Selenium and prostate cancer: the puzzle isn’t finished yet

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Selenium is an essential trace element and antioxidant whose potential anticarcinogenic effects have excited the field of cancer research. In secondary analyses of the Nutritional Prevention of Cancer trial (NPC), 200 μg selenium/d was associated with a 52% reduction in the risk of prostate cancer (1). These strong secondary results from the NPC contributed to the rationale for conducting the largest-ever randomized placebo-controlled trial for the primary prevention of prostate cancer, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) (2). The SELECT was conducted in 35,533 men recruited between 2001 and 2004 throughout the United States, Canada, and Puerto Rico. The intervention was stopped after a median follow-up of 5.5 y, 1.5 y early, because of convincing evidence that there was no association between selenium (200 μg l-selenomethionine/d) or vitamin E (400 IU all rac-tocopheryl acetate/d), alone or combined, and risk of screening-detected prostate cancer (3).

In this issue, Hurst et al (4) present a dose-response meta-analysis examining the shape of the relation between selenium status and risk of prostate cancer. They report that plasma selenium concentrations between 135 and 170 ng/mL are associated with statistically significant 15–25% reductions in risk of prostate cancer compared with 60 ng/mL, and the results were even stronger for advanced disease (40–50% decreased risk). In addition, the results for toenail selenium were consistent with the plasma data and suggested a 71% decreased risk of prostate cancer (RR: 0.29; 95% CI: 0.14, 0.61) among men with toenail selenium concentrations of 0.85–0.94 μg/g, which is approximately equivalent to plasma concentrations of 120–150 ng/mL. Hurst et al’s meta-analysis has many strengths, including the focus on plasma and toenail selenium, both of which are validated biomarkers of long-term selenium intake (5); an outcome of advanced prostate cancer; the robustness of the results; and limited study heterogeneity, particularly among studies with prospective exposure data.

Why do the conclusions of the dose-response meta-analysis and SELECT differ? Perhaps they don’t—they just provide different pieces in the puzzle of selenium and prostate cancer. Prostate cancer is a heterogeneous disease with both lethal and indolent forms. In the Hurst et al meta-analysis, stronger associations were observed for risk of advanced prostate cancer. This is consistent with the secondary results of the NPC, which examined risk of non-screening-detected prostate cancer, an outcome enriched with lethal forms of the disease. The SELECT examined risk of screening-detected prostate cancer, which does not distinguish between indolent and aggressive disease. In addition, the secondary results from the NPC showed that the protective effect of selenium in relation to prostate cancer was only among men with low plasma selenium at baseline (<123 ng/mL) (6). The median plasma selenium concentration at baseline in the SELECT was ~135 ng/mL, which was already in the risk-reduction range identified by Hurst et al and above the baseline concentrations at which supplementation conferred a benefit in the NPC.

A key limitation of the Hurst et al meta-analysis is the lack of data examining the risk of prostate cancer above plasma selenium concentrations of 170 ng/mL. It is possible that the shape of the curve plateaus whereby greater values provide no additional benefit; alternatively, it may be a U-shaped relation in which higher selenium concentrations confer an increased risk of prostate cancer compared with an optimal moderate concentration. In either scenario, increasing plasma selenium concentrations to 250 ng/mL, as was done in the SELECT, would confer no additional advantage relative to 135 ng/mL. A U-shaped relation between selenium and prostate cancer is supported by evidence from a randomized placebo-controlled trial conducted in dogs, the only other animal that naturally develops prostate cancer. Dogs supplemented with a moderate amount of selenium had the lowest levels of DNA damage and the highest levels of apoptosis in their prostate; there was no difference in DNA damage or apoptosis in dogs supplemented with high compared with low selenium (7). The moderate selenium amounts equated to toenail concentrations of 0.67–0.92 ppm, which is consistent with the results reported by Hurst et al.

Additional evidence to support a relation between selenium and prostate cancer comes from studies examining the interaction between genetic variants related to selenium metabolism, plasma selenium, and risk of aggressive prostate cancer (8–11). Superoxide dismutase 2 (SOD2) is a mitochondrial enzyme that converts reactive oxygen species to oxygen and hydrogen peroxide. Among men with the AA genotype in rs4880 (a single nucleotide polymorphism in SOD2) in the Physicians Health Study, high plasma selenium concentrations were associated with a 92% decreased risk of advanced prostate cancer (3).

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2 Supported by NIH training grant R25 CA112355, the Prostate Cancer Foundation, and the Steven and Christine Burd-Safeway Endowed Chair in Urology, University of California, San Francisco.

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First published online May 23, 2012; doi: 10.3945/ajcn.112.042119.
risk of aggressive prostate cancer compared with low concentrations (OR: 0.18; 95% CI: 0.07, 0.48); the inverse association was weaker among men with the VA/VV genotype ($P_{\text{interaction}} = 0.01$) (8). Similarly, in a clinical cohort of men with nonmetastatic prostate cancer, higher plasma selenium was associated with a non-significant 40% reduction in risk of aggressive prostate cancer among men with the AA genotype (RR: 0.60; 95% CI: 0.32, 1.12); among men with the VA/VV genotype, higher plasma selenium was associated with an 82% increased risk of aggressive prostate cancer (RR: 1.82; 95% CI: 1.27, 2.61) (10). Given these results and the findings from Hurst et al, selenium is likely most relevant to the etiology of advanced or aggressive prostate cancer, and the relation may depend on genetic variants.

Clearly, the role of selenium in the etiology of prostate cancer is complex. Hurst et al’s dose-response meta-analysis clarifies the shape of the relation between low to moderate concentrations of selenium and risk of prostate cancer. Future studies need to finish the puzzle by examining the shape of the relation between plasma selenium concentrations >170 ng/mL, focus on risk of clinically relevant aggressive prostate cancer, examine postdiagnostic intake in relation to disease progression, consider interactions with genetic variants, and thoroughly address potential confounding and effect modification by factors that affect oxidative stress (eg, smoking, obesity, physical activity, other dietary antioxidants). In the meantime, selenium supplements should not be recommended for prostate cancer prevention; first, we must complete the puzzle to ensure that any public health and clinical recommendations are safe and effective.

ELR had no conflicts of interest. JMC is a shared owner of a patent related to using nutrients and genetics to predict risk of prostate cancer aggressiveness (not commercialized).

REFERENCES