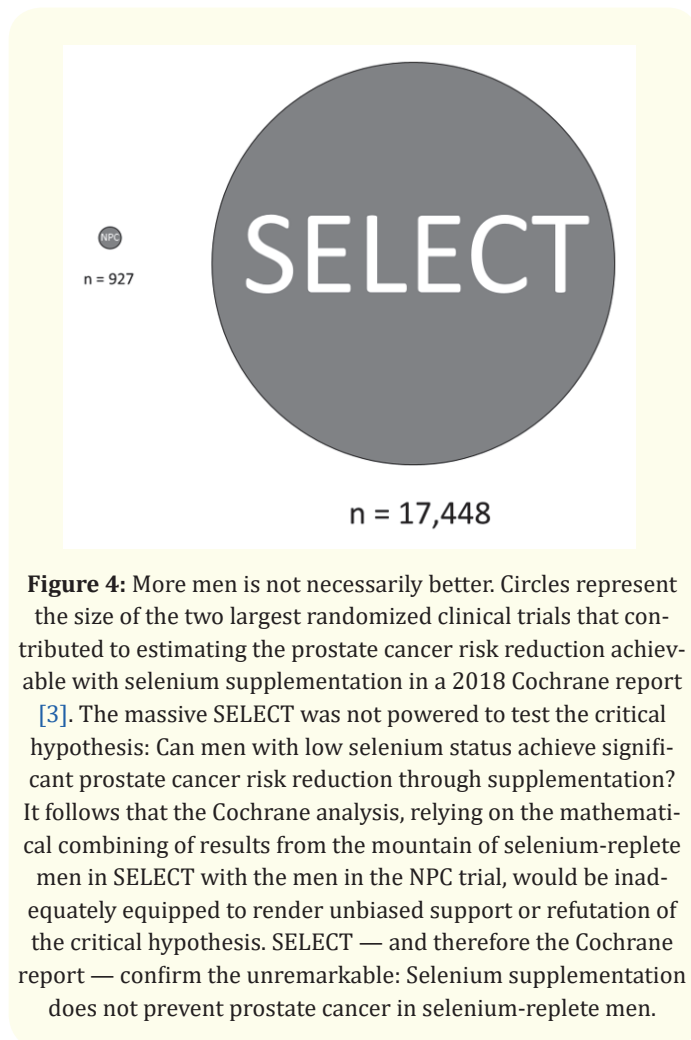


Figure 4: More men is not necessarily better. Circles represent the size of the two largest randomized clinical trials that contributed to estimating the prostate cancer risk reduction achievable with selenium supplementation in a 2018 Cochrane report [3]. The massive SELECT was not powered to test the critical hypothesis: Can men with low selenium status achieve significant prostate cancer risk reduction through supplementation? It follows that the Cochrane analysis, relying on the mathematical combining of results from the mountain of selenium-replete men in SELECT with the men in the NPC trial, would be inadequately equipped to render unbiased support or refutation of the critical hypothesis. SELECT — and therefore the Cochrane report — confirm the unremarkable: Selenium supplementation does not prevent prostate cancer in selenium-replete men.

But the prostate cancer risk reduction achievable with selenium supplementation — the precious nut so conspicuously revealed by the men of the NPC trial — could not be cracked by SELECT. As it was said for the squirrel and the mountain, so it can be written about NPC and SELECT: Talents differ.

Looking back to move forward

Looking back at the ground we have uncovered, we now attempt a meaningful synthesis. A compelling message from a randomized cancer prevention study was delivered to the academic community 23 years ago: Daily supplementation with 200 µg of high selenium yeast significantly reduces prostate cancer incidence. Eventually, the beneficial effect of selenium supplementation on prostate cancer protection in these men was shown not to be universal, but rather limited to those with the lowest selenium status prior to supplementation. Men with higher selenium status did not benefit. Subsequent studies strengthened the idea that more selenium is not necessarily better. A U-shaped dose-response between selenium status and prostatic DNA damage in dogs provided a new framework to interpret the apparently disparate findings from human populations. Later, dose-response meta-analysis of human studies brought this idea into clearer view. The massive SELECT study was neither designed nor powered to validate or refute the stance that prostate cancer risk reduction is achievable with selenium supplementation in men disadvantaged by low selenium status. Instead, the negative findings of SELECT undermined momentum for further inquiry, allowing a stiffening of opinion against the prospect that cancer risk reduction can be achieved through selenium supplementation.

For research results to have an impact on public health decisions requires appropriate confirmation through additional studies, a confirmation called for in 1996 [1] but never answered, an affirmation that neither SELECT nor any other randomized interventional study conducted to date aimed to provide. For those who embrace U-shaped thinking as an integrative framework to understand the selenium-prostate cancer connection, no quantity of null results after selenium supplementation of selenium-replete populations will diminish their enthusiasm. As we grow to see the lack of benefit in SELECT as more expected than unexpected, no stop sign to further inquiry stands before us. The idea that men with low selenium status can benefit from daily selenium supplementation — the notion delivered to us more than two decades ago — can and should be safely and rigorously evaluated. We must continue to ask: Who will benefit? This is the core question, the drumbeat of today’s personalized medicine and precision nutrition. Rededicating ourselves to refining the answer to this question as it relates to selenium and prostate cancer should remain central to our practice as we move forward.

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