

UCLA
Nutrition Bytes

Title

Selenium and Prostate Cancer

Permalink

<https://escholarship.org/uc/item/7zp8q7fc>

Journal

Nutrition Bytes, 9(2)

ISSN

1548-4327

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Publication Date

2003

Peer reviewed

Why the Recent Focus on Nutrition and Prostate Cancer?

Prostate cancer is the second most common cancer afflicting American men. Figures estimate that in 2003 approximately 220,900 new cases will be diagnosed in the United States, and one in six men will be diagnosed in their life. Prostate cancer is the second leading cause of cancer death in men in the United States, exceeded only by lung cancer. About 28,900 men in the United States will die of prostate cancer in 2003 (1).

While the prevalence of prostate cancer is clear, the treatment is not. The options include surgical removal of the prostate and radiation therapy, but impotence and urinary incontinence are potential consequences from these procedures. For most men, these complications are difficult to swallow.

Like many health disorders, the interplay between genetics and lifestyle are probably linked in prostate cancer. However the etiology of the disease is unknown; we cannot explain epidemiological finding such as why African Americans have the highest incidence of prostate cancer in the world (4). The intervention involved in prostate cancer is not attractive, but there is potential for preventive measures. Since prostate cancer is an age dependent malignancy with high incidence and long latency period, it is an ideal disease to target for chemoprevention (3). The mortality and morbidity of prostate cancer have inspired studies to investigate possible dietary modifications that would be more cost efficient and less invasive for the patient than current treatment (5).

Selenium for Dummies

Selenium is an essential trace mineral that is a cofactor for an antioxidant enzyme, glutathione peroxidase. Normal oxygen metabolism produces damaging free radicals, and selenium helps control disease by limiting free radicals in the body.

Plants are the main source of dietary selenium throughout the world. The levels of selenium in the soil determine the amount of selenium found in foods. Nebraska and the Dakotas have high levels of selenium in the soil whereas parts of China and Russia have very low levels. Selenium deficiency is most often seen in places like China and Russia, where it is difficult to obtain dietary levels of the mineral. Below is a table of selenium content for various foods taken from an NIH article (6):

Food Source	Micrograms	% Daily Value
1 oz of dried Brazil nuts	840	1200
3.5 oz of canned Tuna	78	111
3 oz of Beef	48	69
3 oz of cooked Cod	40	57
1 cup of Noodles	35	50
1 cup of Mac n' Cheese	32	46
3.5 oz of roasted Turkey Breast	31	44
2 slices of whole wheat Bread	20	29
1 cup of cooked Oatmeal	16	23
1 large raw Egg	15	21

The daily recommended intake of selenium is 70 micrograms.

The Landmark Study that Sparked the Debate

In 1996, Clark published his study on the effects of selenium for cancer prevention in patients with skin carcinoma. He randomized 1312 patients with a history of basal cell or squamous cell carcinomas from 1983-1991 and gave them an oral administration of 200 micrograms per day of selenium or placebo (7). He concluded that the selenium treatment did not significantly affect the incidence of basal cell or squamous cell skin cancer. However, a surprising result was that there was a significant reduction in total cancer mortality (29 deaths in the selenium group, 7 deaths in controls) total cancer incidence (77 cancers for selenium, 119 in controls) and incidences of lung, colorectal, and prostate cancers.

In Vivo Models in Support of Selenium

In 2003, a report by Waters et al. investigated the effects of selenium on DNA damage and apoptosis in canine prostates. The in vivo canine model was used because humans and dogs are the only 2 species in which prostate cancer occurs spontaneously and frequently (8). After 7 months of treatment, the percentage of prostate epithelial cells with extensive DNA damage was significantly lower in the selenium dogs. The 38 dogs treated with selenium had about double the apoptotic cells compared to control. The canine model supports Clark's original findings, but human models were still necessary to see if varying levels of physiological selenium might have any adverse effects.

A report in 2000 by Yoshizawa, Willet, and Morris found that baseline selenium levels varied substantially among men. When matched case-control data were analyzed, higher selenium levels were associated with a reduced risk of advanced prostate cancer. Their data accounted for family history of prostate cancer, body mass index, calcium intake, lycopene intake, saturated fat intake, vasectomy, and geographical region between the case matches (19).

The Mechanisms of Selenium

The findings of the above studies support the effect of selenium on prostate cancer growth, but the definitive molecular targets and the signaling mechanism for selenium remain elusive.

In 2003, Dong, et al. published a study examining the growth arrest of prostate cells following selenium treatment in vitro. Following exposure of prostate cancer cells to 5 μ M of monomethylated selenium metabolite (MSA-a biological metabolite of selenium), cell number was reduced by 25%, and the MSA treated cells showed a decrease in the number of cells synthesizing DNA. MSA was also shown to increase apoptosis; many negative cell cycle regulators were induced by MSA such as CDK inhibitors and RB binding protein, whereas numerous cyclins and CDKs necessary for DNA replication and mitosis were inhibited by MSA. In addition 2 groups of apoptotic genes, Toll-like receptor 2 and caspase 9 were upregulated by MSA (10). The results from Dong, et al. are interesting because the chemopreventive properties of foods usually focus on their antioxidant capacity. This study demonstrates that rather than its role as a cofactor for glutathione peroxidase, selenium affects gene transcription and the cell cycle.

