Selenium Accumulation in Prostate Tissue During a Randomized, Controlled Short-term Trial of L-Selenomethionine: a Southwest Oncology Group Study

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Abstract Purpose: Epidemiologic and clinical data suggest that selenium could prevent prostate cancer, but it has not been shown that supplemental selenium leads to an increased concentration of selenium in prostate tissue compared with adjacent tissue.

Experimental Design: We conducted a randomized, controlled, short-term trial of L-selenomethionine (SeMet) versus observation in men with organ-confined prostate cancer. The primary endpoint was the measurement of selenium concentration in prostate tissue and seminal vesicle (SV). We assessed baseline selenium levels in serum and in toenail specimens (reflecting long-term intake) and post-intervention selenium levels in serum, and in prostate and SV tissues using hydride generation atomic fluorescence spectroscopy.

Results: Sixty-six eligible patients were randomly assigned to the SeMet (n = 34) or observation (n = 32) arm; both arms had similar baseline patient characteristics. Baseline serum selenium was similar in the two groups (P = 0.64). Baseline toenail selenium levels were slightly higher in the SeMet group than in the control group (P = 0.07). After the intervention, the mean serum selenium level increased 15% in the SeMet arm and was higher than in the observation arm (P = 0.001). The selenium concentration in prostate tissue was 22% higher in the SeMet arm (n = 26) than in the observation arm (n = 25; 1.80 versus 1.47 ppm; P = 0.003, Wilcoxon rank sum test) and remained significantly higher after adjusting for chronic selenium intake (P = 0.021, ANCOVA). SV selenium concentration was similar in both groups (P = 0.384) and was lower than in prostate tissue.

Conclusions: The present study is the first to show that selenium taken as oral supplementation accumulates preferentially in the human prostate gland as opposed to the SV. These findings support the hypothesis that oral selenium supplementation may contribute to the cancer preventive effects of selenium.
supplemental selenium that examined selenium levels in prostate tissue (11). The limitations of the study included the availability of only transitional zone prostate tissue (from patients undergoing transurethral resection for benign prostatic hypertrophy), no sampling of other tissues to assess selectivity of selenium uptake in prostate tissue, and lack of control for chronic (dietary) selenium intake. The present study offers the first randomized trial of selenium concentration in the peripheral zone of the human prostate tissue compared with concentration in the seminal vesicle (SV) following selenium supplementation in patients scheduled for prostatectomy.

**Materials and Methods**

The Southwest Oncology Group coordinated this multicenter National Cancer Institute trial of patients recruited at the following Southwest Oncology Group–affiliated institutions: University of Texas M.D. Anderson Cancer Center, University of Texas San Antonio, Brooke Army Medical Center, and Baylor College of Medicine.

**Patient eligibility.** Eligible patients must have had pathologically determined primary prostatic adenocarcinoma confined to the prostate and a scheduled prostatectomy. Patients were excluded if they took >3 days of >150 μg/d of selenium supplementation in the month prior to randomization or had a concurrent cancer. Selenium supplementation other than the study drug was disallowed on study. All patients were randomized at the Southwest Oncology Group Statistical Center no more than 1 working day prior to initiation of selenium supplementation or observation. Patients were stratified based on their registering institution. The protocol was Institutional Review Board–approved at all institutions, and each patient gave written informed consent to participate in the trial.

**Study design and treatment plan.** This clinical-laboratory study began with a randomized, controlled trial of 200 μg/d of oral selenium supplementation as l-selenomethionine (SeMet) versus standard-of-care observation for 14 to 31 days prior to prostatectomy in men with organ-confined prostate cancer (Fig. 1). The accrual goal was 60 total patients, 30 in each study arm. The primary end point was the level of selenium in prostate tissue as determined by the laboratory analyses described below. Ancillary variables included pretreatment and posttreatment levels of prostate-specific antigen (PSA) and serum selenium, and pretreatment toenail clippings as a measure of chronic selenium intake. Toxicity was assessed by the National Cancer Institute Common Toxicity Criteria v 2.0. At study entry, all patients filled out a questionnaire on their current and past vitamin and mineral intake.

