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Perspective

Body Measurements Differentiation of Damuscus (Shami) Cyprus Goats in Sudan

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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 selenium 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).

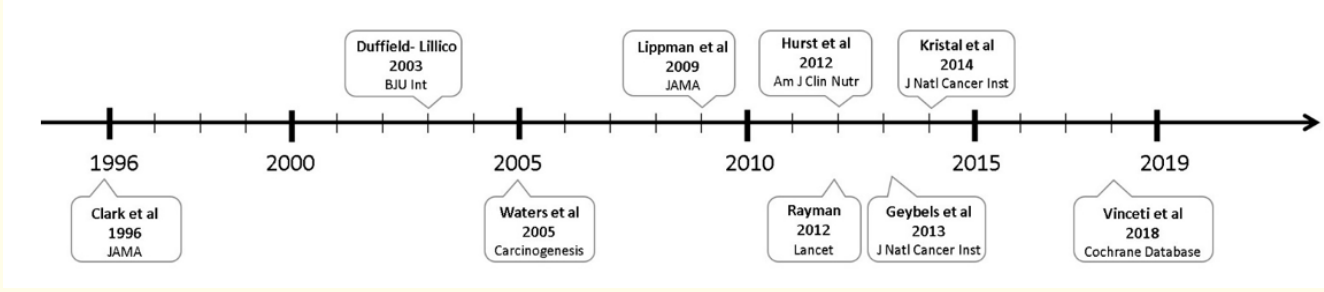

Figure 1: Looking back to move forward: An evolutionary timeline of scholarly contributions that have shaped the intellectual debate on prostate cancer risk reduction achievable through selenium supplementation.

Clark., *et al.* [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* [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.* [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].

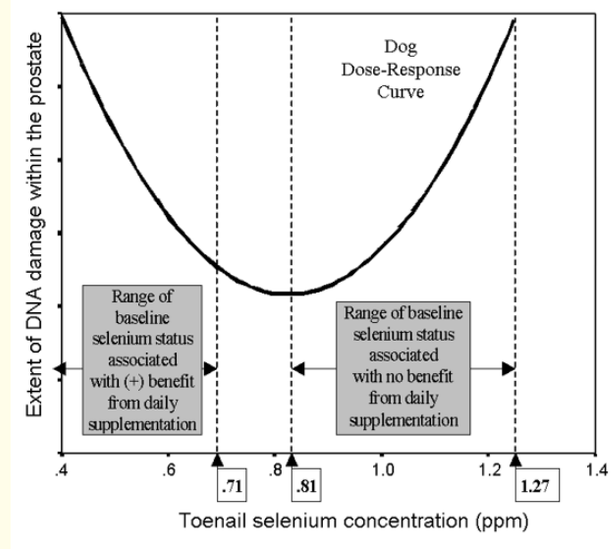

Figure 2: Dog U-curve helps to explain the impact of baseline selenium status on human prostate cancer risk reduction achieved by selenium supplementation in the Nutritional Prevention of Cancer (NPC) trial. Men in the lowest tertile of selenium status prior to supplementation (left grey box) benefited from selenium supplementation, whereas men in the highest tertile before supplementation (right grey box) did not benefit from selenium supplementation [9] (with permission). More selenium is not necessarily better.

Lippman., *et al.* [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].

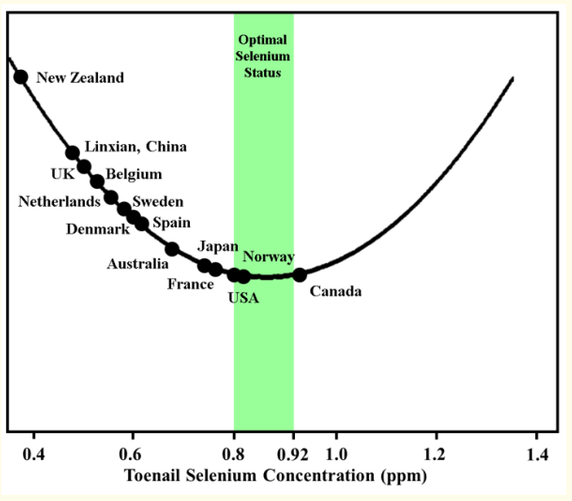

Figure 3: Average selenium status of men living in 13 countries: Implications for cancer prevention trial design. The average man living in many countries (USA and Canada are exceptions), has a selenium status that falls well below the optimal level for prostate cancer risk reduction predicted by the 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].

Hurst., *et al*. [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 [15]

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