Advanced Prostate Cancer Risk in Relation to Toenail Selenium Levels

Milan S. Geybels, Bas A.J. Verhage, Frederik J. van Schooten, R. Alexandra Goldbohm, Piet A. van den Brandt

Background Selenium may prevent advanced prostate cancer (PCa), but most studies on this topic were conducted in populations with moderate to high selenium status. We investigated the association of toenail selenium, reflecting long-term selenium exposure, and advanced PCa risk in a population from the Netherlands where low selenium status is widespread.

Methods The analysis was conducted in the prospective Netherlands Cohort Study, which included 58 279 men aged 55 to 69 years at baseline in 1986. All cohort members completed a baseline questionnaire, and approximately 79% of participants provided toenail clippings, which were used for toenail selenium measurements using instrumental neutron activation analysis. Incident advanced PCa case subjects from the entire cohort were identified during 17.3 years of follow-up. The study employed a case–cohort design for which a random subcohort was sampled at baseline. Hazard ratios and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models. All tests were two-sided.

Results Complete toenail selenium data were available for 898 advanced (International Union Against Cancer stage III/IV) PCa case subjects and 1176 subcohort members. The average toenail selenium concentration of subcohort members was 0.550 µg/g. Toenail selenium was associated with a reduced risk of advanced PCa; adjusted hazard ratio for the highest vs lowest quintile was 0.37 (95% CI = 0.27 to 0.51; \( P_{\text{trend}} < .001 \)). For stage IV PCa, men in the highest vs lowest quintile of toenail selenium had an adjusted hazard ratio of 0.30 (95% CI = 0.21 to 0.45; \( P_{\text{trend}} < .001 \)).

Conclusions Toenail selenium was associated with a substantial decrease in risk of advanced PCa.


Selenium is an essential micronutrient that is incorporated into proteins as part of the amino acid selenocysteine and exerts important biological functions through its presence in these selenoproteins (1,2). The intake of selenium varies hugely worldwide as a result of global variations in the selenium soil content and related variability in the selenium content of foods (3,4). Although the average selenium intake is high in the United States, low selenium intake is estimated to be widespread in Europe (3,4). Selenium-containing supplements also add to these intakes, especially in the United States where dietary supplements are commonly used (4). Within the United States, however, selenium intake may vary substantially, and low selenium status may be common in certain US regions (5).

The association of selenium and prostate cancer (PCa) has been studied in a number of prospective studies, with some analyses showing an inverse association, particularly for advanced PCa, and others showing no relationship (6). Interestingly, the association has been mainly studied over a relatively narrow range of selenium, with levels from moderate to high. Most studies were conducted in populations from the United States that did not include men with low selenium status who are at higher risk of less-overt selenium deficiency (3,6). Most studies of selenium and PCa risk used blood for exposure monitoring, but selenium concentrations can also be measured in toenails (6). Although blood selenium reflects recent exposures in the order of weeks, toenail selenium reflects exposures that have occurred over 6 months to 1 year and is, therefore, ideal for monitoring long-term exposure (6,7). Three prospective studies of toenail selenium and PCa risk have been conducted, and one of these studies is a previous analysis in the Netherlands Cohort Study, which had a follow-up for incident PCa of 6.3 years (8). The analysis showed an association with a reduced risk of overall PCa and a non-statistically significant association with a reduced risk of advanced PCa. The study included only 183 advanced PCa case subjects and, therefore, had limited power to study the relationship. Also, because of the limited follow-up time in the study, the potential effect of long-term follow-up on the association could not be examined. The two other prospective studies of toenail selenium and PCa also had a small number of case subjects and a limited follow-up (6).
Despite the evidence from large prospective studies of an inverse association between selenium and PCa (6), such a relationship is not supported by the Selenium and Vitamin E Cancer Prevention Trial (SELECT) (9,10). The clinical trial among American men showed no association of selenium supplementation and PCa incidence after a median follow-up of 7 years (10). One possible explanation for the null result is the high median baseline selenium level of men in SELECT (136 µg/L) (4,11,12). In an earlier clinical trial, it was shown that selenium supplementation to men with blood selenium concentrations of more than 122 µg/L does not reduce the risk of cancer and in fact may even increase cancer risk (4,13,14).