**Laboratory analyses.** Selenium standards were purchased from CPI (Santa Rosa, CA). Teflon digestion vessels were purchased from Savillex (Minnetonka, MN). Analytic spectrophotometric grade water and chemicals were purchased from Fisher Scientific (Hampton, NH). Glassware and polypropylene tubes were acid-washed with 10% HNO₃, and the Teflon sample vials were acid-washed with 30% HNO₃, followed by thorough rinses with reagent grade water. All samples were coded, and lab personnel were blinded to the study arm. Venous whole blood samples (7 mL) were collected in trace element–free glass tubes (Vacutainer, Becton Dickinson and Co., London, England) and kept at 4°C. Serum was then separated from the red cell component by centrifugation and placed in a separate tube for storage at −20°C prior to atomic fluorescence analysis.

Three to four small nail clippings were obtained from the big toe of each patient prior to starting SeMet or observation. Nail clippers were sterilized prior to each use. Nail samples were clean and without evidence of fungus, medication, chemicals, or paint/nail polish.

Core and punch biopsy samples were obtained from the prostate gland as soon as the prostate was removed from the patient. The organ was oriented in a sagittal longitudinal view. Two sets of sextant core biopsies (a total of 12 cores) were obtained bilaterally from the apex, middle, and base (similar to those obtained in the clinical setting) using a standard prostate biopsy gun armed with a short cutting biopsy needle. Core biopsies were placed on a glass slide until all 12 cores were collected. A single drop of reagent grade water was placed on the slide to keep the tissue moist until all the cores were harvested. All 12 cores were placed into a single, uniquely labeled polypropylene NUNC Cryotube and then snap-frozen in liquid nitrogen and stored at −70°C until they were processed for elemental analysis. A punch biopsy from each prostate gland was obtained following a standardized protocol previously described (16). Briefly, the prostatectomy specimen was sectioned in a plane perpendicular to the posterior surface, and a 6-mm punch biopsy tool was inserted at a point with no visible evidence of tumor in order to harvest a 150 to 200 mg sample of prostate tissue, which was processed as described for the core biopsies. Four pathology technicians (one at each of the four study sites) collected all tissue samples from the peripheral zone of the prostate and from the SV by following a standardized biopsy procedure outlined in the protocol.

SV specimens were obtained by snipping the tip (−8 mm) of the SV contralateral to the dominant prostate tumor. This was done only if the pathologist determined that the entire SV was visibly free of tumor. Tissue was placed in a uniquely labeled polypropylene NUNC Cryotube and then snap-frozen in liquid nitrogen and stored at −70°C until it was processed for elemental analysis.

Blood and tissue specimens were analyzed for elemental selenium concentrations using hydride generation atomic fluorescence spectrometry. Prostate and SV tissues were placed in a Labconco Lyph-Lock 12 freeze-drier and lyophilized to dryness, after which they were prepared for analysis by wet digestion. Prostate biopsies, nail clippings, and aliquots of SV and serum samples were weighed into Teflon vessels and digested under high pressure and temperature with ultrapure nitric acid in a microwave oven (OI Model MDS). Specimens were cooled, exposed to ultra-pure hydrogen peroxide, and heated a second time under atmospheric pressure. They were then diluted to volume with deionized water and transferred to polyethylene bottles. Aliquots of digest solution were transferred to polypropylene vessels for reduction of selenium(VI) to selenium(IV). After the addition of concentrated HCl (Baker Instrex Analyzed grade), the specimens were heated for 60 minutes at 95°C in a graphite heating block (CPI). After cooling, deionized water was added to obtain a final concentration of 3 mol/L HCl. Each batch of samples included one procedural blank, one spiked blank, one certified reference material, one duplicate sample, and one spiked sample. Calibration standards were prepared from commercial standards (CPI) and processed through the reduction step.

![Fig. 1. Study design.](image-url)
Selenium analysis was done on a PSA Millennium Excalibur atomic fluorescence spectrometer. Samples and standards, which contained selenium(IV) in a 3 mol/L HCl aqueous matrix, were mixed with sodium borohydride under closed conditions. Selenium hydride was stripped from solution in a gas-liquid separator and decomposed in an air-hydrogen flame. Selenium atoms were detected by atomic fluorescence using a boosted hollow cathode lamp and a solar blind detector. Selenium concentrations in specimens were determined by comparison with calibration standards, using peak area and unweighted linear regression analysis. Concentrations were reported in parts per million (ppm) on a dry weight basis for the prostate and SV and on a wet weight basis for serum.

