Research Article

1,4-Phenylenebis(Methylene)Selenocyanate, but Not Selenomethionine, Inhibits Androgen Receptor and Akt Signaling in Human Prostate Cancer Cells

Nicole D. Facompre¹, Karam El-Bayoumy¹, Yuan-Wan Sun¹, John T. Pinto², and Raghu Sinha¹

Abstract

The lack of treatment for worried-well patients with high-grade prostatic intraepithelial neoplasia combined with issues of recurrence and hormone resistance in prostate cancer survivors remains a major public health obstacle. The long latency of prostate cancer development provides an opportunity to intervene with agents of known mechanisms at various stages of disease progression. A number of signaling cascades have been shown to play important roles in prostate cancer development and progression, including the androgen receptor (AR) and phosphatidylinositol 3-kinase/Akt signaling pathways. Crosstalk between these two pathways is also thought to contribute to progression and hormone-refractory prostate disease. Our initial investigations show that the naturally occurring organoselenium compound selenomethionine (SM) and the synthetic 1,4-phenylenebis(methylene)selenocyanate (p-XSC) can inhibit human prostate cancer cell viability; however, in contrast to SM, p-XSC is active at physiologically relevant doses. In the current investigation, we show that p-XSC, but not an equivalent dose of SM, alters molecular targets and induces apoptosis in androgen-responsive LNCaP and androgen-independent LNCaP C4-2 human prostate cancer cells. p-XSC effectively inhibits AR expression and transcriptional activity in both cell lines. p-XSC also decreases Akt phosphorylation as well as Akt-specific phosphorylation of the AR. Inhibition of Akt, however, does not fully attenuate p-XSC–mediated down-regulation of AR activity, suggesting that inhibition of AR signaling by p-XSC does not occur solely through alterations in the phosphatidylinositol 3-kinase/Akt survival pathway. Our data suggest that p-XSC inhibits multiple signaling pathways in prostate cancer, likely accounting for the downstream effects on proliferation and apoptosis. Cancer Prev Res; 3(8); 975–84. ©2010 AACR.

Introduction

Prostate cancer is the most commonly diagnosed malignancy in men in the United States and the second leading cause of cancer-related deaths (1). Issues of recurrence and hormone resistance combined with the lack of treatment for men with high-grade prostatic intraepithelial neoplasia, a premalignant condition, present a major public health problem. Thus, mechanism-based alternative and/or adjuvant therapies and strategies for prevention and treatment are critically needed.

Diet rich in selenium, organoselenium compounds, or selenized yeast have been shown in epidemiologic and preclinical studies, as well as in some clinical intervention trials, to have a protective role against prostate cancer (reviewed in ref. 2). Perhaps the most notable and exciting evidence for the protective role of organoselenium in the form of selenized yeast emerged from a clinical study by Clark et al. (3). In contrast, preliminary data accrued from the prematurely halted Selenium and Vitamin E Cancer Prevention Trial (SELECT) that investigated the effects of selenomethionine (SM), a major component of selenized yeast, showed no effect of SM on prostate cancer rates (4). Several hypotheses have been offered that may explain the lack of effect of SM in the SELECT study (5). Considering this lack of effect, there is an even more pressing need to develop and test mechanism-based organoselenium compounds. The results of preclinical studies as well as small-scale clinical trials using various analogues of organoselenium can assist in making an informed evaluation on whether selenium supplementation would benefit (or harm) specific populations (5, 6).

Studies in prostate cancer cell lines show that the dose and form of organoselenium can determine its diverse cellular responses. For example, organoselenium can manifest its chemopreventive activity either by conversion...
to a variety of selenometabolites such as methylselenol or seleno α-keto acids and/or by incorporation into a number of antioxidant selenoproteins, namely, glutathione peroxidase and thioredoxin reductase (7). In this study, we compared the effects of two structurally distinct organoselenium compounds, naturally occurring SM and synthetic 1,4-phenylenebis(methylene)selenocyanate (p-XSC; Fig. 1A), on critical prostate cancer signaling pathways in androgen-responsive and androgen-independent human prostate cancer cells. Studies in prostate cancer cell lines have shown that SM at nonphysiologic levels can inhibit growth, induce cell cycle arrest, and alter the expression of a number of genes and proteins important for prostate cancer survival (8–11). However, limited studies in animal models of prostate cancer show SM to be largely ineffective at inhibiting tumor incidence and growth (12–14). p-XSC, which was developed in our laboratory, has been shown to be more effective than SM at inhibiting tumorigenesis in a number of preclinical animal models (15–18). We have previously shown that p-XSC is effective at inhibiting both LNCaP and LNCaP C4-2 (here onward referred to as C4-2) human prostate cancer cell growth (10, 11).

