Comparative Effects of Two Different Forms of Selenium on Oxidative Stress Biomarkers in Healthy Men: A Randomized Clinical Trial

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Abstract

Epidemiologic and laboratory studies indicate that dietary selenium protects against prostate cancer. Results from clinical trials suggest that selenium-enriched yeast (SY) but not selenomethionine (SeMet) may be effective at reducing prostate cancer risk. Our objectives were to directly compare for the first time the effects of SeMet and SY on prostate cancer relevant biomarkers in men. We performed a randomized double blind, placebo-controlled trial of SY (200 or 285 μg/day) and SeMet (200 μg/day) administered for 9 months in 69 healthy men. Primary endpoints included blood levels of selenium-containing compounds and oxidative stress biomarkers [urine 8-hydroxy-2′-deoxyguanosine (8-OHdG) and 8-iso-prostaglandin-F1α (8-iso-PGF2α) and blood glutathione (GSH)]. Secondary endpoints included plasma glucose and PSA levels. Compliance was high in all groups (>95%). Plasma selenium levels were increased 93%, 54%, and 86% after 9 months in SeMet and low- and high-dose SY groups, respectively, and returned to baseline levels after a 3-month washout (P < 0.05). Levels of 8-OHdG and 8-iso-PGF2α were decreased 34% and 28%, respectively, after 9 months in the high-dose SY group (P < 0.05). These decreases were greatest in individuals with low baseline plasma levels of selenium (<127 ng/mL). No changes in serum PSA or blood glucose and GSH were observed. Overall, we showed for the first time, reductions in biomarkers of oxidative stress following supplementation with SY but not SeMet in healthy men. These findings suggest that selenium-containing compounds other than SeMet may account for the decrease in oxidative stress. Cancer Prev Res; 7(8); 796–804. ©2014 AACR.

Introduction

Prostate cancer is the second leading cause of cancer-related deaths in men (1). Diet-derived agents including selenium have been shown to have chemopreventive potential against prostate cancer (2, 3). Epidemiologic and laboratory investigations have shown that dietary selenium is protective against the development of cancer at many sites including the prostate (3–7). In the Nutritional Prevention of Cancer (NPC) study (8), supplementation with selenium-enriched yeast (SY) in men was associated with an approximately 50% reduction in cancer morbidity and mortality, including a 63% decrease in prostate cancer incidence, with subjects having low baseline plasma selenium levels (<122 ng/mL) showing the greatest benefit (9). However, in the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which was designed to test the protective effects of selenomethionine (SeMet) and vitamin E individually and in combination against prostate cancer (10), no protection was observed supporting the notion that SeMet is a form of selenium which is not highly active against prostate cancer (10). This is in line with laboratory studies which have consistently demonstrated that although multiple organic forms of selenium have antitumor activity, SeMet alone was relatively inactive (11). These results suggest that although SeMet represents a major form of selenium in SY, it is not likely the form responsible for the chemopreventive properties of SY. Although results from previous studies support the chemoprotective efficacy of SY (8, 9) but not SeMet (10), no direct comparison between SY and SeMet supplementation.
in men has been reported. Direct comparisons in laboratory animals have revealed differing results. In the rat, McCormick and colleagues (12) reported the lack of protective effect of both SeMet and SY against the development of prostate cancer. In dogs, no differences were observed in tissue selenium levels or in the levels of several biomarkers of prostate epithelial DNA damage, proliferation, or apoptosis between SY and SeMet supplemented groups (13). In contrast with the above-mentioned studies, supplementation with different forms of selenium (selenite, SeMet, and SY) resulted in clear differences in gene expression profiles in mice; SY was the only form associated with a pattern of decreased DNA damage (14).

To directly compare the effects of SY and SeMet for the first time in humans, we conducted a double blind, placebo-controlled, randomized trial in healthy adult men. Our primary objectives were to determine and compare the effects of these different forms of selenium on prostate cancer relevant biomarkers including blood selenium levels and blood and urinary biomarkers of oxidative stress. A secondary objective in this trial was to determine the impact of SY and SeMet on PSA and glucose levels.