A study in 2002 by He, et al. reported that selenium-mediated apoptosis is involved in the membrane death receptor DR-5. They found that selenium upregulated the DR5 expression and caspase 8 activation (11). The caspase family are aspartate specific cyteiny proteases. These results reiterate the hypothesis that the mechanism of selenium chemoprevention involves the genes that regulate cellular apoptosis.

Venkateswaran, Koltz, and Fleshner found in 2002 that selenium upregulated levels of CDK inhibitors like Cip1/p21, which inhibit the cell cycle, but there were differences based on whether the prostate cancer cells were hormone sensitive. Prostate cancer cells may be hormone sensitive (LNCaP cells) or insensitive (PC3 cells), and they propose that the selenium induced inhibition may involve an androgen receptor (13). One problem with their in vitro model is that the dose they used was about 5-8 times the normal selenium levels found in our body. The in vitro model is difficult to generalize to in vivo situations of prostate cancer growth because our bodies should not have this much plasma selenium. In vivo models must examine the risks of elevated plasma selenium levels.

A study in 2000 by Menter, Sabichi, and Lippman tested selenium on various types of prostate cancer cells. They found that selenium had different effects in prostate cancer versus normal cells; the growth inhibition and apoptosis in cancer cells are dose dependent, and selenium has greater activity in androgen sensitive cells. They investigated the cell cycle arrest at the G2-M transition and found that selenium may induce G2-M arrest in prostatic carcinoma by the cdc2 gene (14).

These in vitro studies are important because they highlight the fact that selenium induced apoptosis is different between cancerous and normal cells. A complication with traditional chemotherapy is that it kills healthy and cancerous cells alike. If the mechanisms on selenium are correct, this would be significant because selenium does not cause normal cell toxicity. Its targets are cancer specific. In addition, the wide variety of gene targets that selenium appear to upregulate and downregulate make it a powerful chemopreventive food because the numerous pathways amplify its benefits.

All that Glitters...

Smith and Mills in 2001 note that excessive selenium consumption may result in such adverse effects as nausea, diarrhea, irritability, fatigue, peripheral neuropathy, hair loss, and nail changes (15). One of the goals in the search for a chemopreventive agent for prostate cancer is that we are trying to minimize the complications that may arise from surgery or radiation therapy. If selenium has equally bad effects, then it becomes less attractive as an alternative to standard therapy.

Labriola and Livingston investigated the interaction between antioxidants and chemotherapy in 1999. Their study reported that many chemotherapeutic agents such as alkylating agents create reactive oxygen species to kill cancerous cells. Dietary antioxidants can quench free radicals generated by the chemotherapeutic agents, therefore, this interaction may inhibit the effectiveness of radiation therapy for prostate cancer patients (16).

Lamson and Brignall state that the concern over antioxidants is valid when the mechanism of chemotherapeutic agents are taken into account, but their research in 1999 also notes that new theories of the effects of chemotherapeutic agents suggest that these agents induce apoptosis, which may actually be assisted by antioxidants (17).

These studies are vital because many patients with prostate cancer might use selenium in addition to standard therapy. The interactions between alternative therapies like selenium and traditional intervention like chemotherapy need to be examined further to identify whether their mechanism do conflict.

Selenium and Clark Revisited: who really benefits from supplementation?

There are several aspects of Clark's study that need to be put into perspective before we can champion selenium as a wonder supplement. The individuals selected for the study were from selenium deficient areas. Patients in the lowest (<106.4 ng/mL) and middle (106.4-121.2 ng/mL) group of baseline plasma levels experienced a significant protective effect from selenium while the upper group (>121.2 ng/mL) did not. It appears that selenium might only be beneficial to patients who are initially deficient to begin with.

Although the blindness of the study was halted, the researchers continued to monitor the patients taking selenium. Dalkin, Lillico, Reid et al. noted in 2001 that the men in the higher baseline group of plasma selenium experienced an increase in prostate cancer risk with selenium supplementation (18).

In 2000, Nomura, Lee, Stemmermann et al. published a study analyzing the protective effects of selenium against prostate cancer. They examined 9345 Japanese-American men between 1971 and 1977 by freezing a sample of their blood. After surveillance for 20 years, 249 tissue-confirmed incident cases of prostate cancer were identified. They found an inverse relationship between plasma selenium levels and the risk of prostate cancer. However, the association was mainly present in current or past cigarette smokers rather than nonsmokers (20). It is known that cigarette smoking decreases plasma selenium levels, so these findings support the claim that only selenium plasma deficient patients benefit from the supplementation.