Statistical analyses. The power calculation was based on the normal approximation for a difference of two independent means with unequal variances (17). A coefficient of variation was used to determine the sample size because it measures variability relative to a mean, and the literature suggests that mean selenium levels may differ appreciably for different tissues (18–20). The study was designed so that if the coefficient of variation was 30%, the study power would be 0.81 to detect a 25% difference in mean prostate selenium levels and a power of 0.92 to detect a 30% difference in mean prostate selenium levels between the two study arms (30 patients per arm, 5% two-sided test). The selenium levels in serum and prostatectomy tissue specimens and serum PSA levels in the SeMet and placebo groups were compared using the Wilcoxon rank sum test (unpaired test). ANCOVA also were applied to compare tissue selenium levels in prostate and SV between the SeMet and placebo groups, as adjusted by level of selenium in toenails, which may be a marker for long-term selenium exposure, and by baseline serum selenium level. All results are reported with a two-sided P value unless otherwise indicated.

Results

Patient characteristics, compliance, and toxicity. Between June 15, 1999 and June 1, 2001, a total of 68 patients were accrued and randomly assigned to receive oral SeMet (200 µg/d; n = 35) or observation (n = 33). Two randomized patients (one in each arm) were deemed ineligible because all eligibility criteria could not be confirmed. Therefore, 66 patients were eligible, 34 in the selenium group and 32 in the observation group. Data from all eligible patients were included in all relevant analyses. All randomized patients had organ-confined pathologically determined primary prostatic adenocarcinoma and were scheduled for a prostatectomy within 14 to 31 days. The two study arms were balanced at baseline with respect to the number of patients, age, time to surgery, Gleason score, serum selenium (a measure of short-term selenium intake; P = 0.64), toenail selenium (a reflection of long-term intake; P = 0.07), and serum PSA (P = 0.73). Mean age was 59 years (range, 36–75 years) in the observation group and 60 years (range, 44–74 years) in the selenium arm. The majority of participants were White males, 94% in the observation arm and 82% in the selenium arm (Table 1). Compliance (determined by pill count and pill diary) on the SeMet arm was ≥85%. No drug-related toxicity was observed.

Specimens. The following numbers of specimens in the selenium arm were adequate for analysis: baseline serum, 34 of 34 that were obtained; post-intervention serum, 28 of 29; toenail, 32 of 34; prostate biopsy, 26 of 31; and SV biopsy, 29 of 31. The following numbers of specimens in the observation arm were adequate for analysis: baseline serum, 30 of 32 that were obtained; post-intervention serum, 28 of 30; toenail, 31 of 32; prostate biopsy, 25 of 30; and SV biopsy, 28 of 30. Five specimens each from the selenium and observation groups were unavoidably lost during analysis by hydride generation atomic fluorescence spectrometry. Five eligible men did not have biopsies collected: two because no prostatectomy was done [one refusal (selenium) and one case of upstaged disease (observation)], and three because the prostatectomies were done at hours when no study technician was available to biopsy the prostate (two from the selenium arm and one from the observation arm). In the selenium arm, 33 patients had serum for PSA analysis at baseline and 32 patients had serum for PSA analysis at both baseline and post-intervention, whereas in the observation arm, 31 patients had serum for PSA analysis at baseline and 21 patients had serum for PSA analysis at both baseline and post-intervention.

Short-term intake of SeMet. Following the intervention, serum selenium levels in the SeMet group were statistically significantly higher than in the observation group (P < 0.001). The increase in serum selenium levels between baseline and the end of intervention was also statistically significantly higher in the SeMet group (versus observation; P = 0.003; Table 2).

Selenium concentrations were measured in both sextant core and punch biopsies of the prostate in most cases; only sextant core or punch biopsy was available in some cases. In the cases where both biopsies were available, the selenium values in punch biopsies and pooled sextant core biopsies did not statistically differ in selenium concentration and were averaged. Mean levels of selenium in prostate biopsy specimens was 22% higher in the treatment group (1.80 ppm; coefficient of variation, 30.6%) than in the control group (1.47 ppm; coefficient of variation, 17.7%; P = 0.003, Wilcoxon rank sum test). We also assessed whether the duration of treatment affected the level of selenium (by quartile) in the prostate tissue of men in the intervention arm. The duration of selenium supplementation (range, 14–31 days) was not significantly associated with the level of selenium in the prostate (correlation coefficient, −0.08; P = 0.93).