Materials and Methods

Trial design

The study (ClinicalTrials.gov: NCT01112449) was conducted with approval from the Institutional Review Boards (IRB) of the Penn State University (PSU), University Park, PA; College of Medicine and Robert Wood Johnson Medical School (New Brunswick, NJ); Recruitment, interviewing, and sample collections were performed at three sites: Penn State Hershey Cancer Institute (Hershey, PA); PSU Clinical Research Center (State College, PA), and the Cancer Institute of New Jersey, (New Brunswick, NJ). Subjects were recruited from local surrounding areas using fliers, newspaper and radio advertisements, online announcements, and word of mouth. Potentially eligible subjects as assessed by telephone prescreening were interviewed in the clinic after providing informed consent. Each subject was screened for eligibility based upon the following criteria: Healthy male nonsmokers, 20 to 79 years of age, normal serum PSA based upon the age- and race-specific cutoffs defined in the 2009 American Urological Association (AUA) Clinical Guidelines (15), no history or evidence of diabetes, prostate cancer, liver, or kidney disease, and not taking >50 μg/day selenium as a dietary supplement.

Eligible subjects were randomly assigned with equal probability using a computer-generated list prepared by the biostatistician to one of four treatment groups: Placebo (non-selenized-yeast), low-dose SY (SY200, 200 μg selenium/day), high-dose SY (SY285, 285 μg selenium/day), and SeMet (200 μg selenium/day; Fig. 1) by the investigational pharmacists. The randomization status was blinded to all others in the study except to the PSU investigational pharmacists until a patient had finished the study and until near the end of the study upon IRB approval. The dose of selenium in the SY200 and SeMet groups were selected to match those used in the NPC (8) and SELECT (10) studies, respectively. The dose of selenium in the SY285 group was selected so that the levels of SeMet would be equivalent to that in the SeMet group, based upon a SeMet concentration in SY of 70% (16). Selenium-enriched yeast (SelenoExcell) was provided by Cypress Systems, Inc.; SeMet was purchased from Sabinsa Corporation and packaged by Cypress Systems, Inc. Placebo, SeMet, and SY capsules were identical in appearance. At baseline, a structured questionnaire was administered to each subject to collect information on demographics, medical history, medications, dietary supplements, alcohol consumption, and cigarette smoking history. Study participants were remunerated with $35 per visit.

After randomization, participants were provided their respective capsules along with instructions for usage. After 3, 6, and 9 months, participants returned to the clinic to receive new and return unused capsules. At 9 months, all subjects were switched to placebo for the final 3 months of the trial (washout period). At baseline and after 3, 6, 9, and 12 months, biologic samples including blood and urine were collected and processed as described below.

Outcome measures included plasma total selenium at baseline, and 3, 9, and 12 months; blood free and protein-bound GSH and urinary 8-OHdG and 8-iso-PGF2α at baseline and 9 and 12 months. Secondary outcomes included blood glucose and serum PSA at baseline, and 3, 6, 9, and 12 months as well as selenium speciation in plasma at baseline and 9 months.

Collection and processing of biologic samples

Fasting venous blood samples were collected between 9:00 am and 3:30 pm into either plain or EDTA-containing tubes and immediately placed on ice. An aliquot of whole blood was removed from the EDTA tube for analysis of glutathione (GSH). Remaining samples were centrifuged at 4°C and resulting plasma or serum was aliquoted and immediately frozen at −80°C. Packed red cells were washed 3× in saline and stored at −80°C. Urine was placed immediately on ice, aliquoted and frozen at −80°C.

Analysis of blood and urine markers

Plasma total selenium levels were determined by atomic absorption spectrophotometry as described previously (17).

