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The Role of Selenium in the Fight against Prostate Cancer in American Men

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Introduction: Prostate Cancer's Impact on the Lives of American Men

Prostate cancer will affect the lives of one in five American men (1). Indeed, the incidence of prostate cancer among American men exceeds all other forms of cancer (2). The American Cancer Society predicts that in 2003, over 220,000 American men will be diagnosed with prostate cancer and 28,900 will die from it, meaning that prostate cancer will remain the second highest cause of cancer death in men (2). Prostate cancer is of particular concern for African American males because they are 60% more likely than their Caucasian counterparts to develop prostate cancer and two times more likely to die from it (1). In response to these incidences and mortality rates, interest in agents that may prevent against prostate cancer continues to grow. One such agent is selenium.

Selenium: Dietary Importance

Selenium is recognized as a vital trace element, a powerful antioxidant, and an essential element in thyroid and immune function (15). The Food and Drug Administration recommends a daily intake of 55 micrograms through consumption of foods high in selenium, such as cereals, meats, bread and fish (15). Practical applications of this recommendation include consumption of three ounces of tuna (100% of RDA), two slices of white bread (20% of RDA), one cup of noodles (50% of RDA), one cup of rice (20% of RDA), one cup of cottage cheese (32% of RDA), one whole egg (20% of RDA), one cup of oatmeal (23% of RDA), half a breast of chicken (44% of RDA) and three ounces of beef (33% of RDA) (15).

Clinical and Molecular Studies Reveal Selenium can Help Prevent Prostate Cancer

The first evidence of selenium's ability to prevent prostate cancer arrived incidentally in 1996. Clark et al. (4) attempted to determine if selenium supplementation would decrease the incidence of skin cancer in patients with a history of basal or squamous carcinoma of the skin. The clinical trial involved 1,312 patients and lasted from 1983-1991. Participants were given a placebo or an oral dose of 200 micrograms of selenium every day for an average of 4.5 years. Though selenium treatment did not significantly affect the incidence of basal or squamous cell carcinoma, it did lower the incidence of prostate cancer by 63% ($p = 0.002$). The surprising and dramatic results suggest that selenium protects against development of prostate cancer.

The trial's reliable parameters bolster the validity of the findings. The experiment was double-blind to prevent care-giver influence. Participants were randomized to minimize confounding factors. Furthermore, the study was multi-centered across the eastern U.S. to prevent sampling bias. Consequently, the Clark et al. study continues to be the most convincing evidence to date that selenium can help prevent prostate cancer.

The Clark et al. publication sparked numerous studies into the molecular processes by which selenium helps prevent prostate cancer. In one such study, Redman et al. (5) treated human prostate cancer cells with selenium. The treated cells demonstrated retarded growth in a near linear relationship with the dosage of selenium administered. Additionally, irregular mitosis and an increase in apoptosis among treated cells were also reported. In 2001, Jiang et al. (8) reported that human prostate cancer cells exposed to selenium exhibited disproportionately higher rates of PARP (poly(ADP-ribose) polymerase) cleavage and DNA fragmentation, both of which commonly precede apoptosis. Thus, both studies suggest that selenium helps prevent prostate cancer by causing cancerous prostate cells to commit suicide.

While the work of Redman et al. and Jiang et al. helped reveal the molecular basis of selenium's prevention of prostate cancer, it was a study published in January of this year by Dong et al. (7) that would provide the most thorough understanding of the molecular workings of selenium to date. The Dong et al. study is noteworthy because, according to its authors, it is the most comprehensive gene expression profiling study of prostate cancer cells after selenium administration. To this end, oligonucleotide arrays were used to profile the gene expression of genes known to regulate cell growth and proliferation.

The Dong et al. study reported several key findings. First, prostate cancer cells treated with selenium increased their expression of p19WAF1 and p21WAF1, proteins known to inhibit the activity of CDK/cyclin complexes. CDK/cyclin complexes stimulate cells to enter the next phase of the cell cycle. Additionally, selenium-treated prostate cancer cells also exhibited profound decreases in expression of proteins required for progression through the cell cycle: CDK1, CDK2 and CDK4 fell by 50%, Cyclin A and Cyclin E2 fell by 70% and DNA polymerase and DNA primase fell by 60%. Expression of known tumor suppressors, BRCA1 and BMP-4, increased 2.9 and 4.8 fold, respectively. In summary, Dong et al. demonstrated that selenium administration to human prostate cancer cells stunted their growth, increased apoptosis and delayed progression through the cell cycle. It stands to reason that this apparent diversity in the effects of selenium on prostate cancer cells explains how selenium is able to provide considerable protection against prostate cancer.

Evidence for Serum Selenium Levels Needed Before Significant Prevention can Occur

In a very recent case control study, Vogt et al. (9) concluded that the protective effect of selenium against prostate cancer surfaces when serum selenium levels are at or beyond 0.135 ug/ml. The Vogt et al. study, published in December of 2002, has several noteworthy strengths in the study's parameters that validate this finding. For instance, the study is multi-centered to minimize sampling bias. More importantly, the study screened for known confounding factors by frequency matching. In this technique, the study's 232 controls were selected such that the frequency of variables known to influence prostate cancer development matched the frequency of these same variables in the study's 212 cases. Vogt et al. frequency matched for all known confounding factors, including age by 10-year categories, race, and family history of prostate cancer.