Mean selenium levels in the SV tissue specimens were similar in the SeMet (1.31 ppm) and control groups (1.13 ppm; P = 0.15; Table 3). Selenium concentrations were higher in prostate than in SV tissue specimens (Table 3). Mean baseline

![Table 1. Patient characteristics](https://example.com/table1.png)

- **Table 1. Patient characteristics**
  - **Characteristic**
  - **Observation**
  - **Selenium**
  - No. of patients
    - 32
    - 34
  - Mean age, y (range)
    - 59 (36–75)
    - 60 (44–74)
  - Race (%)
    - White: 30 (94)
    - African-American: 2 (6)
    - Mean days to prostatectomy
      - median range
        - 20 (18–14–30)
        - 21 (21,15–31)
    - Mean Gleason score
      - median range
        - 6 (6, 6–7)
        - 6 (6, 3–8)
    - Mean toenail selenium, ppm
      - median range
        - 0.82 (0.76, 0.47–1.84)
        - 0.92 (0.91, 0.55–1.38)
PSA levels were similar in the selenium (6.6 ng/mL) and observation (6.5 ng/mL) groups, and PSA levels were not altered by selenium intake ($P = 0.76$; Table 4).

**Chronic intake of selenium.** Chronic selenium intake is reflected in toenail selenium level. We measured toenail selenium in both groups at randomization (baseline). Mean toenail selenium in the observation group was 0.82 ppm (SD, 0.27) compared with 0.92 ppm (SD, 0.25) in the SeMet group. Median (range) toenail selenium level in the observation group was 0.76 ppm (0.47-1.84 ppm) compared with 0.91 ppm (0.55-1.38 ppm) in those randomized to the SeMet group (Table 1). Although toenail selenium trended towards being higher in the SeMet group than the observation group, there was no statistically significant difference ($P = 0.071$).

According to the Wilcoxon rank sum test, prostate selenium level in the SeMet group was significantly increased after treatment compared with the observation group. Because baseline levels of selenium in prostate biopsies and SV tissue were not available, chronic selenium intake (measured in toenails) and baseline serum selenium levels were incorporated into the ANCOVA model to adjust for the potential differences in prostate and SV selenium levels after treatment (Fig. 2). The significantly higher mean level of selenium in prostate tissue biopsy specimens in the treatment compared with control group remained significant (12% higher, $P = 0.021$, ANCOVA) after adjustment for chronic selenium intake. The results indicate that prostate tissue selenium level, but not SV tissue selenium level, was affected by short-term selenium intake.

Selenium levels in the SV tissue specimens were similar in the SeMet and control groups ($P = 0.15$), and remained similar after controlling for chronic selenium intake ($P = 0.38$). Interestingly, chronic selenium intake was positively correlated in both the study groups with selenium concentration in the prostate (Pearson’s $r = 0.44$, $P = 0.01$), but not in the SV (Pearson’s $r = 0.09$, $P = 0.56$; Fig. 2). This finding suggests that chronic selenium intake preferentially accumulates in the prostate (as opposed to the SV), paralleling the differential selenium accumulation resulting from short-term selenium intake.

### Discussion

This randomized study shows that, compared with control (observation), short-term intake (14-31 days) of SeMet supplementation resulted in a significant increase in selenium concentration in prostate tissue (12.1%; $P = 0.021$, ANCOVA) and serum (14.7%; $P = 0.001$) but not in the SV ($P = 0.38$) after adjusting for chronic selenium intake. Chronic selenium accumulation, as represented by toenail selenium, also correlated with prostate ($P = 0.01$) but not with SV selenium levels ($P = 0.56$), and adjustment for selenium stores enhanced the difference in selenium levels between the prostate and SV associated with supplemental selenium. Short-term selenium

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**Table 2. Serum selenium concentration**