Selenium speciation in plasma. Plasma SeMet, methylselenocysteine (MSC), selenate, and selenite were analyzed by Ion Chromatography Inductively Coupled Plasma Collision Reaction Cell Mass Spectrometry by Applied Speciation and Consulting, LLC.

Glutathione and glutathionylated proteins. Total GSH (GSH and glutathione disulfide) and protein-bound GSH were analyzed as described previously (18, 19). Hemoglobin was determined by spectrophotometrically using Drabkin’s reagent (20).

8-Iso-prostaglandin-F2α (8-iso-PGF2α) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) in urine were analyzed by ELISA (Cayman Biochemical Cat. Nos. 516351 and 589320). Creatinine was determined by reaction with picrate as described previously (21).
PSA and glucose. Serum PSA was determined using the ADVIA Centaur XP Immunoassay System (Siemens Healthcare Diagnostics Inc.). Blood glucose levels were determined using an Ortho Vitros 5600 analyzer.

Statistical analysis
Comparison of plasma selenium levels at each time point between groups was performed by ANOVA with adjustment of multiple comparisons using Tukey method. Plasma levels of selenium metabolites were compared between baseline and 9 months using the Welch Two Sample $t$ test (22).

Changes in serum PSA, plasma glucose and blood GSH and protein-bound GSH and urine 8-isoprostane and 8-OHdG levels from baseline at different time points were compared between the four treatment groups using ANOVA. Changes from baseline for urinary 8-OHdG and 8-isoprostane at 9 months were compared for each treatment group by baseline plasma selenium level tertile using ANOVA.

Results

Study subject characteristics
The clinical phase of the study was conducted from May 2008 until June 2013. A total of 130 subjects were randomized, of which 69 were included in the analysis (Fig. 1). Of the 61 randomized subjects not included in the analysis, 25 discontinued intervention before completion, 8 were lost to follow-up, 25 had not completed the protocol as of June 1, 2013, and 3 were excluded from analysis due to lack of compliance (Fig. 1). The characteristics of these study participants are summarized in Table 1. All subjects were nonsmokers (nonsmoker for at least for 1 year before entry into the study) and had no history of chronic disease or high-dose antioxidant supplement usage. Subjects ranged from 23 to 78 years of age (mean $\pm$ SD = 51.1 $\pm$ 14.0 years). No significant differences were observed between subjects by age, weight, or BMI between treatment groups. A total of 70% of subjects fell within the normal to overweight categories with 30% being obese (BMI > 30).

Compliance and adverse effects
A total five of subjects (two in the placebo group, two in the SY285 group, and one in the SeMet group) were removed from protocol due to adverse events: High PSA (1, SY285 group), prostate cancer (1 in SY285 group and 1 in SeMet group), and high blood glucose levels (two in placebo group). Among the participants that completed the study, no serious adverse effects were reported regardless of arm. All potential adverse events reported were minor (e.g., headaches and colds) and none were attributed to protocol treatment. Compliance was consistently high when needed.
assessed by either pill count or patient diary entries. Percent compliance was 97.0 ± 4.7 (mean ± SD) in all subjects and did not differ between treatment arms (placebo, 95.9 ± 5.4; SY200, 97.8 ± 3.9; SY285, 96.1 ± 6.3; SeMet, 98.0 ± 3.1).

Plasma selenium levels
Plasma selenium levels were not different between groups at baseline (Fig. 2) and were consistent with those reported in the SELECT trial (10). In all selenium-treated groups, there was a progressive increase in levels from 3 to 9 months followed by a return to baseline after the 3-month washout. In the SY groups, the increases were dose dependent reaching a maximum increase above baseline of 86% in the SY285 group and 54% in the SY200 group. When comparing the change from baseline between the four groups for months 3, 9, and 12 separately, significant differences were observed between all three selenium groups and placebo (P < 0.0001) and between both the SeMet and SY285 groups and the SY200 group, respectively (P < 0.05). At 12 months, statistical differences were observed between both SeMet and SY285 groups and placebo only (P < 0.001).