We investigated toenail selenium levels of participants in the Netherlands Cohort Study. The study was conducted over a wide range of selenium that included low selenium. After a follow-up of 17.3 years, the analysis included 898 advanced PCa case subjects. The aim of the analysis was to investigate whether higher toenail selenium levels are associated with a decreased risk of advanced PCa.

**Methods**

**Study Population**

The Netherlands Cohort Study included 58 279 men, aged 55 to 69 years at baseline in September 1986. All cohort members completed a baseline questionnaire, and approximately 79% of participants provided toenail clippings from all toes, which were used for selenium measurements (15). Cancer case subjects were identified by annual record linkage to the Netherlands Cancer Registry and the Dutch Pathology Registry (16,17). The Netherlands Cohort Study has a case–cohort design; case subjects are derived from the entire cohort, and the person-time experience is estimated from a subcohort randomly sampled from the full cohort at baseline (n = 1688) (18). In our analysis, we excluded all case subjects with prevalent cancer other than skin cancer at baseline and men with incomplete or inconsistent dietary questionnaire data (19,20). The Netherlands Cohort Study has been approved by the institutional review boards of the TNO Nutrition and Food Research Institute and Maastricht University. Participants were informed that by returning the completed questionnaire and toenail sample they would be giving their consent to participate in a study of the etiology of cancer in relation to diet.

**Ascertainment and Classification of PCa Case Subjects**

During 17.3 years of follow-up, 3451 incident PCa case subjects were identified. In this analysis, we evaluated advanced PCa only [International Union Against Cancer (UICC) stage III/IV (21)], which was defined as T3 or T4, N+, or M1 at diagnosis (n = 1196). Stage IV (UICC) PCa is a subset of advanced PCa and was defined as stage T4, N+, or M1 at diagnosis (n = 753). A number of case subjects had missing data on tumor stage (n = 216). Baseline characteristics (eg, age, smoking, and PCa family history) were not different between case subjects with and without data on tumor stage.

**Exposure Assessment**

Selenium concentrations were measured in toenail clippings by the Reactor Institute Delft, using instrumental neutron activation analysis of the 77Se isotope. Each sample went through six cycles of 17-second irradiation at a thermal neutron flux of \(3 \times 10^{16} \text{ m}^{-2} \text{s}^{-1}\), 3-second decay, and 17-second counting at 1 cm from a 40% germanium detector. The accuracy of the analysis was checked by a certified bovine liver standard (Standard Reference Material 1577b of the US National Institute of Standards and Technology). This method and the Netherlands Cohort Study toenail selenium project have been described in more detail previously (22–24).

Toenail selenium measurements for the subcohort were carried out in 1992. In 2002, toenail selenium levels of advanced PCa case subjects diagnosed during the first 6.3 years of follow-up were determined (8). In 2011, toenail selenium levels of advanced PCa case subjects diagnosed during 6.3 to 17.3 years of follow-up were measured. In 1992, the Snelle Buizen Post facility was used for instrumental neutron activation analysis, and, since 1996, the Carbonfiber Autonomous Facility for Irradiation and Analysis facility has been used. To assess the validity and comparability of these two methods, toenail selenium levels of the same 40 subcohort members were determined in 1996 with the Carbonfiber Autonomous Facility for Irradiation and Analysis facility in addition to the original assessment with the Snelle Buizen Post facility (25). The mean selenium level assessed by the Carbonfiber Autonomous Facility for Irradiation and Analysis facility (0.552 µg/g; standard deviation [SD] = 0.05) was similar to the mean selenium level assessed by the Snelle Buizen Post facility (0.551 µg/g; SD = 0.04), with a Pearson correlation coefficient of 0.95 (P < .01) (25). It was concluded that both methods were valid and comparable.

