Serum Selenium Level and Prostate Cancer: A Case-Control Study

Gholamreza Pourmand, Sepehr Salem, Kamran Moradi, and Mohammad Reza Nikoobakht
Urology Research Center, Sina Hospital, Medical Sciences/University of Tehran, Tehran, Iran

Parvin Tajik
Department of Epidemiology and Biostatistics, School of Public Health, Medical Sciences/University of Tehran, Tehran, Iran

Abdolrasoul Mehrsai
Urology Research Center, Sina Hospital, Medical Sciences/University of Tehran, Tehran, Iran

Selenium is a potential chemopreventive agent against prostate cancer. This study sought to evaluate and compare the serum selenium level in men with newly diagnosed prostate cancer and noncancerous patients. Between 2005 and 2006, this prospective case-control study was performed on patients referred to Sina and Imam University hospitals, Tehran, Iran; it included 62 men with clinicopathologically confirmed diagnosis of prostate cancer (case group) and 68 men with no detectable prostate cancer (normal digital rectal examination and prostate-specific antigen (PSA) level) or any other malignant disease (control group). The serum selenium level was assessed using Zeeman graphite furnace atomic absorption spectrometer (Varian Company, Australia). The mean serum selenium level in the case and control group was 66.3 ± 17.7 µg/l and 77.5 ± 22.5 µg/l, respectively (P = 0.002). Serum selenium was inversely associated with prostate cancer risk. After adjustment for age, body mass index (BMI), and smoking, the odds ratio was 0.16 and 95% confidence intervals were 0.06 to 0.47 (P trend = 0.001) comparing the highest with the lowest tertile (≥ 89.3 µg/l). No correlation was observed between serum selenium level and age, BMI, or PSA level. In conclusion, serum selenium levels in prostate cancer cases were lower than in controls, which supports the hypothesis that selenium may protect against prostate cancer.

INTRODUCTION
Prostate cancer is the most commonly diagnosed visceral cancer among men in most Western countries and the third in Iran, whereas the etiology of this disease still remains elusive. The incidence of prostate cancer and its mortality rates are remarkably different in diverse geographic regions and among various racial/ethnic populations (1–3). Generally, prostate cancer is slow growing and may not cause any symptoms until late in the disease (1,4). Although few studies have offered much insight into what the risk factors of this disease are, a growing number of researchers have found evidences suggesting that nutrients such as selenium may protect men against this cancer (4–9).

Selenium is an essential trace element occurring in a wide range of foods such as meat, seafood, grains, eggs, and so forth (6,7,10). The chemoprotective effects of selenium against a variety of malignancies have been demonstrated in animals and cell lines (11–13). The anticancer activity of selenium has been attributed to its roles in inhibiting cellular proliferation; inducing apoptosis; facilitating DNA repair by activation of p53; disruption of androgen receptor signaling; and being a key component of glutathione peroxidase, which protects cells from peroxide damage (7,13–18). Several studies have shown an inverse relation between selenium concentrations in human biologic samples (such as serum, plasma, and nails) and prostate cancer incidence and mortality (19–26). In contrast, some studies have reported no association between selenium levels and the risk of prostate cancer (27–30).

To further evaluate the possible protective effect of selenium against prostate cancer, we compared serum selenium concentration between a group of patients newly diagnosed with prostate cancer and a group of men without prostate cancer.

MATERIALS AND METHODS

Study Population
From November 2005 to December 2006, this prospective case-control study was performed in patients referring to the urology clinics of Sina and Imam University Hospitals, Tehran, Iran. The case group was consisted of 62 incidental patients who had clinicopathologically confirmed diagnosis of prostate cancer.
cancer. The control group included 68 consecutive unmatched men referred to our clinics during the same period who had no evidence of prostate cancer [normal digital rectal examination and prostate specific antigen (PSA) level] or any other malignant disease. The minimum age of control patients was 45 years. Subjects with history of supplementary selenium consumption, metabolic diseases, immunodeficiency disorder, or any previous intervention on prostate (surgery, hormonal therapy, or radiotherapy) were not included in our study.

The study was performed in accordance with the Declaration of Helsinki and subsequent revisions and approved by the ethics committee at Tehran University of Medical Sciences. Meanwhile, before the study performance, the written informed consents had been obtained from all participants.

### Data Collection

A well-trained interviewer blinded to case status visited all participants and registered the information regarding their age, body mass index (BMI), smoking habit, and family history of prostate cancer. The patients’ characteristics of each group are presented in Table 1. Furthermore, the participants were asked to estimate their usual diet up to 1 mo prior to the interview using a 37-food-item questionnaire, which was specifically designed to evaluate only frequency of the selenium-rich foods consumption in the two study groups. The PSA level was also recorded.