Furthermore, Vogt et al. also considered variables not mentioned in the literature as confounding factors. These variables include alcohol consumption, current smoking status, number of cigarettes smoked per day, daily energy intake, intake of foods high in animal fat, education, income, month of blood draw, serum cholesterol, and serum lycopene. The variable was considered a confounder if independent addition of the variable caused an odds ratio between the case and control group to shift by over 10%. None of these variables confounded the selenium-prostate cancer relationship such that an odds ratio shifted by over 10%. Nonetheless, the fact that Vogt et al. screened for potential confounding factors in addition to known confounding factors highlights the rigorous parameters under which the study was conducted.

Another case-control study by Knekt et al. (13) appears to disagree with Vogt et al. that selenium protects against prostate cancer above serum selenium levels of 0.135 ug/ml. Indeed, the Knekt

et al. study of 1,096 prostate cancer cases and 2,192 matched controls suggests that selenium offers no observable protection against prostate cancer. However, close inspection reveals a shortcoming in this study that might explain this conclusion. The study's participants live in Finland. This is an important point because people living in Finland are more likely to be deficient in selenium, due in large part to the low soil content of selenium in Finland (3). Indeed, Finnish citizens have such a poor intake of selenium that the Finnish government has fortified the soil with selenium for nearly 20 years now (11). Thus, it is not surprising that the mean serum selenium in the control and case groups were a dismal 0.1143 ug/ml and 0.1148 ug/ml, respectively. A comparison of these mean serum selenium values to mean serum selenium values in the Vogt et al. study and other similar epidemiological studies confirms that the mean serum selenium in the Knekt et al. study are very low (9). Therefore, the Knekt et al. study may have failed to report a protective effect of selenium against prostate cancer because selenium levels in its Finnish subjects were far too low to have any impact. Thus, this study does not contradict the Vogt et al. study as initially thought. Indeed, it supports Vogt et al.'s findings that serum selenium levels above 0.135 ug/ml are needed for selenium to help prevent prostate cancer.

Practical Considerations: What Does this all Mean for the Clinician?

The aforementioned clinical, molecular and epidemiological evidence demonstrate that selenium does indeed help prevent prostate cancer when the trace element reaches sufficient levels in the serum. The logical next step for clinicians is to consider selenium supplementation to help their patients prevent prostate cancer. An article published earlier this month by Moyad in *Current Opinion in Urology* lays down many of the guidelines on how a clinician can do this (17).

One of the article's most salient recommendations is that selenium supplementation be considered only in men who ingest less than the RDA of 55 micrograms of selenium (17). This caveat is important because supplementation in individuals with normal or high selenium ingestion can cause selenium toxicity (4) and is suspected of carcinogenesis (16). A clinician can readily determine if a patient is not ingesting sufficient levels of selenium through an assay of the baseline selenium content in the patient's plasma (17).

If baseline selenium content in the plasma reveals poor selenium intake, Moyad recommends that selenium supplementation through food be considered before giving the patient selenium pills. Such a patient can easily consume enough selenium in their diets by incorporating one or more selenium-rich food sources mentioned earlier in this paper. A likely reason for this preference of food sources of selenium over supplement sources is that the FDA does not regulate supplements and thus the purity and content of selenium supplements is questionable. Another reason for this recommendation is that selenium from food sources is more likely to be absorbed than selenium from supplements.

Moyad continues that selenium supplementation should be administered such that the patient's selenium intake meets the RDA of selenium. Supplementing selenium until the RDA is met is important because fulfilling the RDA will help ensure that the patient's serum selenium is above 0.135 ug/ml (9). By way of review, a serum selenium value above 0.135 ug/ml is critical because, as reported by Vogue et al., this is the threshold level above which selenium was shown to prevent prostate cancer (9).

In summary, men of all ages now have another reason (in addition to those outlined in second paragraph of the paper) to consume the recommended daily 55 micrograms of selenium. Meeting this RDA, either through foods or supplements, is particularly important for men who have one or more of the risk factors for developing prostate cancer: Caucasian men over the age of 50, African American men over the age of 45 and men with a family history of prostate cancer.

The Future of Selenium Supplementation in Prostate Cancer

Although selenium supplementation to prevent prostate cancer is accepted medical practice in individuals with demonstrated low levels of selenium intake, many questions remain unanswered about selenium's role in prostate cancer. For instance, now that we know that selenium can help prevent cancer, will selenium supplementation help those men already diagnosed with prostate cancer? How about men who are in a transition state that often precedes prostate cancer, known as high-grade prostate intraepithelial neoplasia (HGPIN)? Will selenium supplementation help prevent prostate cancer from developing in these men? Finding the answers to these questions provides the grounds for future research into the therapeutic role of selenium in prostate cancer. Until such time that these and other questions are rigorously studied and their answers applied to the clinical setting, the role of selenium in the fight against prostate cancer will largely remain a preventive one.

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