Plasma selenium speciation
Selenium speciation analyses were conducted in plasma samples collected at baseline and after 9 months from a subset of subjects randomly selected from the SeMet and high-dose SY groups (n = 5 per group; Table 2). These groups were selected on the basis of the equivalent doses of SeMet. Selenite was detected in all samples, whereas, selenate and MSC levels were below the limits of detection. SeMet was not detected in baseline samples but was detected in all 9-month samples. After 9 months of supplementation, significant increases from baseline were observed for SeMet and selenite in both groups (P < 0.001). Overall, increases in SeMet and selenite could only account for 0.8% and 5.1%, respectively, of the increases observed for selenium at 9 months. Increases in SeMet levels from undetectable at baseline to 0.74 ng/mL in the SeMet group and 0.55 ng/mL in the SY285 group were not significantly different between groups. Likewise, increases in selenite levels of 166% in the SeMet group and 88% in the SY285 group were not significantly different between groups.

Biomarkers of oxidative stress
Levels of 8-iso-PGF2α in urine were measured as a biomarker of lipid peroxidation (Fig. 3A, top). A dose-responsive decrease was observed for the SY groups reaching a maximum decrease of 28% occurring in the SY285 group after 9 months (P < 0.05). Levels returned to baseline after the 3-month washout. No significant changes were observed in the SeMet, SY285, or placebo groups.

Table 1. Study subject characteristics at baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Age, y</th>
<th>Race/ethnicity</th>
<th>BMI (kg/m²)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (plain yeast)</td>
<td>18</td>
<td>48.1 ± 14.6</td>
<td>White: 17 (94%)</td>
<td>30.0 ± 4.79</td>
</tr>
<tr>
<td>SY (200 µg/d)</td>
<td>16</td>
<td>50.7 ± 16.2</td>
<td>Black: 1 (6%)</td>
<td>28.0 ± 3.20</td>
</tr>
<tr>
<td>SY (285 µg/d)</td>
<td>15</td>
<td>51.3 ± 12.0</td>
<td>Asian: 0 (0%)</td>
<td>27.8 ± 3.14</td>
</tr>
<tr>
<td>SeMet (200 µg/d)</td>
<td>20</td>
<td>54.0 ± 13.4</td>
<td>White: 17 (85%)</td>
<td>28.5 ± 3.79</td>
</tr>
</tbody>
</table>

aValues are mean ± SD (range).

Figure 2. Effect of supplementation with SeMet or SY on plasma selenium levels in adult men. Subjects were randomized to placebo (n = 18), 200 µg/day SY (n = 16), 285 µg/day SY (n = 15), or 200 µg/day SeMet (n = 20). Supplementation continued for 9 months followed by a 3-month washout. Plasma total selenium levels were assessed by atomic absorption spectrophotometry. Symbols and bars, mean and SE values, respectively. ‡, Significantly different from placebo, P < 0.0001; †, significantly different from the low-dose SY group, P < 0.005; †, significantly different from the low-dose SY group, P < 0.05.
8-OHdG levels in urine were measured as a biomarker of oxidative damage to DNA (Fig. 3A, bottom). A dose-responsive decrease was observed for the SY groups reaching a maximum decrease of 34% in the SY285 group after 9 months (P < 0.05). Levels returned to baseline after the 3-month washout. No significant changes were observed in the SeMet, SY285, and placebo groups.

### Glutathione and protein glutathionylation

Levels of free and protein-bound GSH were measured in whole blood at baseline and after 9 and 12 months (Table 3). There were no changes in either free or bound levels of GSH in any of the four study groups.

### Glucose and PSA

At baseline, all subjects had normal fasting blood glucose and serum PSA levels; no differences were observed for either glucose or PSA between groups (Table 3). In all groups, glucose and PSA levels were each unchanged during the course of the study.