Available toenail material from all toes was used for the selenium determination. We excluded participants who did not provide a toenail sample or had a sample with a too low sample weight (<10 mg). Baseline characteristics (eg, age, smoking, and PCa family history) were not different between men with and without toenail selenium data. Complete toenail selenium data were available for 898 advanced PCa case subjects and 1176 subcohort members.

**Statistical Analysis**

We compared average toenail selenium levels of case subjects diagnosed in different years of follow-up to evaluate the potential influence of prediagnostic cancer at baseline on toenail selenium levels. Cox proportional hazards regression was used to obtain hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between quintiles of toenail selenium and advanced PCa risk. Standard errors were estimated by using the robust Huber–White sandwich estimator to account for additional variance introduced by sampling from the cohort (18,26). Cutoff points for each quintile were based on the distribution of toenail selenium in the subcohort. P values for linear trends were calculated by using median values within toenail selenium quintiles. For the continuous analysis, we used an increment of 0.045 µg/g of toenail selenium, which is the width of the central quintile. We completed age-adjusted and multivariable models adjusted for age, first-degree family history of PCa, smoking status, duration of smoking, and frequency of smoking. We adjusted for cigarette smoking because it has been shown to be an important predictor of toenail selenium status (5,23). The proportional hazards assumption was tested using the scaled Schoenfeld residuals (27), and we found no violation of the assumption. Time on study (follow-up) was used as time scale. Results were unchanged when age instead of time on study was used as time scale.
Several other variables were considered as potential confounders, including nonoccupational physical activity, education level, body mass index, history of diabetes, long-term use of nonsteroidal anti-inflammatory drugs, black tea consumption, and intake of energy, alcohol, calcium, catechin, lycopene, red meat, and vitamin E. None of these was included in the final models, as they had little effect on the effect estimates or precision. We studied whether the association of toenail selenium and advanced PCa risk differed according to follow-up time by stratifying the follow-up time into two periods: less than 8 years and 8 or more years. Effect modification of the association between quintiles of toenail selenium and advanced PCa risk by other covariates was tested by using cross-product terms in the regression models and by examining stratum-specific hazard ratio estimates. The Wald statistic was used to test for interaction. The following variables were considered as potential effect modifiers: first-degree family history of PCa, smoking status, body mass index, black tea consumption, and dietary antioxidant score. The antioxidant score is a measure of combined intake of β-carotene, catechin, lycopene, vitamin C, and vitamin E (sum of quartile scores that range from 0 [low intake] to 3 [high intake]); it has been described in more detail previously (28). All tests were two-sided, with a P value of less than .05 considered to be statistically significant. Analyses were performed using STATA software (Release 12, STATA Corporation, College Station, TX).

Results

Case subjects and subcohort members had an average toenail selenium level of 0.527 µg/g and 0.550 µg/g, respectively. We evaluated mean toenail selenium levels of case subjects diagnosed in different years of follow-up, and we found no trend toward lower or higher levels, indicating that there was no effect of preclinical disease (Table 1). Compared with subcohort members, case subjects were more likely to have a first-degree relative affected with PCa and less likely to have a history of diabetes (Table 2).

Toenail selenium was associated with a decreased risk of advanced (stage III/IV) PCa. Adjusted hazard ratios for increasing quintiles of toenail selenium were 1.00 (referent), 0.75 (95% CI = 0.57 to 1.00), 0.59 (95% CI = 0.44 to 0.79), 0.43 (95% CI = 0.31 to 0.58), and 0.37 (95% CI = 0.27 to 0.51) (P\text{trend} < .001) (Table 3). The association was slightly more pronounced for stage IV PCa, with an adjusted hazard ratio for the highest vs lowest quintile of toenail selenium of 0.30 (95% CI = 0.21 to 0.45; P\text{trend} < .001) (Table 3).