A serum sample, 5 ml, was taken from all participants. The serum was put in sealed containers consisting of 0.5 cc sodium citrate and kept in 4°C until the time of measuring selenium level. After making the serum smooth using 0.1% Tritonx-100 solution in a 10 ml pipette, it was diluted to 10 (vol) and modified by 100 ppm nickel nitrate solution and 0.1% nitric acid; then the selenium level of serum was measured using the graphite furnace atomic absorption spectrometer (GFAAS; Zeeman, Varian Company, Australia). All samples and standards were analyzed in duplicate. The accuracy of the procedure was evaluated by analyzing commercially available samples of lyophilized human serum sernom™ trace element serum L 1, MR4206, indicating a recommended value of 79.8 µg/l. The coefficient of variation was 5.4%.

### TABLE 1

Comparison of demographic and baseline characteristics of patients in both groups (Mean ± SD)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cancer group</th>
<th>Control group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>70.0 ± 7.6</td>
<td>68.1 ± 8.1</td>
<td>0.17&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.2 ± 2.1</td>
<td>24.3 ± 3.0</td>
<td>0.86&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum selenium level (µg/l)</td>
<td>66.3 ± 17.7</td>
<td>77.5 ± 22.5</td>
<td>&lt;0.002&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Family history of positive prostate cancer</td>
<td>2 (3.2%)</td>
<td>1 (1.5%)</td>
<td>0.60&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Smoking habit&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>0.46&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Never</td>
<td>45 (72.6%)</td>
<td>50 (73.5%)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>12 (19.4%)</td>
<td>9 (13.2%)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>5 (8.1%)</td>
<td>9 (13.2%)</td>
<td></td>
</tr>
<tr>
<td>Prostate-specific antigen (ng/ml)</td>
<td>23.9 ± 25.8</td>
<td>5.7 ± 4.4</td>
<td>&lt;0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tumor grading</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (GS&lt;sup&gt;g&lt;/sup&gt; &lt; 7)</td>
<td>17 (27.4%)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Intermediate (GS&lt;sup&gt;g&lt;/sup&gt; = 7)</td>
<td>22 (35.5%)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>High (GS&lt;sup&gt;g&lt;/sup&gt; &gt; 7)</td>
<td>23 (37.1%)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Treatment procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>24 (38.7%)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>36 (58.1%)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>2 (3.2%)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Nutritional selenium consumption</td>
<td>8.54 ± 1.84</td>
<td>8.45 ± 1.78</td>
<td>0.78&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>n = 62.<br><sup>b</sup>n = 68.<br><sup>c</sup>Independent samples t-test.<br><sup>d</sup>Fisher’s exact test.<br><sup>e</sup>Current smokers; is used to smoke cigarettes or had quit smoking for <2 years before the blood sample donation date. Former smokers; used to smoke and had quit for ≥2 years before the blood sample donation time.<br><sup>f</sup>χ<sup>2</sup> test.<br><sup>g</sup>GS = Gleason score.
**Statistical Analysis**

All the data were recorded, and statistical analysis were performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, Version 11.5) software. Continuous variables were compared between the 2 groups by independent samples t-test. Pearson’s correlation was also calculated for assessing the association of two continuous variables. Chi-square test or Fisher’s exact test were used for comparison of categorical variables between the two groups. The selenium was analyzed as tertiles of which the cut-off points were based on the distribution of the serum selenium level in controls. The effect of different parameters on the risk of prostate cancer was estimated by odds ratios (OR) and corresponding 95% confidence intervals (CI), which were derived from an unconditional logistic regression model. Based on previous knowledge, we adjusted for age, BMI, and smoking status. A value of \( P < 0.05 \) was considered significant.

**RESULTS**

The total number of 130 patients (62 cases and 68 controls) entered the study. The mean age (range) of the cases and controls was 70 yr (50–90) and 68.1 yr (47–84), respectively. Demographic and baseline characteristics of the participants are shown and compared in Table 1. There were no statistically significant differences in age, BMI, and smoking habits in the two study groups.