### Discussion

This is the first clinical trial aimed at comparing the effects of two different forms of selenium on biomarkers that are likely to influence prostate cancer risk in men. In a randomized double-blind, placebo-controlled trial in healthy men, we have observed that SY but not SeMet (the formulation used in the largest prostate cancer chemoprevention study; ref. 10; ever conducted) was effective at reducing the levels of oxidative stress as assessed by reductions in biomarkers of lipid peroxidation (8-iso-PGF2α) and oxidative damage to DNA (8-OHdG), despite inducing similar increases in plasma selenium levels. Although the mechanisms of chemoprevention by selenium remain unclear, enhanced protection against oxidative stress is thought to be involved (23–27). Selenium supplementation in the form of sodium selenite was previously shown to decrease biomarkers of oxidative stress (lymphocyte 8-oxodG and urinary excretion 8-oxoGuo) in individuals carrying the BRCA1 mutation (28). This difference in effectiveness of SY versus SeMet in protecting against oxidative stress may, in part, help explain the results of previous trials which demonstrated the effectiveness of SY (NPC; ref. 8), but not SeMet (SELECT; ref. 10), at reducing the risk for prostate cancer. In fact SY was the only form associated with a pattern of decreased DNA damage in rodents (14).

In the present study, we observed that both SeMet and SY increased plasma selenium levels and, for SY, the increases were dose dependent. The increases observed for the SY285 group were comparable with the SeMet group, despite the total dose of selenium being 85 μg/day greater in the SY285 group. Because the dose of SeMet was the same in both the SeMet and SY285 supplements, these results suggest that SeMet is the form of selenium in yeast that is responsible for enhancing plasma total selenium levels. These results are consistent with previous findings which indicate that SeMet-containing proteins (where SeMet is incorporated nonspecifically in place of Met), the most abundant source of selenium in plasma (29–32), are the major source for the variation of selenium in plasma (33–35). Although we were not able to measure the impact of SY or SeMet on prostate selenium status, in a recent clinical study, SY supplementation was associated with a dose-dependent increase in total selenium levels in prostatic tissues that

### Table 2. Plasma selenium speciation

<table>
<thead>
<tr>
<th>Analyteb</th>
<th>Group</th>
<th>Baseline</th>
<th>9 Months</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selenium</td>
<td>SeMet</td>
<td>139 ± 7.0</td>
<td>256 ± 14.9</td>
<td>117 ± 13.2</td>
</tr>
<tr>
<td>GSH</td>
<td>SY285</td>
<td>129 ± 8.7</td>
<td>256 ± 26.9</td>
<td>128 ± 30.2</td>
</tr>
<tr>
<td>Selenite</td>
<td>SeMet</td>
<td>&lt;0.12</td>
<td>0.736 ± 0.16</td>
<td>0.616 ± 0.16</td>
</tr>
<tr>
<td>GSH</td>
<td>SY285</td>
<td>&lt;0.12</td>
<td>0.550 ± 0.07</td>
<td>0.430 ± 0.07</td>
</tr>
<tr>
<td>Selenite</td>
<td>SeMet</td>
<td>2.97 ± 0.22</td>
<td>7.90 ± 0.37</td>
<td>4.93 ± 0.42</td>
</tr>
<tr>
<td>GSH</td>
<td>SY285</td>
<td>4.47 ± 0.49</td>
<td>8.43 ± 0.32</td>
<td>3.96 ± 0.24</td>
</tr>
</tbody>
</table>

*Values are mean ± SE (n = 5).

*bSelenate and MSC concentrations were below detection limits (0.12 ng/mL for selenate and 0.16 ng/mL for MSC) in all samples.

cSignificantly different from baseline (P < 0.001).
appeared to be greater than that previously observed with SeMet (36). Collectively, these results indicate that the selenium disposition in plasma may differ from that in the target organ (prostate).