Various selenium compounds have been shown to interfere with androgen receptor (AR) signaling and phosphatidylinositol 3-kinase (PI3K)/Akt signaling in prostate cancer cells (19–25). Altered activity and crosstalk between these pathways seem to be a prominent feature of prostate cancer progression and the transition to androgen independence (26–29). However, studies aimed at determining whether selenium-mediated downregulation of androgen signaling is a result of inhibition of its crosstalk with Akt are limited. In this study, we investigated the effects of SM and p-XSC on AR and Akt signaling and explored whether crosstalk between these two pathways plays a role in the cellular responses to different forms of organoselenium.

Materials and Methods

Reagents and cell lines

SM was purchased from PharmaSe, Inc., and p-XSC was synthesized as reported previously (30). Akt inhibitor VIII was purchased from EMD Chemicals. Androgen-responsive LNCaP cells were obtained from the American Type Culture Collection and androgen-nonresponsive, and therefore androgen-independent, C4-2 cells were obtained from Dr. Warren D.W. Heston (The Lerner Research Institute, The Cleveland Clinic Foundation, Cleveland, OH).

![Fig. 1. A, structures of p-XSC and SM. B, effects of SM and p-XSC on cell viability. Cell viability was measured by MTT assay in LNCaP and C4-2 human prostate cancer cells treated with a range of doses of SM and p-XSC after 1.5 and 24 h of exposure. Results are expressed as percent of control. *, P < 0.05; **, P < 0.01; ***, P < 0.001.](image-url)
**Cell cultures and organoselenium treatments**

LNCaP cells were maintained in RPMI 1640 with 10% heat-inactivated fetal bovine serum. C4-2 cells were maintained under the same conditions but with 10% fetal bovine serum. Cells that were to be stimulated by dihydrotestosterone (DHT) were grown and treated in phenol red–free RPMI 1640 supplemented with 10% charcoal-stripped fetal bovine serum. Cells were maintained at 37°C in a humidified atmosphere of 5% CO2 and were routinely passaged when they were 70% to 80% confluent. Following incubation, cells were harvested from plates by either trypsinization or gentle scraping and washed with PBS.

Cells were plated in 10-cm dishes (10⁶ per plate) or 96-well plates (5,000 or 10,000 per well) depending on the assay, grown for 48 hours, and then treated with either SM or p-XSC. Both LNCaP and C4-2 cells were incubated in medium containing SM at doses ranging from 0 to 100 μmol/L or p-XSC at doses not exceeding 20 μmol/L. The vehicles for SM and p-XSC were saline and DMSO, respectively. Treatments were continued for 24 hours to examine the longer-term effects of these compounds on cellular processes or for a shorter exposure time of 1.5 hours to evaluate early changes in molecular targets because literature data have shown that organoselenium-mediated alterations of the AR and Akt signaling pathways can be seen as early as 1 hour after treatment (24, 31). After incubation, cells were processed for further analysis.

**Cell viability assay**

Briefly, LNCaP and C4-2 cells were plated in triplicate in 96-well plates. Following treatment for 1.5 or 24 hours with a range of doses of SM (2.5-100 μmol/L) or p-XSC (1.25-20 μmol/L), MTT assay was done as previously described to determine cell viability (11). A solution of MTT (Sigma) in phenol red–free RPMI 1640 at a final concentration of 0.5 mg/ml (50 μg total MTT/well) was added to each well and cells were incubated in the dark at 37°C for 4 hours. The MTT solution was then removed, 100 μL of DMSO were added to each well, and absorbance was read at 570 nm using a SPECTRAMax PLISS³⁸⁴ plate reader (Molecular Devices Corporation). The assay was done in triplicate and results are expressed as percent of untreated or vehicle-only control.