Table 4 shows the association between quintiles of toenail selenium and risk of advanced PCa stratified by period of follow-up. Adjusted hazard ratios of advanced PCa (highest vs lowest quintile) for less than 8 years and 8 or more years of follow-up were 0.47 (95% CI = 0.30 to 0.76) and 0.31 (95% CI = 0.21 to 0.45), respectively. The different outcome was also observed for stage IV PCa. The average age at diagnosis for advanced PCa case subjects who were diagnosed after less than 8 years of follow-up and after 8 or more years of follow-up was 68.5 (SD = 4.2) and 74.5 years (SD = 4.7), respectively (not in tables). The percentage of first-degree family history of PCa was higher for men who were diagnosed after less than 8 years of follow-up (5.3%) compared with those diagnosed after 8 or more years of follow-up (2.8%). Other characteristics were not different for these case subject groups.

Table 1. Mean toenail selenium level and standard deviation of men with advanced prostate cancer, per year of follow-up, Netherlands Cohort Study, 1986 to 2003*

<table>
<thead>
<tr>
<th>Case subjects†</th>
<th>No. of case subjects</th>
<th>Toenail selenium level, µg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>All case subjects</td>
<td>898</td>
<td>0.527</td>
</tr>
<tr>
<td>1</td>
<td>21</td>
<td>0.524</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>0.530</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>0.531</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>0.538</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>0.505</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>0.542</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>0.508</td>
</tr>
<tr>
<td>8</td>
<td>76</td>
<td>0.555</td>
</tr>
<tr>
<td>9</td>
<td>68</td>
<td>0.526</td>
</tr>
<tr>
<td>10</td>
<td>77</td>
<td>0.511</td>
</tr>
<tr>
<td>11</td>
<td>77</td>
<td>0.553</td>
</tr>
<tr>
<td>12</td>
<td>65</td>
<td>0.523</td>
</tr>
<tr>
<td>13</td>
<td>54</td>
<td>0.539</td>
</tr>
<tr>
<td>14</td>
<td>54</td>
<td>0.517</td>
</tr>
<tr>
<td>15</td>
<td>56</td>
<td>0.538</td>
</tr>
<tr>
<td>16</td>
<td>56</td>
<td>0.524</td>
</tr>
<tr>
<td>17</td>
<td>56</td>
<td>0.500</td>
</tr>
<tr>
<td>18</td>
<td>15</td>
<td>0.471</td>
</tr>
</tbody>
</table>

* Advanced (International Union Against Cancer stage III/IV) prostate cancers were stage T3 or T4, N+, or M1 at diagnosis. SD = standard deviation.
† Mean toenail selenium level of subcohort members was 0.550 µg/g (SD = 0.129).
‡ The large standard deviation is the result of an extreme, but biologically plausible, observation (4.174 µg/g).

Discussion

This prospective long-term follow-up study in the Netherlands showed that toenail selenium was associated with a decreased risk of advanced PCa, with men in the highest vs the lowest quintile of toenail selenium having a 63% reduced risk.

Strengths of our study include the prospective design, population-based approach, long and nearly complete follow-up of the study population through linkage to cancer registries, and detailed data on potential confounders. We specifically evaluated advanced PCa, and our study included a large number of these case subjects. Our study was conducted over a wide range of selenium that included low selenium. We used toenail selenium for exposure monitoring, which reflects long-term selenium intake.

The study has some limitations as well. Selenium levels of study participants were determined at different points in time, and this may have introduced bias. To avoid bias by analyzing stored toenail samples at different time points, the same standard reference
material was used to check the accuracy of the neutron activation analyses over time. Another limitation is that we only measured selenium at baseline and had no repeated exposure measurements.