Our current finding that the impact of SY on oxidative stress biomarkers was greatest in men with low baseline plasma selenium levels are consistent with a recent report of SY supplementation in healthy men (37) and provides further support for the importance of baseline selenium in predicting the efficacy of supplementation. Epidemiologic investigations have linked low selenium intake and levels with increased risk for prostate cancer (38–40) including the recent prospective study in the Netherlands, where a strong association between toenail selenium levels and advanced prostate cancer was observed in a population with relatively low levels of selenium (6). In the NPC, the greatest protective effects were observed in individuals with low baseline selenium and no beneficial effects were observed in individuals with levels above 122 μg/L (9).

This is consistent with the present trial where optimal beneficial effects on oxidative stress biomarkers were observed in individuals in the lowest tertile for baseline plasma selenium (mean 127 ± 38, and 70.1 ± 38 mg/mg creatinine for placebo, SY200, SY285 and SeMet groups, respectively). Association of reductions in oxidative stress biomarker levels by SY with baseline selenium levels in plasma. Urinary levels of 8-iso-PGF_2α and 8-OHdG for subjects in the 285 μg/day SY group were examined by baseline plasma selenium tertile. Mean baseline plasma selenium levels (top) and mean changes in 8-OHdG (middle) and 8-iso-PGF_2α (bottom) from baseline at 9 months are reported by baseline selenium tertile. Bars, mean and SE values. Tertile baseline plasma cutpoints (mg/mL) are 127 and 138. *; Significantly different from baseline, P < 0.05.

Figure 3. Effect of supplementation with SeMet or SY on urinary biomarkers of oxidative stress in healthy men. Subjects were randomized to placebo (n = 18), 200 μg/day SY (n = 16), 285 μg/day SY (n = 15), or 200 μg/day SeMet (n = 20). Urinary levels of 8-iso-PGF_2α and 8-OHdG were determined by ELISA and corrected for urinary dilution by dividing by urinary creatinine levels, and plasma selenium, determined by atomic absorption spectrophotometry. A, urinary levels of 8-iso-PGF_2α (top) and 8-OHdG (bottom) by treatment arm. Bars represent mean change in biomarker values from baseline after 9 and 12 months with associated standard error values. Baseline values for 8-iso-PGF_2α were 199 ± 96, 180 ± 87, 217 ± 117, and 206 ± 114 mg/mg creatinine for placebo, SY200, SY285 and SeMet groups, respectively. Baseline values for 8-OHdG were 66.8 ± 22, 72.7 ± 43, 90.1 ± 38, and 70.1 ± 38 mg/mg creatinine for placebo, SY200, SY285 and SeMet groups, respectively. B, association of reductions in oxidative stress biomarker levels by SY with baseline selenium levels in plasma. Urinary levels of 8-iso-PGF_2α and 8-OHdG for subjects in the 285 μg/day SY group were examined by baseline plasma selenium tertile. Mean baseline plasma selenium levels (top) and mean changes in 8-OHdG (middle) and 8-iso-PGF_2α (bottom) from baseline at 9 months are reported by baseline selenium tertile. Bars, mean and SE values. Tertile baseline plasma cutpoints (mg/mL) are 127 and 138. *; Significantly different from baseline, P < 0.05.
are consistent with those of SELECT (42). The lack of a protective effect of SY (200 μg/day) on prostate cancer in high-risk men in the recently completed Negative Biopsy Trial may be due to the late stage of disease when intervention was started but may also reflect the relatively higher baseline levels of plasma selenium observed in this trial compared with NPC (43).

Although SeMet does not seem to be the active chemopreventive agent in SY, it is currently not known which agents may be responsible for this activity. Interest in MSC as one such agent stems from preclinical studies, which show that it is more effective than SeMet at impacting prostate cancer-related pathways in preclinical models (5). We recently identified a number of proteins that are prostate cancer-related pathways in preclinical models show that it is more effective than SeMet at impacting as one such agent stems from preclinical studies, which prevention agent in SY, it is currently not known which baseline levels of plasma selenium observed in this trial may also reflect the relatively higher high-risk men in the recently completed Negative Biopsy...
Selenium-Enriched Yeast Reduces Oxidative Stress

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