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Beyond the Abstract

Your Selenium Intake, Your Prostate, and "U"

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BERKELEY, CA (UroToday.com) - Personalizing nutrition for disease prevention — minimizing the risk for diseases such as prostate cancer by optimizing nutrient intake — remains one of the major challenges that scientists and health professionals face today. Emerging data on the relationship between selenium intake and human health point to a U-shaped dose-response, suggesting that more selenium is not necessarily better. Now a recent study[1], conducted by Chiang and co-workers at the Gerald P. Murphy Cancer Foundation and featured by UroToday, sheds new light on the anti-cancer action of selenium in the aging prostate that aligns with this new U-shaped thinking.

In the study published in *Biofactors*[1], investigators used carefully controlled laboratory experiments to show that selenium can trigger the preferential elimination of DNA-damaged prostatic cells. The work introduces a potentially important perspective on the anti-cancer action of selenium that is independent of its antioxidant protection. By documenting the ability of selenium to sweep away damaged cells — a process termed "homeostatic housecleaning" — the new study builds upon a growing body of evidence that the apparent anti-cancer benefit of selenium supplementation in humans and animals cannot be explained solely by antioxidant protection, because it occurs at selenium levels at which selenium-dependent antioxidant enzymes are already maximized.

The evolving idea that selenium might act by sweeping away damaged prostatic cells rather than by protecting cells from damage was set in motion by the results of a randomized feeding trial in dogs — the only non-human species to frequently develop prostate cancer during aging.

In that study[2], dietary selenium supplementation lowered DNA damage but increased apoptosis (cell suicide), leading to the hypothesis that organic selenium might exert its cancer-preventive effect by selectively increasing apoptosis in the most highly DNA-damaged cells. Following this line of reasoning, to achieve a significant lowering of DNA damage level in surviving prostatic cells, selenium would have to *preferentially* eliminate the most damaged cells, because a non-selective triggering of apoptosis would not explain the overall DNA damage reduction. Dogs in the feeding trial with the lowest prostatic DNA damage had selenium status which paralleled the selenium status of men who had reduced prostate cancer risk in 2 large studies — the Nutritional Prevention of Cancer (NPC) Trial and the Health Professionals Follow-Up Study[3]. This parallelism increased confidence that the *in vivo* observations made in dogs could be highly relevant to human prostate cancer protection. The investigators then moved into the cell culture laboratory, developing an *in vitro* model system in which DNA damage level could be carefully controlled in both canine and human cells. Their results point to a new way in which selenium might render an aging prostate more resistant to cancer.

But when it comes to identifying the optimal selenium dose for prostate cancer risk reduction, it is not likely that more selenium will always be better. A recent meta-analysis of the dose-response between selenium and prostate cancer risk in men showed a U-shaped relationship between toenail selenium level and risk for prostate cancer[4]. Landing in the trough of the U — achieving mid-range selenium status – is more desirable than being too low or too high. This stance is bolstered by the extensive review of the scientific literature by Rayman[5], who 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." Moreover, the results of a large prospective cohort in the Netherlands published earlier this year[7] show men with toenail selenium levels in this mid-range had a 63% reduction in risk of advanced prostate cancer compared to men with low selenium – lending further support for the U-shaped thinking about selenium. And when careful dose-specific analysis of data from dogs was performed, mid-range selenium status (0.67-0.92 ppm in toenails) was associated with an 84% decreased likelihood of high prostatic DNA damage and the highest cell suicide rate among cells in the aging

prostate[6]. Taken together, the possibility that the trough of the U-shaped selenium curve is precisely where the homeostatic housecleaning effect of selenium demonstrated in the cell culture experiments is maximized offers a new, working explanation for why more selenium is not always better.

One benefit of the new U-shaped thinking about selenium and cancer risk reduction is that it provides a context of clarity for interpreting the disappointing results of SELECT. Great hope for developing selenium as a practical approach for achieving prostate cancer risk reduction was invested in SELECT, the largest-ever prostate cancer prevention trial[8]. But null findings in SELECT[9] dashed earlier optimism raised by Larry Clark's landmark NPC trial and three decades of animal studies. When one considers the relatively high selenium status of men in SELECT prior to the start of the study, U-shaped thinking renders the null results of SELECT *more expected than unexpected*[6]. Prior to supplementation, the average subject in SELECT already had mid-range selenium status (estimated 0.91 ppm in toenails). These baseline levels were too high to expect that further selenium intake would lower prostate cancer risk. This U-shaped thinking raises speculation as to whether careful analysis of those men in SELECT with the lowest baseline selenium concentration might actually reveal that this subset of men achieved prostate cancer risk reduction from daily selenium supplementation[10]. As stated by Geybels and colleagues in their recent paper in the *Journal of the National Cancer Institute*: "It would, therefore, be of great interest to see SELECT results stratified by baseline selenium level."[7]

Inevitably, prostate cancer is the product of dysregulated homeostasis within the aging prostate. The new research highlighted here lends further support to the notion that selenium may play an important role in promoting prostatic homeostasis, thereby favoring cancer risk reduction. By guiding more informed speculations and provoking new research questions, new findings such as these will continue to shape the ongoing intellectual debate, deepening our understanding of selenium and prostate cancer. As the research continues, men are looking for ways to optimize their selenium intake for disease prevention. Measuring their selenium status and then titrating selenium levels to mid-range status would seem to offer men a practical and informed approach, rather than blindly taking selenium supplements and risking the downside of unnecessary oversupplementation

References:

1. Chiang, E. C., Bostwick, D. G., Waters, D. J. (2013) Homeostatic housecleaning effect of selenium: Evidence that noncytotoxic oxidant-induced damage sensitizes prostate cancer cells to organic selenium-triggered apoptosis. *Biofactors* 39:575-588.

2. Waters, D. J., Shen, S., Cooley, D. M., et al. (2003) Effects of dietary selenium supplementation on DNA damage and apoptosis in canine prostate. *J Natl Cancer Inst* 95:237-241.

3. Waters, D. J., Shen, S., Glickman, L. T., et al. (2005) Prostate cancer risk and DNA damage: Translational significance of selenium supplementation in a canine model. *Carcinogenesis* 26:1256-1262.

4. Hurst, R., Hooper, L., Norat, T., et al. (2012) Selenium and prostate cancer: Systematic review and meta-analysis. *Am J Clin Nutr* 96:111-122.

5. Rayman, M. P. (2012) Selenium and human health. *Lancet* 379:1256-1268.

6. Chiang, E. C., Shen, S., Kengeri, S. S., et al. (2010) Defining the optimal selenium dose for prostate cancer risk reduction: Insights from the U-shaped relationship between selenium status, DNA damage, and apoptosis. *Dose-Response* 8:285-300.

7. Geybels, M. S., Verhage, B. A., van Schooten, F. J., et al. (2013) Advanced prostate cancer risk in relation to toenail selenium levels. *J Natl Cancer Inst* 105:1394-1401.

8. Klein, E. A. (2004) Selenium: Epidemiology and basic science. J Urol 171:S50-S53.

9. Lippman, S. M., Klein, E. A., Thompson, I. M. Jr., et al. (2009) Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial. *JAMA* 301:99-51.

10. Waters, D. J., Shen, S., Kengeri, S. S., et al. (2012) Prostatic response to supranutritional selenium supplementation: Comparison of the target tissue potency of selenomethionine vs. selenium-yeast on markers of prostatic homeostasis. *Nutrients* 4:1650-1663.

Written by:

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