<table>
<thead>
<tr>
<th>Selenium concentration</th>
<th>Baseline</th>
<th></th>
<th>Post-study</th>
<th></th>
<th>Change in serum selenium (post-study minus baseline)</th>
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<tr>
<td></td>
<td>Observation</td>
<td>Selenium</td>
<td>Observation</td>
<td>Selenium</td>
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<td>Observation</td>
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<tr>
<td>No. ($n$)</td>
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<td>34</td>
<td>28</td>
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<tr>
<td>Mean*</td>
<td>0.12</td>
<td>0.12</td>
<td>0.10</td>
<td>0.14</td>
<td>$-0.020$</td>
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<tr>
<td>Median*</td>
<td>0.12</td>
<td>0.12</td>
<td>0.10</td>
<td>0.13</td>
<td>$-0.016$</td>
<td>0.010</td>
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<tr>
<td>SD</td>
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<td>0.02</td>
<td>0.02</td>
<td>0.04</td>
<td>0.022</td>
<td>0.043</td>
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<tr>
<td>Max*</td>
<td>0.15</td>
<td>0.15</td>
<td>0.16</td>
<td>0.25</td>
<td>$-0.069$</td>
<td>$-0.055$</td>
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<tr>
<td>Min*</td>
<td>0.08</td>
<td>0.04</td>
<td>0.06</td>
<td>0.07</td>
<td>0.020</td>
<td>0.102</td>
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<tr>
<td>Wilcoxon rank sum test</td>
<td>$P = 0.64$</td>
<td></td>
<td>$P &lt; 0.001$</td>
<td></td>
<td>$P = 0.003$</td>
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*Selenium concentrations reported in parts per million.

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**Table 3. Tissue selenium concentration**

<table>
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<tr>
<th>Selenium concentration</th>
<th>Prostate ($n = 51$)</th>
<th></th>
<th>SV ($n = 57$)</th>
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<tr>
<td></td>
<td>Observation</td>
<td>Selenium</td>
<td>Observation</td>
<td>Selenium</td>
<td></td>
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<tr>
<td>$n$</td>
<td>25</td>
<td>26</td>
<td>28</td>
<td>29</td>
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<td>Mean*</td>
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<td>1.80</td>
<td>1.13</td>
<td>1.31</td>
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<tr>
<td>Median*</td>
<td>1.42</td>
<td>1.74</td>
<td>1.12</td>
<td>1.31</td>
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<tr>
<td>SD</td>
<td>0.26</td>
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<td>0.35</td>
<td>0.51</td>
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<tr>
<td>Max*</td>
<td>2.13</td>
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<td>1.99</td>
<td>2.58</td>
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<tr>
<td>Min*</td>
<td>1.12</td>
<td>1.15</td>
<td>0.39</td>
<td>0.58</td>
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<tr>
<td>Wilcoxon rank sum test</td>
<td></td>
<td></td>
<td>$P = 0.003$</td>
<td></td>
<td>$P = 0.15$</td>
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</table>

*Selenium concentrations reported in parts per million.*
supplementation produced no detectable change in PSA levels. These data provide the first evidence we are aware of that selenium accumulates preferentially in the human prostate (versus in the SV) following short-term oral supplementation.

Selenium has been prospectively studied as a chemopreventive agent in the Nutritional Prevention of Cancer trial, a double blind, randomized placebo-controlled clinical trial designed to test whether selenized yeast (200 μg/d selenium) could prevent the recurrence of non–melanoma skin cancer in 1,312 patients (8). The final analysis of the entire blinded treatment period showed a statistically significant increase in non–melanoma skin cancer, although a secondary end point analysis revealed a striking 49% reduction in prostate cancer incidence \( (P = 0.009; \text{ref.9}) \). This protective effect seemed to be confined to men with a PSA of ≤4 ng/mL; the selenium benefit was also restricted to men in the lowest tertiles of baseline selenium levels (9), which is consistent with other clinical results (1–6).

Our findings that selenium accumulates in the “target” organ may contribute to the understanding of protective selenium mechanisms against prostate cancer and suggests that there is a potential role for a direct effect of selenium in prostate tissue.

