

Larry Clark's Legacy: Randomized Controlled, Selenium-Based Prostate Cancer Chemoprevention Trials

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Abstract: *Several important clinical trials under way at the Arizona Cancer Center seek to build on the results of Clark's 1996 study of selenium and decreased risk of prostate cancer. Those results, an unanticipated end point of a clinical trial, suggest that selenium has significant preventive power. The studies under way involve continued follow-up of the study cohort that generated the 1996 results and trials of selenium among men with negative biopsies, men with high-grade prostatic intraepithelial neoplasia, men with prostate cancer treated with selenium before prostatectomy, and men with prostate cancer who have chosen watchful waiting rather than active intervention. These studies promise important opportunities to validate Clark's original results.*

Introduction

Several prostate cancer chemoprevention studies under way at the University of Arizona were inspired largely by the results of the trial of Clark et al. (1) of selenium among men and women who had been treated for basal or squamous cell skin cancer. The study of Clark et al. was originally designed to prevent the recurrence of skin cancer among these individuals. Selenium was found not to decrease the risk of skin cancer recurrence. However, individuals in the experimental group, treated with selenium at 200 µg/day in baker's yeast, experienced sizable decreases in the risks of primary cancers of the colon and rectum, prostate, and lung. Prostate cancer incidence decreased by a striking 65%. These results are important; the study was an experiment, so experimental subjects were exposed to much higher levels of selenium over the trial's duration than were controls. Subjects were, on average, treated for 4.5 yr. The experimental design provides excellent documentation that selenium supplementation had a substantial effect on blood levels; within 1 yr, experimental subject blood levels had reached a new equilibrium, with those levels approximately doubled. In addition, because assignment to the treatment group was randomized, the probability of confounding of the treatment

effect by other factors that might have altered risk of prostate cancer was decreased.

Additional studies of the prostate cancer effect are necessary to confirm the trial results and to extend them to other populations. The greatly decreased prostate cancer observed in the study was not originally anticipated, and this decreases our confidence in the effect (2). We have designed and initiated four new double-blind, randomized trials to confirm the observation of Clark et al. (1,2) that selenium treatment decreased the risk of prostate cancer. These trials will be conducted among men at various degrees of elevated prostate cancer risk.

The results of this important trial demonstrated how little we understand regarding the mechanisms by which selenium might affect the risk of cancer. The trial left a number of scientific issues to be considered. One of these is the content of the high-selenium baker's yeast used in the trial of Clark et al. (1,2). They used a selenized yeast that was commercially available. Part of the attractiveness of this agent was that it was readily available as a food supplement. The disadvantage was that it had not been analyzed for the different forms of selenium with as much detail as is desirable. This selenized yeast contains several selenium compounds, of which only a few have been identified: L-selenomethionine, selenocysteine, Se-methylselenocysteine, selenoethionine, selenogluthathione, selenodigluthathione, and selenite are believed to be the most prominent and active (3,4). Recent evaluations of this selenized yeast reveal that most of the selenium is in the form of L-selenomethionine (5). The mechanisms by which selenomethionine might protect are not completely understood. Selenomethionine is metabolized and stored in the same manner as methionine (4). Catabolism of the selenomethionine then yields selenocysteine, which yields several selenoproteins and methylselenol. It has been experimentally documented (4) that methylselenol may be highly active in blocking a number of carcinogenic pathways. We are presently involved in a series of studies designed to provide more detailed speciation of the high-selenium yeast that had been used by Clark et al. In addition, the mechanisms by which any chemopreventive effects might be realized are not known. Ip recently pointed out that,

in the unfolding of research with selenium, epidemiological and clinical trial results are ahead of basic science understanding (4). A great deal of basic science evidence has been accumulated, and this science suggests a number of mechanisms by which selenium may have a protective effect against cancer (4). We are not able to convincingly confirm or dismiss any of these possible causal mechanisms.

The four studies under way at the Arizona Cancer Center seek to extend our understanding. These randomized, placebo-controlled, double-blind trials offer opportunities to confirm the results of Clark et al. (1,2) and to explore the mechanisms by which selenium compounds might work. These trials, involving intervention at different phases of the development of clinical prostate cancer, complement one another. The use of a unitary, as opposed to a complex, mixture is explored; the treatment in one trial is pure selenomethionine; the other trials use high-selenium baker's yeast. As mentioned, it is hypothesized that selenomethionine, one of the major compounds in selenized yeast, is responsible for the protective effects observed by Clark et al. This trial will provide an important opportunity to evaluate that hypothesis, inasmuch as none of the other forms of selenium in selenized yeast will be present. This offers a limited opportunity to explore whether the primary compound in selenized yeast, selenomethionine, has effects that are different from those of the full range of selenium compounds present in selenized yeast.