There have been three previous prospective analyses of toenail selenium and PCa risk. One of these studies was an earlier analysis in the Netherlands Cohort study (8). The analysis included case subjects who were diagnosed during 6.3 years of follow-up, and the relative risks of overall and advanced PCa were assessed (540 PCa case subjects; 183 advanced case subjects). The study showed that men in the highest vs lowest quintile of toenail selenium had a decreased risk of overall PCa (HR = 0.69; 95% CI = 0.48 to 0.99) and advanced PCa (HR = 0.62; 95% CI = 0.37 to 1.05). A US-based study by Helzlsouer et al. (117 case subjects and 233 control subjects) showed a hazard ratio of overall PCa of 0.38 (95% CI = 0.17 to 0.85) for men in the highest vs lowest quintile of toenail selenium (29). Advanced PCa risk was not assessed in that study. Mean toenail selenium was higher in the study by Helzlsouer et al. compared with that in the Netherlands Cohort Study (quintile medians ranging from 0.66–0.96 µg/g and 0.43–0.67 µg/g, respectively). In another US-based study of toenail selenium, Yoshizawa et al. specifically evaluated advanced PCa (30). The study included 181 advanced PCa case subjects and 181 control subjects, and toenail selenium quintile medians ranged from 0.66 to 1.14 µg/g. The authors reported an adjusted odds ratio of 0.35 (95% CI = 0.16 to 0.78) for men in the highest vs the lowest quintile of toenail selenium.

Most observational studies of selenium and PCa have used plasma/serum rather than toenails for exposure monitoring (6). Data of these studies have been pooled in a recent meta-analysis that evaluated both overall PCa (nine studies) and advanced PCa (six studies) (6). For overall PCa, the authors found a gradual reduction in risk over the plasma/serum selenium range investigated (60–170 µg/L), with an estimated relative risk at 135 and 170 µg/L of 0.85 (95% CI = 0.74 to 0.97) and 0.75 (95% CI = 0.65 to 0.86), respectively. The association was more pronounced for advanced PCa (same range of selenium), with an estimated relative risk at 135 and 170 µg/L of 0.86, respectively. Most of the pooled studies were conducted in the United States where selenium intake is often high.

Our results further support that selenium intake may be an important modifiable factor that reduces the risk of advanced PCa. We specifically evaluated advanced PCa because these cancers have a poor prognosis and are, therefore, clinically relevant. Several studies have provided evidence that the relationship between selenium and cancer may be U-shaped, with a higher risk associated with levels both below and above an optimal selenium range (4,31). The Nutritional Prevention of Cancer trial showed that selenium...
Table 3. Hazard ratio (HR) and 95% confidence interval (CI) for the association between quintiles of toenail selenium and risk of advanced prostate cancer, Netherlands Cohort Study, 1986 to 2003

<table>
<thead>
<tr>
<th>Measure</th>
<th>Quintiles of toenail selenium level, boundaries in µg/g*</th>
<th>Unit increment†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (≤0.469)</td>
<td>2 (0.469 to ≤0.515)</td>
</tr>
<tr>
<td>Person-years subcohort</td>
<td>3203</td>
<td>3283</td>
</tr>
<tr>
<td>Advanced (stage III/IV) prostate cancer§, No. case subjects</td>
<td>261</td>
<td>214</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.00</td>
<td>0.78</td>
</tr>
<tr>
<td>Multivariable-adjusted</td>
<td>1.00</td>
<td>0.75</td>
</tr>
<tr>
<td>Stage IV prostate cancer¶, No. case subjects</td>
<td>168</td>
<td>147</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.00</td>
<td>0.83</td>
</tr>
<tr>
<td>Multivariable-adjusted</td>
<td>1.00</td>
<td>0.79</td>
</tr>
</tbody>
</table>