The mean serum selenium level (range) in case and control groups was 66.3 \( \mu \text{g/l} \) (25.5–112) and 77.5 \( \mu \text{g/l} \) (25–123.2), respectively; this difference was proved to be statistically significant \((P = 0.002)\). Binary logistic regression model was fitted with serum selenium level tertiles, age, BMI, and smoking (never, former, current) as the predictors of prostate cancer. As shown in Table 2, serum selenium level was negatively associated with the risk of prostate cancer. After adjustment for age, BMI, and smoking, the OR was 0.48 (95% CI = 0.21–1.10).

**DISCUSSION**

The findings of our study indicated that selenium concentrations, as measured in serum, were lower in cases compared to controls. This was in agreement with the previous studies (19–26), which have suggested that there is a possible inverse association between selenium and prostate cancer.

Perhaps the most persuasive evidence for a chemopreventive effect of selenium in human prostate carcinogenesis derives from the Nutritional Prevention of Cancer (NPC) trial, a randomized study to evaluate selenium supplementation (200 \( \mu \text{g/day} \)) and skin cancer prevention, which was found as a secondary end points 52% reduced risk of prostate cancer incidence \((OR = 0.48, 95\% \text{ CI} = 0.28–0.80, P \text{ trend} = 0.005)\) in 64 prostate cancer cases (19,20). Other recent results supported the prostate cancer-protection effect of selenium in human biologic samples. Yoshizawa et al. (1998) in the Health Professionals Follow-up Study, prospectively examined toenail selenium level in 181 patients with advanced prostate cancer and showed that men in the highest quintile of selenium concentration had 65% lower risk of prostate cancer \((OR = 0.35, 95\% \text{ CI} = 0.16–0.78, P \text{ trend} = 0.03)\) (21). Nomura and associates (2000), in a cohort of 249 Japanese American men, also found a decreased risk of prostate cancer in the highest quartile of serum selenium \((OR = 0.5, 95\% \text{ CI} = 0.30–0.9, P \text{ trend} = 0.02)\) (22).
uated 52 cases and 96 matched controls and reported a similar inverse association of plasma selenium levels and prostate cancer risk (OR = 0.24, 95% CI = 0.08–0.77, P trend = 0.01) (23). Vogt et al., in 2003, conducted a case-control study of prostate cancer risk in American Whites and Blacks (212 cases and 233 controls) and found protective effect of serum selenium in prostate cancer (OR = 0.71, 95% CI = 0.39–1.28, P trend = 0.11) (24). Similarly, Van den Brandt and colleagues (2003) found that baseline selenium status, which they assessed on the basis of toenail selenium content, was negatively related to subsequent diagnosis of prostate cancer (OR = 0.69, 95% CI = 0.48–0.99, P trend = 0.008) in a cohort of 1,211 men followed for 6.3 years (25). Li et al. in 2004 showed a statistically significant inverse association between prediagnostic plasma selenium levels and the risk of advanced prostate cancer when the PSA level was greater than 4 ng/ml (OR = 0.49, 95% CI = 0.28–0.86, P trend = 0.002) and also suggested that higher levels of selenium may slow prostate cancer tumor progression in 586 cases and 577 controls (26). Furthermore, in line with these studies, two recent meta-analyses of observational studies from diverse populations reported the potential effect of selenium against the development of prostate cancer (8,9). In contrast with our study and the studies mentioned above, some other reports have observed no relation between selenium levels and prostate cancer. Goodman and associates (2001) in 235 cases and 456 controls found no association between prostate cancer risk and serum selenium concentrations (OR = 1.02, 95% CI = 0.65–1.60, P trend = 0.69) in a cohort from the Carotene and Retinol Efficacy Trial (27). In 2004, Lipsky et al. evaluated 150 participants (70 cases and 80 controls) and reported toenail selenium levels may not influence prostate cancer incidence (28). Similarly, Allen and colleagues (2004) suggested that selenium concentration, as measured in nails of 300 case-control pairs, had not strongly associated with prostate cancer risk (OR = 1.24, 95% CI = 0.73–2.10, P trend = 0.58) (29). Recently, Peters et al. (2007) observed no inverse association between prediagnostic serum selenium concentration and the risk of prostate cancer in a large cohort study with 724 cases and 879 matched controls (OR = 0.84, 95% CI = 0.62–1.14, P trend = 0.70) (30). However, Peters et al. found that higher serum selenium levels may reduce prostate cancer risk in men who reported a high intake of vitamin E, in multivitamin users, and in smokers (30).

It is mentionable that this controversy will be answered by trials such as Selenium and Vitamin E Cancer Prevention Trial (SELECT) in which they assess directly the efficacy of selenium in the prevention of prostate cancer. The SELECT is an ongoing randomized trial designed to answer whether selenium and vitamin E prevent the risk of prostate cancer (31).