**Cell death ELISA**

LNCaP and C4-2 cells were plated in duplicate in 96-well plates. Following treatment for 24 hours with SM (10, 50, and 100 μmol/L) or p-XSC (2.5, 5, and 10 μmol/L), cells were assayed for the presence of cytoplasmic histone-associated DNA fragments characteristic of apoptosis using the Roche Cell Death ELISA kit according to the manufacturer's instructions. Enrichment factor values were calculated as follows: [A₄₅₀ - A₄₉₀]sample/[A₄₅₀ - A₄₉₀] control. The assay was done in triplicate and results are expressed as fold induction of apoptosis compared with untreated or vehicle-only controls.

**Immunoblotting**

Immunoblotting was done as previously described to determine changes in molecular markers (10). Briefly, LNCaP and C4-2 cells were treated with SM (5, 10, 50, and 100 μmol/L) or p-XSC (5 and 10 μmol/L) for 1.5 or 24 hours, harvested by scraping, and washed with PBS. Protein extraction was carried out using cell lysis buffer [20 mmol/L Tris (pH 7.5), 150 mmol/L NaCl, 1 mmol/L EDTA, 1 mmol/L EGTA, 1% Triton X-100, 2.5 mmol/L sodium pyrophosphate, 1 mmol/L β-glycerophosphate, 1 mmol/L Na3VO4, 1 μg/mL leupeptin] with freshly added 1 mmol/L phenylmethylsulfonyl fluoride. Equal amounts of protein (35 μg) were separated on 10% SDS-PAGE gels and transferred onto nitrocellulose membranes. Primary antibodies used at 1:1,000 dilution for immunoblotting were Akt, phospho-Akt (Ser473), cleaved poly(ADP-ribose) polymerase (PARP; Asp214), and AR from Cell Signaling Technology; phospho-AR (Ser 210) from Abcam, Inc.; and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) from Santa Cruz Biotechnology. Antimouse and antirabbit secondary antibodies (Cell Signaling) were used at a dilution of 1:3,000. Band expressions were developed using enhanced chemiluminescence reagents from Amersham and density was analyzed using VisionWorks software (UVP, Inc.). All immunoblotting experiments were repeated three times. The results are presented as representative blots from single experiments and/or in a graph form as the average of the measured band densities from three experiments.

**Quantitative real-time PCR**

Total RNA was isolated, using the TRIzol reagent (Life Technologies, Inc.), from LNCaP and C4-2 cells treated with 10 μmol/L of SM or p-XSC and that had been stimulated with the AR ligand DHT at a final concentration of 10 nmol/L to activate AR signaling. The RNA was pelleted by centrifugation, washed using 75% ethanol, and dissolved in RNase-free water. cDNA synthesis was carried out with the Superscript First Stand Synthesis System (Invitrogen) according to the manufacturer's instructions using oligo(dt) as the primer. PCR was done using the RT² SYBR Green Master Mix (Superarray Bioscience Corporation). Primers were used at a final concentration of 100 nmol/L in 25-μL PCR reactions. cDNA-negative controls were run for each target gene. GAPDH expression was determined for each sample and used to normalize the expression of the target gene. Relative expressions are depicted as percent of the normalized untreated control. The sequences of the primers were as follows: GAPDH, 5'-AAGGTCGGAGTCAACGGATTTGGT-3' (forward) and 5'-ACAAAGTGGTCGTTGAGGGCAATG-3' (reverse); PSA, 5'-GGTCTGTTGAGGGCGACGAT-3' (forward) and 5'-CTTAGGTTGAACCTGGGCCAC-3' (reverse). For PSA, thermocycling conditions were initiated with a 10-minute 95°C activation step followed by 40 cycles of 94°C for 15 seconds, 56°C for 30 seconds, and 72°C for 30 seconds. For GAPDH, thermocycling conditions were initiated with a 10-minute 95°C activation step followed by
40 cycles of 95°C for 15 seconds, 62°C for 30 seconds, and 72°C for 45 seconds. Reactions were run in duplicate and experiments were repeated three times. Relative expressions were calculated using the ΔΔCt method. The results are presented as representative raw data from single experiments and/or in a graph form as the average of the relative expressions from three experiments.

Statistics
Results were expressed as mean ± SE. Statistical significance was analyzed using either the Student t test or two-factor ANOVA. Differences were considered significant at P < 0.05.