Many potential preventive mechanisms have been proposed for selenium, including direct and indirect effects (21). Selenoproteins may act as antitumorigenic proteins and protect against DNA damage from xenobiotics. These mechanisms likely rely on the presence of selenium in a given tissue. The direct effects of selenium on prostate cancer cells may involve a wide range of effects on regulatory proteins, including nuclear factor \( \kappa B \), androgen receptor, PSA, kallikrein 2, protein kinase C, p21, caspase-8, and manganese superoxide dismutase (21–27).

Both organic and inorganic selenium seem to be used efficiently in the body. The metabolism of inorganic selenium is tightly regulated and serves as a precursor to the synthesis of selenoproteins such as glutathione peroxidase, thioredoxin reductase, and selenoprotein P, which act as antioxidants and may help protect cells against xenobiotic insults. Organic forms of selenium, such as SeMet, are not as tightly regulated and can be incorporated into general proteins such as albumin in place of methionine. SeMet also can be channeled into the inorganic selenium metabolism pathway by trans-sulfuration.

There is mounting evidence that selenium is incorporated into the catalytic sites of selenoproteins (28–34). Selenoprotein

<table>
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<th>Table 4. Serum PSA</th>
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<td>Serum PSA</td>
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<td></td>
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<tr>
<td>No. (n)</td>
</tr>
<tr>
<td>Mean (range)</td>
</tr>
<tr>
<td>Wilcoxon rank sum test</td>
</tr>
</tbody>
</table>

\* Concentration of PSA reported in ng/mL.

Supplemental Figure 2. Scatter plots and regression curves of ANCOVA models. Selenium levels (ppm) in prostate (top left) and SV (bottom left) were incorporated into the ANCOVA model to adjust for potential difference in chronic intake of selenium (as measured in toenail). Selenium levels (ppm) in prostate tissue (top right) and SV (bottom right) adjusted for baseline serum selenium. The vertical separation of curves in the prostate tissue indicates the effects of both long-term (top left) and short-term (top right) selenium intake of selenium on the prostate. This effect is not present in the SV (bottom).
P and Sep15 are 2 of the 25 recently described human selenoproteins containing selenocysteine (32). It is interesting to note that nucleotide polymorphisms of the two aforementioned proteins have been identified as functionally altered in their ability to incorporate selenium (35); therefore, they may be particularly important in protecting against the development of prostate cancer (36). Selenium also serves as a source of antitumorigenic seleno-metabolites, particularly methyl selenyl (26, 27, 37, 38). We have previously shown that selenium selectively inhibits the growth and division of malignant but not normal prostate cells in a dose-dependent manner (22), findings recently confirmed by others (23). The relationship between selenium dose and prostate carcinogenesis is complex, however, and over-accumulation of selenium is potentially dangerous, as indicated by the "U"-shaped dose-response curve of selenium in association with increased DNA damage in aging dogs (39).

The well-known difference in prostate cancer frequencies in different zones of the prostate raises the question of whether selenium concentrates differently in the transitional, central, or peripheral zone of the prostate. An intriguing previous finding (12) indicated significantly higher concentrations of selenium in the peripheral zone, in which prostate cancer generally develops, than in the transitional zone; this finding, however, did not involve supplementation. There has been only one previous randomized study of selenium supplementation examining levels in the human prostate, which examined only (and found increased selenium in) the transitional zone (11). Our randomized, controlled study found that selenium supplementation resulted in increased selenium levels in the peripheral zone, in which prostate cancer develops most frequently (40), and that selenium accumulated selectively in the prostate instead of the SV. This selectivity provides further biological plausibility for the observational data (1–6) and secondary clinical data (8, 9) suggesting selenium activity against prostate cancer development. Although it is not clear why selenium uptake was preferential for the prostate, it may be that homeostasis is more dependent on selenium in the prostate than in the SV.

The Selenium and Vitamin E Cancer Prevention Trial and other trials outlined elsewhere (21, 41) are addressing important questions of selenium biology, including whether selenium works primarily on subclinical, microscopic cancer or in preventing or reversing preneoplastic lesions. For example, biopsies taken during the course of the Selenium and Vitamin E Cancer Prevention Trial will allow selenium and nonselenium groups to be compared for the secondary end point of prostatic intraepithelial neoplasia. Although many questions about selenium mechanisms and biology remain, the present findings bolster the biological rationale for testing selenium in prostate cancer chemoprevention trials.

References


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