Science Peels the Onion of Selenium Effects on Prostate Carcinogenesis

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The role of the essential trace element selenium in prostate cancer was first (and last) editorialized in the Journal in 1998 in conjunction with the report of the first large prospective observational study of selenium and the risk of advanced prostate cancer (1,2). Although the principals for the 1998 study were the same as those for the observational study by Li et al. (3) in this issue of the Journal, much has changed in the basic scientific understanding of selenium. The onion, an allium vegetable that concentrates selenium, is an apt metaphor for the scientific work of peeling back the layers of molecular effects and mechanisms underlying the strong selenium epidemiology in the prostate.

The past 6 years have seen the publication of seven prospective epidemiologic studies of selenium status and prostate cancer (including the study in this issue of the Journal) (2–8), with a collective total of nearly 2000 case subjects. The studies involved low [Europe (8)] moderate [Maryland (5)], and high [Hawaii (4)] selenium status populations, and all but one found a protective effect associated with higher concentrations of selenium. Furthermore, low plasma selenium levels are associated with increases in other cancers and human diseases (9). Although the findings of the observational studies have been encouraging and consistent regarding the prostate, the most powerful evidence to date for the beneficial effect of selenium is the 49% reduction in prostate cancer incidence in the randomized, placebo-controlled Nutritional Prevention of Cancer (NPC) trial, in which selenium was administered at 200 μg/day (10,11). On the basis of the NPC trial, epidemiologic studies, a randomized prevention trial in China of selenium in combination with other minerals and vitamins (12), and early preclinical data (13–17) available in 2000, selenium was included in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) in 32 400 men to definitively test the role of supplementation with selenium and/or vitamin E in the prevention of prostate cancer (18).

Before addressing the basic science behind the results of these selenium studies, we will highlight two important aspects of the study by Li et al. (3): selenium effects by stage of disease and selenium effects by baseline prostate-specific antigen (PSA) levels. The finding that selenium was associated with a reduced risk of advanced prostate cancer (stage C or D) is consistent with the findings of three of four other epidemiologic studies (2–4) that assessed this variable and supports the hypothesis of Li et al.—that selenium affects tumor progression rather than premalignancy. This finding also is consistent with the observation that selenium was associated with a greater reduction in risk for men with PSA levels of greater than 4 ng/mL than for men with PSA levels of 4 ng/mL or less. These stage and PSA associations seemingly are at odds, however, with the NPC findings that the protection conferred by selenium was largely due to reduced local disease and was limited almost exclusively to men with PSA levels of 4 ng/mL or less (11). The discrepancy between the results of Li et al. (3) and those of the NPC may be due, in part, to differences in study designs (i.e., observation versus intervention) and to enormous differences in the doses and durations of exposure that were assessed.

Although associated with lower PSA levels, the risk reduction in the NPC study does not necessarily conflict with the hypothesis of Li et al. (3) that selenium slows tumor progression (3). First, the curves of prostate cancer incidence for the placebo and selenium arms separated early in the NPC study, which would not be expected for effects on the decades-long process of premalignant tissue transforming into malignant tissue. Second, prostate cancer is far more prevalent in men with lower PSA levels than is generally thought. Thompson et al. (19) recently reported that the prevalence of prostate cancer (detected by biopsy after 7 years of close follow-up) was surprisingly high at 15% among 3820 men with PSA levels of 4.0 ng/mL or less on the placebo arm of the Prostate Cancer Prevention Trial (PCPT). This rate begins to approach that reported heretofore for men with PSA levels of 4–10 ng/mL (20), suggesting that future exploratory analyses probably should set the PSA cut point substantially below 4 ng/mL. Therefore, the NPC result may have been based on slowing or halting the progression of microscopic, subclinical prostate cancer. Moreover, transformation was likely prevented or delayed, as suggested by the durability of the separation of the prostate cancer curves. This important issue of preventing or delaying transformation to cancer versus treating subclinical, microscopic cancer has been debated since publication of the primary reports of other large-scale trials, including the PCPT (19,21,22). In either case, the effect of selenium would be beneficial.