Results
Effects of SM and p-XSC on cell viability
We investigated the effects of SM and p-XSC on cell viability by MTT assay after 1.5 and 24 hours of treatment. p-XSC (10 μmol/L) began to inhibit LNCaP and C4-2 cell viability after a short duration (1.5 hours) of treatment (Fig. 1B). SM at doses of up to 100 μmol/L showed no inhibition of LNCaP or C4-2 cell viability after 1.5 hours (Fig. 1B). At 24 hours, p-XSC dose-dependently inhibited LNCaP and C4-2 cell viability with IC50 of 7.0 and 7.6 μmol/L, respectively (Fig. 1B). However, SM still had no effect on both cell types.

Dose-response effects of SM and p-XSC on apoptosis
We investigated the effect of SM and p-XSC on apoptosis in LNCaP and C4-2 cells using Cell Death ELISA. p-XSC treatment resulted in 2.5-, 3.7-, and 5.8-fold increases in apoptosis in LNCaP cells at concentrations of 2.5, 5, and 10 μmol/L, respectively (Fig. 2A). Similarly, in C4-2 cells, p-XSC induced 2.9-, 3.5-, and 4.4-fold increases in apoptosis at concentrations of 2.5, 5, and 10 μmol/L, respectively (Fig. 2B). SM showed no induction of apoptosis in LNCaP cells at concentrations up to 100 μmol/L. SM caused a significant decrease (32%; P < 0.05) in apoptosis in C4-2 cells at the lowest dose tested (10 μmol/L) but had no effect at higher doses (50 or 100 μmol/L). We also analyzed the effects of SM and p-XSC on apoptosis by examining PARP cleavage. PARP is a major target of caspases in vivo (32, 33). Immunoblot analysis of cell lysates from LNCaP and C4-2 cells showed increased levels of cleaved PARP (Asp 214) in cells treated with 5 and 10 μmol/L p-XSC (Fig. 2A and B). LNCaP and C4-2 cells treated with doses of SM ranging from 5 to 100 μmol/L showed no detectable PARP cleavage, supporting the above finding that SM is not inducing apoptosis in these cells. No induction of PARP cleavage was seen after 1.5 hours of treatment with either p-XSC or SM in LNCaP and C4-2 cells (data not shown). Taken together, these results show that p-XSC significantly and dose-dependently induces apoptosis similarly in LNCaP and C4-2 cells and that inhibition of cell viability by p-XSC is due, at least in part, to programmed cell death.

Effects of SM and p-XSC on AR and Akt pathway proteins
To determine the effect of SM and p-XSC on AR signaling, we first examined the effects of these compounds on
AR protein levels in LNCaP and C4-2 cells. SM and p-XSC significantly reduced AR protein levels in LNCaP cells after 24 hours although p-XSC was superior to SM (Fig. 3A and B). p-XSC also significantly reduced AR protein levels in C4-2 prostate cancer cells, whereas SM showed a nonsignificant increase in AR protein expression (Fig. 3A and B).

We also investigated, by Western blot analysis, the effects of SM and p-XSC on Akt phosphorylation and phosphorylation of AR at a major Akt-specific phosphorylation site, Ser 210, in LNCaP and C4-2 cells (34). After 24 hours of treatment, both p-XSC and SM at doses of 10 μmol/L and higher reduced the levels of AR phosphorylated at Ser 210 in both cell types (data not shown). No inhibitory effects were seen in C4-2 cells treated with SM. However, this downregulation of AR phosphorylation correlated with the decreased levels of total AR protein. Therefore, we next examined AR phosphorylation after 1.5 hours of exposure. SM decreased total AR protein levels after 1.5 hours of treatment in LNCaP cells, but caused nonsignificant changes in AR and Akt phosphorylation (Fig. 3C). SM, however, dose-dependently increased AR phosphorylation in C4-2 cells at this time point (Fig. 3C). After 1.5 hours, p-XSC did not alter total AR levels in LNCaP or C4-2 cells but decreased Akt-mediated phosphorylation of the AR at Ser 210 as well as Akt phosphorylation at Ser 473 in both cell lines (Fig. 3C). These effects on Akt phosphorylation were undetectable after 24 hours of treatment with these compounds (data not shown), suggesting that alteration of the PI3K/Akt pathway may be an early event in selenium-mediated modulation of prostate cancer cell growth.
Effects of SM and p-XSC on AR activity

We examined the effects of SM and p-XSC on AR transcriptional activity by measuring the RNA expression of prostate-specific antigen (PSA), an androgen-regulated gene. p-XSC (10 μmol/L) significantly decreased PSA mRNA levels in both LNCaP and C4-2 cells (Fig. 4A and B). SM (10 μmol/L) showed no significant change in PSA expression in either LNCaP or C4-2 cells (Fig. 4A and B).