* Divided into quintiles on the basis of the distribution among subcohort members.
† Tests for dose–response trends were performed by fitting the median toenail selenium level per quintile as a continuous variable. The tests were two-sided.
‡ Per 0.045 µg/g toenail selenium increment (width central quintile).
§ Advanced (International Union Against Cancer stage III/IV) prostate cancers were stage T3 or T4, N+, or M1 at diagnosis.
|| Adjusted for age at baseline (years), first-degree family history of prostate cancer (no, yes), smoking status (current, noncurrent), duration of smoking (years), and frequency of smoking (cigarettes/day).
¶ Stage IV (International Union Against Cancer) prostate cancers were stage T4, N+, or M1 at diagnosis.
### Table 4. Hazard ratio (HR) and 95% confidence interval (CI) for the association between quintiles of toenail selenium and risk of advanced prostate cancer, by period of follow-up, Netherlands Cohort Study, 1986 to 2003

<table>
<thead>
<tr>
<th>Measure</th>
<th>Quintiles of toenail selenium level, boundaries in µg/g*</th>
<th>Unit increment†</th>
<th>( P_{\text{trend}} )†</th>
<th>( P_{\text{trend}} )†</th>
<th>( P_{\text{trend}} )†</th>
<th>( P_{\text{trend}} )†</th>
<th>( P_{\text{trend}} )†</th>
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<tbody>
<tr>
<td>Advanced (stage III/IV) prostate cancer§</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;8 years of follow-up, No. case subjects</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.00 (0.70 to 1.04)</td>
<td>0.51 (0.34 to 0.78)</td>
<td>0.32 (0.20 to 0.50)</td>
<td>0.43 (0.28 to 0.66)</td>
<td>&lt;.001</td>
<td>0.91 (0.81 to 1.02)</td>
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</tr>
<tr>
<td>Multivariable-adjusted</td>
<td></td>
<td></td>
<td>1.00 (0.74 to 1.12)</td>
<td>0.52 (0.33 to 0.82)</td>
<td>0.32 (0.19 to 0.52)</td>
<td>0.47 (0.30 to 0.76)</td>
<td>&lt;.001</td>
</tr>
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<td>≥8 years of follow-up, No. case subjects</td>
<td>1.00 (0.79 to 1.08)</td>
<td>0.68 (0.50 to 0.94)</td>
<td>0.53 (0.38 to 0.73)</td>
<td>0.35 (0.24 to 0.50)</td>
<td>&lt;.001</td>
<td>0.88 (0.83 to 0.94)</td>
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<tr>
<td>Age-adjusted</td>
<td>1.00 (0.74 to 1.03)</td>
<td>0.62 (0.45 to 0.87)</td>
<td>0.45 (0.32 to 0.65)</td>
<td>0.31 (0.21 to 0.45)</td>
<td>&lt;.001</td>
<td>0.87 (0.81 to 0.93)</td>
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<tr>
<td>Stage IV prostate cancer¶</td>
<td></td>
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<tr>
<td>&lt;8 years of follow-up, No. case subjects</td>
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</tr>
<tr>
<td>Age-adjusted</td>
<td>1.00 (0.80 to 1.25)</td>
<td>0.58 (0.36 to 0.94)</td>
<td>0.39 (0.23 to 0.66)</td>
<td>0.46 (0.28 to 0.76)</td>
<td>&lt;.001</td>
<td>0.94 (0.81 to 1.09)</td>
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<tr>
<td>Multivariable-adjusted</td>
<td></td>
<td></td>
<td>1.00 (0.81 to 1.30)</td>
<td>0.59 (0.35 to 0.98)</td>
<td>0.39 (0.22 to 0.67)</td>
<td>0.50 (0.29 to 0.86)</td>
<td>.002</td>
</tr>
<tr>
<td>≥8 years of follow-up, No. case subjects</td>
<td>1.00 (0.81 to 1.15)</td>
<td>0.56 (0.39 to 0.82)</td>
<td>0.46 (0.31 to 0.68)</td>
<td>0.22 (0.14 to 0.35)</td>
<td>&lt;.001</td>
<td>0.95 (0.78 to 0.92)</td>
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<tr>
<td>Age-adjusted</td>
<td>1.00 (0.76 to 1.11)</td>
<td>0.51 (0.34 to 0.76)</td>
<td>0.38 (0.25 to 0.69)</td>
<td>0.20 (0.12 to 0.33)</td>
<td>&lt;.001</td>
<td>0.84 (0.76 to 0.92)</td>
<td></td>
</tr>
</tbody>
</table>