The first study is being conducted among men who have been biopsied for prostate cancer but whose biopsy was negative: the negative biopsy trial. The second trial involves treatment with selenium of men with high-grade prostatic intraepithelial neoplasia (HGPIN). The third trial involves selenium treatment of men with localized prostate cancer before prostatectomy. The fourth trial, watchful waiting, will test selenium as a chemotherapeutic agent among men with confirmed prostate cancer. These selenium intervention studies range from evaluations of selenium among high-risk individuals who have not been diagnosed with prostate cancer to attempts to alter the course of clearly invasive prostate cancer. All will evaluate changes in prostate-specific antigen (PSA), and all are restricted to individuals who are not taking PSA-altering drugs.

Negative Biopsy Trial

Men with persistently elevated PSA are at substantially elevated risk of prostate cancer (6) and, thus, represent a high-priority target for prostate cancer chemoprevention studies. A recent negative biopsy of the prostate will help ensure, to the degree possible, that these men do not already have clinical prostate cancer. As many as one-fourth of these men will have early prostate cancer, missed by the biopsy, so they represent a group that is less homogeneous than desired. In general, however, men whose biopsies are negative are likely to have minimal disease, and it is possible that selenium may be active against the progression of cancer at

this minimal disease stage. The randomization procedure will help ensure that they are equally distributed in the treatment groups. Thus 700 men with negative biopsies but elevated PSA will be randomized to placebo or 200 or 400 μg of selenium in high-selenium baker's yeast. Follow-up is expected to be up to 57 mo. Outcomes anticipated include diagnosed prostate cancer and the rate of rise in the PSA before the end of treatment and follow-up. This trial will evaluate the ability of selenium, first, to decrease the incidence of clinical prostate cancer and, second, to halt or slow the preclinical progression of prostate cancer. This trial, funded by the National Cancer Institute (NCI), should be directly generalizable to those patients at high risk of prostate cancer but who have not yet been diagnosed. So far, 210 men have been randomized to this trial.

HGPIN Trial

Men with HGPIN are at substantially elevated risk of subsequent prostate cancer (7,8). However, such men are not treated by surgery or by irradiation. The identification of a compound that would decrease the risk of cancer development among these men could be of great value. This trial, funded by the NCI, is being conducted through the Southwest Oncology Group. Altogether, 470 men with HGPIN, who have had two or more biopsies that indicate no prostate cancer, will be assigned to placebo or to 200 μg of selenium daily as selenomethionine. They will be followed for ≥ 3 yr. Those who have not had additional biopsies will be scheduled for biopsy at the end of the follow-up period. The primary end point in this study is the diagnosis of biopsy-proven prostate cancer. Secondary end points, biomarkers of change, include apoptosis and proliferation. Machine-vision imaging will also be used to evaluate change in nuclear characteristics and degradation of basal cell integrity in the glands and ducts (9,10). This study will evaluate the activity of selenium immediately before neoplastic growth becomes transformed into invasive growth. An important possible limitation of the study is that a small percentage of these men will have prostate cancer missed by the biopsies. The use of multiple biopsies at baseline, however, should minimize this problem. This study has registered 85 subjects.

Preprostatectomy Trial

This trial is funded by the Department of Defense to enroll 110 men with biopsy-diagnosed, localized prostate cancer who elect treatment with prostatectomy and agree to treatment with selenium or placebo during the period before surgery. Subjects will be assigned to placebo or 200 or 400 μg of selenium per day as high-selenium baker's yeast. Subjects will be evaluated primarily during the 6- to 8-wk period between biopsy and prostatectomy. This short study period is necessitated by the fact that men who have been diagnosed with prostate cancer are usually anxious to be treated as soon