To determine whether p-XSC specifically inhibits androgen-induced PSA expression, we further compared its effects on PSA mRNA levels in unstimulated cells with those in cells stimulated with the AR ligand DHT. Inhibition of PSA expression was significantly enhanced in LNCaP cells stimulated with DHT compared with unstimulated cells (Fig. 4C), suggesting that the decrease in PSA mRNA levels is due, at least in part, to inhibition of AR transcriptional activity.

Role of Akt in p-XSC–mediated inhibition of viability and PSA in LNCaP and C4-2 cells

To determine whether the inhibition of Akt by p-XSC was contributing to the downstream effects on cell

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**Fig. 4.** Effects of SM and p-XSC on the androgen target gene PSA. PSA mRNA levels were measured by quantitative real-time PCR in LNCaP (A) and C4-2 (B) cells treated with 10 μmol/L of SM or p-XSC (1.5 h) and stimulated with 10 nmol/L DHT. The results are presented as representative raw data (fluorescence versus cycle number) from single experiments and/or in a graph form as the average of the relative expressions (normalized to GAPDH mRNA levels) from three experiments. C, PSA mRNA levels were measured in LNCaP and C4-2 cells treated with 10 μmol/L p-XSC and stimulated with DHT, and the percent inhibition (compared with untreated controls) was compared with treated cells not stimulated with DHT. *, P < 0.01; **, P < 0.001.
viability, we first treated the cells with an Akt-specific inhibitor and then exposed them to p-XSC for 1.5 hours. The inhibitor alone at a final concentration of 2 μmol/L (at which there is a dramatic inhibition of Akt phosphorylation in LNCaP and C4-2 cells) decreased the viability of LNCaP cells by less than 10% and that of C4-2 cells by about 20% (Fig. 5A). p-XSC decreased viability similarly in both untreated LNCaP cells and cells pretreated with the Akt inhibitor, suggesting that inhibition of Akt by p-XSC does not solely account for the decrease in cell viability. Inhibition of cell viability by p-XSC in C4-2 cells was slightly, albeit significantly, attenuated by pretreatment with the Akt inhibitor, suggesting a more important role for p-XSC–mediated inhibition of Akt signaling in these cells. However, it is clear that in both LNCaP and C4-2 cells, p-XSC may be inhibiting additional targets/pathways contributing to prostate cancer cell death.

To investigate whether inhibition of Akt is a factor in the downregulation of AR activity by p-XSC, we measured the effects of SM and p-XSC on PSA mRNA levels in the presence of an Akt inhibitor. LNCaP and C4-2 cells were exposed to the inhibitor and then treated with either SM or p-XSC (10 μmol/L) and subsequently with DHT to stimulate AR activity. Treatment of both LNCaP and C4-2 cells with the Akt inhibitor alone significantly decreased PSA mRNA levels, showing that Akt affects AR transcriptional activity in these cells (Fig. 5B). Results showed that inhibiting Akt signaling before exposure to p-XSC had no attenuating effect on the AR-inhibiting activity of the compound. In fact, the combination of the Akt inhibitor and p-XSC seems to enhance inhibition of PSA expression, suggesting that p-XSC may target AR signaling via mechanisms in addition to or other than Akt downregulation.