The serum level of selenium is different in various parts of the world; the highest and the lowest amounts are reported in Finland (41.7 µg/l) and Canada (158.3 µg/l), respectively (32–34). In a study in Iran, the mean selenium serum level in healthy adults was reported as 100.3 µg/l and in men was 102.2 ± 12 µg/l (32). Some studies have indicated that plasma selenium decreases by aging, particularly in men above the age of 70. Furthermore, prostate cancer risk increases dramatically with advancing age (23,32,35). In our study, the mean serum level of selenium was less than 80 µg/l in all participants with a mean age of around 70 years. Their low serum levels of selenium could be explained through their old age. However, our results were in contrast with the reports mentioned above.

According to the NPC trial, selenium level of 80 µg/l is considered the minimum level of selenium necessary in bloodstream for maximum production of selenoproteins such as glutathione peroxidase and others (20). There was a remarkable difference between the mentioned number and the amount obtained in the prostate cancer group of the present study (66.3 µg/l). This is while the mean serum selenium level of the control group (77.5 µg/l) is close to 80 µg/l.

Based on the findings of previous studies, as the PSA increases, the preventive effect of selenium in the progress of prostate cancer amplifies and hinders the formation of progressive cancers (26). In the present research, the serum selenium level did not demonstrate any changes in the increase of PSA within the statistical limits. The progress of the disease, which requires follow-ups for a long time, was not investigated in this research.

Some studies have reported that the prescription of selenium supplement did not affect on BMI. In addition, these studies have found no correlation between serum selenium level and the amount of BMI (20,28,29), which is in line with our findings.

Several studies have reported that the inverse association between selenium levels and risk of prostate cancer was strongest in cases with advanced disease (21,22,25–27). These findings suggest that selenium may not only be involved in incidence but may also play a role in progression of prostate cancer. However, no significant decrease in serum selenium concentrations among cases was noted with increasingly aggressive grade in our study and the Vogt et al. study (24), which might be owing to the small sample size of our study.

The role of smoking in prostate cancer is not clear. In line with our finding, most of the studies that have used incident prostate cancer cases in analysis have observed no association between smoking status and risk of prostate cancer development (21,27,36). By contrast, the selenium and prostate cancer association with smoking has been found in the other observational studies (22,24,25,30).

We decided not to match cases and controls. Matching on factors that are affected by exposure or disease can irreparably bias the study data (37). We assumed that this could be the case for age, BMI, and smoking status for which their possible confounding effect was controlled by using multivariable logistic regression model. This strategy can be considered as the strength of our study.

We realize that the study could have some limitations including its low statistical power as a result of recruiting low
number of cases and controls. Another is the possibility that the cancer might have affected the nutritional status and thereby selenium concentrations, which produces a reverse causality problem. The single assessment of serum concentrations is the other limitation. However, the concentration of selenium in a single specimen of blood has been shown to serve reasonably well as a measure for ranking participants according to the long-term selenium intake (38).

According to the findings of the present study, the nutritional selenium consumption in participants was comparable in both cancer group and control group; and no meaningful statistical difference was illustrated, thus supporting the hypothesis that the diet of Iranian people with equal socioeconomic levels is relatively similar.

Considering the fact that the prevalence of prostate cancer and the intake amount of selenium are different in various geographical regions, it was not possible to study the issue in separate geographical regions. Hence, further studies for determining serum levels in various geographical regions of the country as well as the sufficiency of selenium diet intakes are warranted.

In conclusion, we observed inverse association between serum selenium concentrations and the risk of prostate cancer in our case-control study, which supports the hypothesis that selenium may protect against prostate cancer. Moreover, the use of supplementary selenium is not recommended until the publication of the SELECT results; however, the increased consumption of available selenium-rich foods is encouraged.

ACKNOWLEDGMENTS

The authors would like to thank the nursing, secretary, and administrative staff of the Urology Research Center, Sina Hospitals, especially Dr. AR Abedi and Mrs. L. Shekapour for her excellent collaboration in the study, and also the laboratory personnel of Atomic Energy Organization of Iran, particularly Mr. M. Ahmad: —faghih for his cooperation in assessment of the serum selenium concentration. Furthermore, we would like to thank Ms. M. Tayebi for her helpful assistance in preparation of the manuscript.

REFERENCES

27. Goodman GE, Schaffer S, Bankson DD, Hughes MP, and Omenn GS: Predictors of serum selenium in cigarette smokers and the lack of association