as possible. The most common clinical practice is to allow 6–8 wk for biopsy-induced inflammation to subside and then to proceed with prostatectomy. No run-in period for patient compliance is included in the trial because of the relatively short time available for treatment. Study end points include immunohistochemical biomarkers of change in healthy tissue, including proliferation, apoptosis, thioredoxin, thioredoxin reductase, and glutathione peroxidase. These selenoproteins are regarded as highly unlikely to be the means by which selenium supplementation could alter prostate cancer risk (11). The levels of these could well reflect the extent of antioxidant tissue defense within the prostate. Fresh prostate tissue will be obtained from prostatectomy for evaluation of selenium levels. This clinical trial will assess whether selenium administration can change the biochemistry of the prostate within a very brief period. It will allow an evaluation of whether what are believed to be important mechanisms of carcinogenesis, proliferation and apoptosis and the balance between them, can be altered by short-term treatment with selenium. At this time, 55 people have been recruited to this study.

Watchful Waiting Trial

There is evidence that, for men with localized disease and low-grade tumors and a life expectancy <10 yr, watchful waiting is a reasonable alternative to aggressive treatment (12,13). A nontoxic chemopreventive agent such as selenium would be an attractive adjuvant to watchful waiting. Thus, with NCI funding, 264 men with localized prostate cancer (PSA <50), who have chosen not to undergo prostatectomy, irradiation, or hormonal treatment, will be treated with placebo or 200 or 800 µg of selenium per day as yeast. In a separate but related study funded by other sources, 30 men were randomized to receive 1,600 or 3,200 µg of selenium per day in yeast. Although no overt toxicity was observed in this arm of the trial, it was halted because of fears of possible long-term adverse effects. In the event of massive overdosing with selenium, kidney and liver damage can be seen; with microgram dosage, however, the only observed toxicity is garlic breath and nail and hair brittleness. We are presently evaluating the results of this small trial. Patients will be followed for up to 4 yr. The end points of this study include selenium toxicity, rates of increase in PSA, need to commence hormonal treatment, and development of regional and distant metastases. This study is among patients who have declined therapy and could thus be considered an evaluation of the therapeutic use of selenium. The principal advantage of this study is its minimizing of the bias that could be introduced by including patients without prostate cancer. One of the most important outcomes of this study will be the evidence accrued on the impact of pharmacological doses of selenium. The dose of 800 µg of selenium per day is approximately four times the dose used by Clark et al. (1) for the major arm of their original study. The 400 and 800 µg/day doses are supraphysiological and will contribute

considerable information regarding evidence of selenosis with long-term use. To date, no evidence of toxicity has been observed among the total of 85 patients recruited.

Summary

These double-blind, randomized trials under way at the Arizona Cancer Center build on the pioneering results reported by Clark et al. (1). The studies will evaluate the activity of selenium at several points along a continuum ranging from short-term effects on healthy and cancerous prostatic tissue in men with diagnosed cancer, to long-term effects on healthy and premalignant tissue in men with HGPIN, to long-term effects on healthy tissue in high-risk men with negative biopsy, to long-term effects on cancerous tissue in men with frank cancer. These complementary studies offer important opportunities to replicate and extend the results of Clark et al. They also offer an opportunity for preliminary evaluation of mechanisms by which selenium treatment could result in the slower development or progression of prostate cancer. Larry Clark realized, well before most students of prevention, the importance of the randomized-controlled trial as a means of identifying preventive strategies. We at the Arizona Cancer Center intend to build on the important foundations established by Dr. Clark.

An important impediment to recruitment to these trials is that a substantial proportion of potential patients are already taking large doses of selenium. That these trials are legitimate, however, requires that the efficacy of selenium cannot be regarded as established. Colditz (2) emphasized that even the promising results of the initial trial of Clark et al. do not legitimate large-scale use of selenium as a chemopreventive agent. A large prostate cancer prevention trial, to be conducted among men at average risk, is about to begin. This trial, the Selenium and E Chemoprevention Trial, will evaluate vitamin E and selenium, considered in a 2 × 2 factorial study design, among 32,800 men. The trial will be led by the Southwest Oncology Group and the Veterans Administration. It will also recruit patients among the Cancer and Leukemia Group B and the Eastern Cooperative Oncology Group. We have proposed a large general population trial that will have substantial statistical power for effects more modest than those observed in the original trial of Clark et al. Although the focus of this trial will be prostate cancer prevention, it will also be open to women; it will be important to evaluate definitively the impact of selenium supplementation among women as well as men. We are in the process of seeking additional grant support to expand this trial.

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