**Discussion**

In this study, we found marked differences in the responses of LNCaP and C4-2 prostate cancer cells to the structurally distinct organoselenium compounds SM and p-XSC. Comparison of the growth effects of SM and p-XSC on LNCaP and C4-2 cells highlighted the significant role that structure and dose play in mediating cellular response to organoselenium compounds. p-XSC is superior to SM at inhibiting prostate cancer cell viability. At the doses examined, only p-XSC was able to induce apoptosis, a critical cellular event in cancer prevention by selenium compounds (35). Although SM has been the supplemental form of selenium used in a handful of clinical prostate cancer trials including the most recent and largest ever conducted SELECT study, it was not able to achieve significant inhibition of LNCaP or C4-2 cells at physiologically relevant doses after 24 hours of treatment and even seemed to be protective in C4-2 cells. By contrast, p-XSC can achieve significant growth inhibition of both LNCaP and C4-2 prostate cancer cells at concentrations as low as 5 μmol/L. SM was able to downregulate AR protein levels in LNCaP cells after 24 hours of treatment, but had no effect on AR activity and therefore did not alter cell growth. It is possible that inhibition of AR by SM may be occurring at a later time point, and thus longer exposures to SM may elicit inhibitory effects on cell growth that were missed after only 24 hours of treatment. These findings underscore the importance of determining the efficacy and understanding the mechanisms of organoselenium compounds because they may possess often quite diversified functions in their ability to prevent or control prostate cancer progression.
It is increasingly evident that crosstalk between AR and other signaling pathways (e.g., PI3K/Akt) may play an important role in advanced prostate cancer. Cell viability analyses in our study showed an increased sensitivity of the C4-2 cells to an Akt-specific inhibitor, which may be due to an increased reliance of androgen-refractory cells on the PI3K/Akt pathway. To our knowledge, the potential for selenium compounds to affect the crosstalk between Akt and AR signaling has not been previously explored. Figure 6 shows our proposed scheme for p-XSC–mediated inhibition of LNCaP and C4-2 human prostate cancer cells.

AR phosphorylation by several kinases including Akt is thought to play a role in the regulation of its function (27, 34, 36). We have shown for the first time that an organo-selenium compound can downregulate Akt-specific phosphorylation of the AR, a potentially pivotal regulatory mechanism and player in androgen independence. Although p-XSC inhibited PSA expression in a manner similar to that of an Akt-specific inhibitor, inhibition of Akt before treatment with p-XSC did not attenuate the effect of p-XSC on PSA mRNA levels. This suggests that p-XSC inhibits AR activity via additional or distinct mechanisms and the inhibition of AR and Akt signaling by this agent may occur independently. We have considered the possibility that p-XSC directly inhibits AR activity. In our previous study, we showed that the covalent binding of p-XSC to cysteinyI moieties within the p50 subunit of NFκB may potentially account for its inhibition of the transcription factor (37). Organoselenium compounds can exhibit higher nucleophilicity than organosulfur (cysteinyI) moieties and thus can facilitate disruption of the charge relay system that involves zinc finger motifs (38). Selenium compounds have been shown to inhibit DNA binding and induce zinc release from DNA repair proteins (38). The DNA binding domain of the AR, which contains two zinc finger motifs each with a four-cysteine coordination site, may be a target for p-XSC.

This study compared the effects of SM and p-XSC on molecular markers at equal doses less than or equal to 10 μmol/L (which include physiologic selenium levels) though SM showed no clear inhibition of LNCaP or C4-2 cells at these concentrations. The concentrations of SM required to achieve significant inhibition are exceedingly higher than those used in the clinic. Preliminary data from our laboratory indicate differences in mechanisms of action between SM and p-XSC. For example, p-XSC causes cell cycle arrest in G1, whereas SM treatment causes cells to accumulate in G2-M, which has also been previously shown by others (39).

Our findings that p-XSC inhibits the growth of both LNCaP and C4-2 prostate cancer cells and modulates clinically relevant signaling pathways lend support for the evaluation of this agent in well-defined animal models of prostate cancer and, ultimately, for its potential use in the management of prostate cancer. Future studies may benefit from exploring the effects of organoselenium at stages beyond localized prostate cancer, as evidence supports a potential role for p-XSC and various other selenium compounds in mediating metastasis and androgen independence, events inherent to increased mortality. With the goal of increasing survivorship and
improving quality of life, investigators should consider the efficacy of organoselenium compounds in future exploration of primary or supplemental treatment options for advanced prostate cancer. However, caution should be exercised because it has been shown that high levels of serum selenium were associated with a slightly elevated risk of aggressive prostate cancer in individuals carrying a certain variant form of the superoxide dismutase (SOD2) gene (6). Clearly, not all individuals seem to benefit from selenium supplementation, and the future design of clinical trials should carefully consider the form and dose of selenium as well as the population's baseline selenium levels and their selenium-dependent genetic polymorphism.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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