* Divided into quintiles on the basis of the distribution among subcohort members.
† Tests for dose–response trends were performed by fitting the median toenail selenium level per quintile as a continuous variable. The tests were two-sided.
‡ Per 0.045 µg/g toenail selenium increment (width central quintile).
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|| Adjusted for age at baseline (years), first-degree family history of prostate cancer (no, yes), smoking status (current, noncurrent), duration of smoking (years), and frequency of smoking (cigarettes/day).
¶ Stage IV (International Union Against Cancer) prostate cancers were stage T4, N+, or M1 at diagnosis.

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supplementation was associated with a reduced risk of total and PCa risk. The association, however, was only present among participants with baseline plasma selenium concentrations in the lowest two tertiles; those in the highest tertile (>122 μg/L) showed a non-statistically significant increase in risk (13,14). In our study, quintile medians of toenail selenium ranged from 0.43 to 0.67 μg/g. This range of toenail selenium was estimated to be equivalent to (quintile medians) 64 to 100 μg/L plasma selenium using the method described by Waters et al. (31). These estimated levels are comparable with observed plasma selenium levels reported in other epidemiological studies in the Netherlands (32–35). Based on results of the Nutritional Prevention of Cancer trial, selenium levels in our study are in the range where additional selenium is expected to be beneficial, in the proposed U-shaped curve (4,31). In addition, we observed that the association of toenail selenium and advanced PCa risk was slightly more pronounced for men diagnosed during later follow-up at an older age. Prostate cancer diagnosed at a younger age is more often related with a positive family history of PCa, and it may be that selenium is less effective for preventing this type of PCa, which may be fundamentally different from sporadic PCa (36,37). Most prior prospective studies of selenium and PCa had a follow-up time that was considerably shorter than in our study and did not include results for separate follow-up periods. Further large and long-term follow-up studies are therefore urgently needed.

Most of our study participants were smokers (either former or current), with only 13.9% of men having never smoked. A number of studies have provided evidence that the inverse association of selenium and PCa risk is particularly evident among smokers (8,38–40). This finding is biologically plausible given that selenium is an antioxidant and smoking results in increased oxidative stress (2). In a stratified analysis, we showed that toenail selenium was inversely associated with advanced PCa risk among smokers but not among never smokers, with no statistically significant interaction. The analysis included only 125 cases among never smokers, and there may be a lack of power.

Prospective studies showing evidence of an association between selenium and reduced PCa risk are not supported by SELECT (10). A number of possible explanations for these different findings have been suggested. In particular, it may be that baseline selenium levels in SELECT were too high to have an effect of further selenium supplementation on the PCa risk (4,11,12). The interquartile range of baseline serum selenium in SELECT was 122 to 152 μg/L, and prior evidence showed that subjects in this range of baseline selenium receive no benefit from selenium supplementation (4,13,14). It would, therefore, be of great interest to see SELECT results stratified by baseline selenium level. Several observational studies showed a greater effect of selenium on advanced vs nonadvanced PCa. Because of prostate-specific antigen screening practices in the United States, in SELECT, PCa was most often diagnosed at localized stages; less than 1% of men diagnosed with PCa in SELECT had stage T3 at diagnosis (10). In comparison, in the Netherlands Cohort Study, where prostate-specific antigen testing is less frequent, 34.7% of incident PCa was advanced PCa.

In conclusion, our large prospective analysis showed that higher toenail selenium was associated with a substantial decrease in risk of advanced PCa. If our results are confirmed, a prevention trial of selenium and PCa in a low-selenium population may be justified.

References


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