What's Next

The controversy and potential involving selenium and prostate cancer has inspired the NIH to begin the SELECT study. It is a 12 year project to examine the effects of Selenium and Vitamin E on prostate cancer incidence and progression. It will examine 40,000 men from 2001-2013 to see whether there is evidence to support the use of selenium (21). These results of the study are highly anticipated by prostate cancer patients and physicians alike.

From the examination of these studies, physicians and patients must work closely to monitor selenium intake. I believe that normalization of selenium levels appears to be the most appropriate course of action because of the proposed risk associated with elevated serum plasma levels and prostate cancer. Even if only plasma deficient patients benefit from selenium supplements, this is still very important because it would significantly lower the risk for prostate cancer in these patients. For now, I would recommend that patients obtain their selenium through diet and multivitamins because supplementation appears risky until further studies prove otherwise. I think that selenium will be a necessary element of prostate cancer treatment because most studies agree that it decreases the growth of cancerous cells. The studies just disagree about whether they can be generalized to all populations of men. When the optimal level of selenium and the proper individuals for supplementation are determined by the SELECT study, selenium will pack a powerful punch in slowing the progression and onset of prostate cancer.

REFERENCES

1. American Cancer Society. <http://www.cancer.org/docroot/home/index.asp>
2. MEDLINEplus. A resource center by the NIH. <http://www.nlm.nih.gov/medlineplus/>
3. Tomoyuki Shirai, Makoto Asamoto, Satoru Takahashi, Katsumi Imaida. Diet and prostate cancer. *Toxicology* 2002; 181-182: 89-94.
4. Vogt T, Ziegler R, Graubard B, Swanson C, Greenberg R, Schoenberg J, Swanson G,

- Hayes R, Mayne S. Serum selenium and risk of prostate cancer in U.S. blacks and whites. *International Journal of Cancer* 2003; 103: 664-670.
5. Nelson M, Reid M., Duffield-Lillico A, and Marshall J. Prostate cancer and selenium. *Urology Clinicians of North America* 2002; 1:67-70.
 6. NIH clinical center. <http://www.cc.nih.gov>
 7. Clark L. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. *JAMA* 1996; 276: 1957-1963
 8. Waters D, Shen S, Cooley D, Bostwick D, Qian J, Combs G, Glickman L, Oteham C, Schlittler D, Morris J. Effects of dietary selenium supplementation on DNA damage and apoptosis in canine prostate. *Journal of the National Cancer Institute* 2003; 95: 237-241
 9. Cohen, Leonard. Nutrition and Prostate Cancer. *Annals of the New York Academy of Science* 2002; 963: 148-155.
 10. Dong Y, Zhang H, Hawthorn L, Ganther H, Clement I. Delineation of the molecular basis for selenium-induced growth arrest in human prostate cancer cells by oligonucleotide array. *Cancer Research* 2003; 63: 52-59.
 11. He Q, Rashid A, Rong R, Hillman MJ, Huang Y, Sheikh M. Death receptor 5 regulation during selenium mediated apoptosis in human prostate cancer cells. *Cancer Biology Therapy* 2002; 3: 287-290
 12. Venkateswaran V, Klotz L, Fleshner N. Selenium modulation of cell proliferation and cell cycle biomarkers in human prostate carcinoma cell lines. *Cancer Research* 2002; 62: 2540-2545.
 13. Menter D, Sabichi A, Lippman S. Selenium effects on prostate cell growth. *Cancer Epidemiology Biomarkers and Prevention* 2000; 9: 1171-1182.
 14. Smith M, Mills E. Select complementary/alternative therapies for prostate cancer. *Cancer Practice* 2001; 9: 253.
 15. Labriola D & Livingston R. Possible interactions between dietary antioxidants and chemotherapy. *Oncology*. 1999; 13: 1003-1012.
 16. Lamson D & Brignall M. Antioxidants in cancer therapy; their actions and interactions with oncologic therapies. *Alternative Medicine Review* 1999; 4: 304-329.
 17. Dalkin B.W, Lilloco, A.J, Reid, M.E et al. Selenium and chemoprevention against prostate cancer; an update on the Clark results. *Proceedings of the American Association for Cancer Research*, March 24-28 2001.
 18. Yoshizawa K, Willett, W.C., Morris, S.J. et al. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *Journal of the National Cancer Institute* 1998; 90: 1219-1224.
 19. Nomura, A.M, Lee, J, Stemmermann G.N. et al. Serum selenium and subsequent risk of prostate cancer. *Cancer Epidemiological Biomarkers* 2000; 13: 200-227.
 20. Moyad, M. Selenium and vitamin E supplements for prostate cancer: evidence or embellishment? *Urology* 2002; 59: 9-19.
 21. Moyad, M. The use of complementary/preventive medicine to prevent prostate cancer recurrence/progression following definitive therapy. *Urology* 2003; 13: 147-151.
 22. Klein EA, Thompson IM, Lippman SM, Goodman PJ, Albanes D, Taylor PR, Coltman C. SELECT: the next prostate cancer prevention trial. Selenium and Vitamin E cancer prevention trial. *J Urol* 2001; 166: 1311-5