Molecular and cellular bases for the published observations of selenium preventive activity in the prostate are emerging and providing biologic plausibility for clinical prostate cancer prevention trials of selenium, such as the SELECT. The primary nutritional role of selenium in regulating the redox state and energy metabolism involves its incorporation as selenocysteine, the 21st amino acid, into selenoproteins. Selenium potentially affects cancer development through its known effects on oxidative stress, DNA repair, inflammation, apoptosis, proliferation, carcinogen metabolism, testosterone production, angiogenesis, fat metabolism, and immune function (9,23–25). The potential for these effects in the prostate is supported by data showing that...
selenium accumulates, reduces DNA damage, and increases apoptosis in the prostates of older dogs and accumulates in human prostates (26,27). Natural organic (e.g., selenomethionine) and inorganic (e.g., selenite) forms of selenium are metabolized via different pathways into selenide, which can then be either phosphorylated and ultimately incorporated as selenocysteine into active selenoproteins or methylated into active metabolites, such as methylselenol (28,29). Therefore, selenium effects can be indirect (via incorporation into selenoproteins) and/or direct (via selenium metabolites). Direct selenium effects, including differential effects on normal versus malignant prostate cells, vary with different metabolites and have been observed in vitro at pharmacologically achievable concentrations of selenium. The most active known metabolites in preclinical studies are natural methylated compounds (e.g., methylselenol) and synthetic organoselenium compounds (e.g., 1,4 phenylenebis(methylene)selenocyanate) (28,29). Scientists are just beginning to examine the molecular basis of direct selenium effects in prostate cancer in studies that involve molecular targets such as manganese superoxide dismutase, p21, caspase-8, NF-κB, protein kinase C, and the androgen receptor (17,25,30–34).

Indirect selenium effects via the enzymatic functions of certain selenoproteins have been analyzed more extensively. The generation of selenocysteine from selenide and its cotranslational incorporation into selenoproteins is a complex process involving selenophosphate synthetase, selenocysteine synthase, selenocysteinyl-tRNA^Sec synthase, and the recognition of selenocysteine by selenocysteine insertion sequence element consensus structures within the 3′-untranslated region of selenoprotein mRNA (35). Besides their well-known effects (e.g., of glutathione peroxidase [GPX]) on intracellular redox, selenoproteins have many other activities, which can vary by cell type, physiologic status, or the presence or absence of incorporated selenocysteine. For example, the selenoprotein thioredoxin reduces without (but not with) selenocysteine appears to induce apoptosis and inhibit growth in certain cell types (36,37). There are questions about the precise role of selenoproteins in selenium cancer prevention studies because GPX, which is the most thoroughly studied of these proteins, is saturated at much lower selenium levels than are required for preventive activity (26). The saturation and activity profiles of newly identified selenoproteins or of recently described single nucleotide polymorphisms (SNPs) of known selenoproteins, however, are not known (23). Bioinformatics and comparative phylogenetics analyses (using selenocysteine insertion sequence element consensus structures) recently described 25 different human proteins containing selenocysteine (38), of which two, Sep15 and Selenoprotein P, are implicated in prostate cancer development and prevention (39,40). We have only just begun to study the functions and genetic variations of these different selenoproteins and how these variations affect disease.

Genetic variations (e.g., SNPs) of only four selenoproteins (Sep15, Selenoprotein P, GPX1, and GPX4) have been identified thus far (40–43), and hundreds more variants will likely be found. Different selenoprotein SNPs may respond differently to selenium supplementation, suggesting their potential association with pharmacogenetic differences in selenium’s preventive effects (44). Epidemiologic studies, including two studies of the variant allele for the cellular antioxidant GPX1 [which was associated with increased risk for both lung (45) and breast (46) cancers] and a study of a GCG repeat polymorphism in GPX1 [which was not associated with prostate cancer (47)], have linked genetic variation to disease. The mounting epidemiologic data on high rates of disease in association with low selenium status provide powerful global evidence supporting the recent laboratory data on the functionality of selenoproteins. Selenoprotein transgenic and conditional knockout models currently in development in mice will help clarify the role of selenium and selenoproteins in cancer risk and prevention (48).

Studies of molecular and cellular effects of selenium in prostate carcinogenesis will contribute to important future hypotheses, such as those for correlative studies planned in the ongoing SELECT (49). The SELECT prospectively established a biorepository for research specimens, including serum and white blood cells, from its planned 32,400 participants. The SELECT is also collecting ancillary data, such as information on diet, supplements, and other medicines, and clinical data on several important prespecified secondary endpoints, such as the incidences of lung and colorectal cancer and heart and Alzheimer disease. The SELECT data and biospecimens and the insights from ongoing mechanistic selenium studies should advance our understanding of selenium in prostate carcinogenesis and many other diseases. The rapidly evolving field of selenium and selenoprotein biology promises to identify novel molecular targets for preventing or delaying various cancers and cardiovascular, neurodegenerative, and other diseases, in which selenium appears to play an important role (9,23,50).

The new epidemiologic data on selenium from Li et al. (3) continue to support the initial impressions of this agent’s tremendous potential as a prostate cancer preventive agent. The emerging laboratory data greatly strengthen the biologic plausibility for this optimism and for the ongoing randomized clinical selenium trials, which ultimately will be necessary to define the potentially complex risk–benefit profile of this promising preventive agent (22,51). Meanwhile, science will continue peeling back layer after layer of the enormously deep and complex onion of selenium effects in the prostate.

REFERENCES


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