Selenium, Genetic Variation, and Prostate Cancer Risk: Epidemiology Reflects Back on Selenium and Vitamin E Cancer Prevention Trial

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The randomized, controlled Selenium and Vitamin E Cancer Prevention Trial (SELECT)1 found that selenium supplementation did not decrease the risk of prostate cancer, which contradicted a secondary finding from the Nutritional Prevention of Cancer (NPC) Study.2 In the wake of SELECT, we expect that many groups will report results from epidemiologic studies on selenium and prostate cancer, some of which may illuminate reasons for SELECT’s null results.

One such effort is reported in this issue of Journal of Clinical Oncology by Chan et al,3 who conducted a cross-sectional epidemiologic study of plasma selenium, an SOD2 variant, and aggressive prostate cancer in men diagnosed with clinically localized or locally advanced prostate cancer and who provided a blood specimen. They observed an unexpected positive association between plasma selenium and aggressive disease. As expected, an SOD2 variant, a substitution of alanine for valine at amino acid 16 in the antioxidant enzyme manganese superoxide dismutase, was not statistically significantly associated with aggressive disease, although the relative risks (RRs) for one or two alanine alleles were above 1.0. Two patterns emerged in the analysis of the joint association of plasma selenium and SOD2: men with low selenium and two alanine alleles had a higher risk of aggressive disease (compared with low selenium and none or one alanine alleles); high selenium seemingly protected men with two alanine alleles; and men with high selenium and none or one alanine allele had a higher risk of aggressive disease (compared with low selenium and none or one alanine allele). In light of these findings, Chan et al3 commented that their data “indicate caution against broad use of selenium supplementation for men with prostate cancer” and that “complete interpretation of results from SELECT may depend on assessment of SOD2 genotype in trial participants.”

Before discussing the broader context (related observational studies, the NPC study, and SELECT) and implications of this study, we will discuss a design feature that complicates drawing etiologic inferences—and thus implications for selenium supplementation—of the study of Chan et al3 findings on the main effects of selenium and aggressive disease in a cohort of men who do not have a diagnosis of prostate cancer at baseline, making at-risk men without prostate cancer the denominator. Table 1 illustrates several hypothetical scenarios (a subset of all possible scenarios) that could explain the higher risk of aggressive prostate cancer found by Chan et al in men with higher plasma selenium. Columns 4 to 6 involve a typical cohort of at-risk men. The cohort of cancer patients (aggressive and nonaggressive) involved in column 7 is derived from the at-risk cohort and reflects the design of Chan et al. Although all are hypothetical, the data and assumptions in Table 1 are consistent with the epidemiologic literature on nutrients and genetic variants and are not out of line with the data of Chan et al (the same can be said of the hypothetical data and assumptions in Table 2, which is discussed below). Scenario D is a plausible scenario in which the increased RR of aggressive disease (1.25) in a design similar to that of the study by Chan et al would be misleading because the true RR of aggressive disease is 0.75, as illustrated by the more informative typical cohort design. Scenarios A to D are all plausible but unknowable because of this study’s design. Differences in implication make it absolutely critical to discern the correct scenario behind the Chan et al results. The implication of hypothetical scenarios A and C—caution against taking a selenium supplement—is diametrically opposed to that of B and D—a recommendation for taking a selenium supplement. The typical cohort design for etiologic research, using at-risk individuals, enables correct implications that are not derivable from a design using cancer patients at baseline.

The design of the study by Chan et al is frequently used in clinical studies of potential biomarker associations or correlations with cancer aggressiveness, where inferences are unambiguous (barring other sources of error). This design also sometimes is used for etiologic research, but investigators should be alert to the etiologic ambiguity it raises for interpreting a positive or inverse association between an exposure and aggressive disease. Previously published studies in at-risk men may help in drawing inferences from the Chan et al findings on the main effects of selenium and SOD2 and their joint effects, which are even more challenging to interpret with a cohort of only cancer patients. Regarding associations between circulating selenium and overall prostate cancer,
most large studies found no association,4-7 whether the study involved populations with low or high selenium exposure or with or without routine prostate-specific antigen (PSA) screening (one small study did find an inverse association).8 Regarding associations between selenium levels and aggressive disease, a study of selenium content in toenails9 and some other studies,4,6 reported inverse, albeit nonlinear, associations and other studies reported no association.5,6 Regarding associations between selenium and nonaggressive disease,4,6 only the Physician’s Health Study (PHS)4 found an association, which was an inverse association8). Regarding associations between selenium and prostate cancer, however, contradicts the findings of some large studies.10-12 Although so weakly in some studies that the authors concluded no association,13,14 in studies finding a moderate association, it was present for aggressive and nonaggressive disease,10,12 but possibly was stronger for the former. The Chan et al3 results are consistent with these results10,12; if the alanine allele is more strongly positively associated with aggressive than nonaggressive disease in a typical, at-risk cohort design, then the RR of aggressive disease would be above 1.0 when using the Chan et al design (Table 2, in which the hypothetical scenario is constructed as are those in Table 1).

The PHS and another cohort study with an at-risk denominator for risk estimation11,13 found a joint association for two alanine alleles plus low selenium with a higher prostate cancer risk (compared with none or one alanine alleles and low selenium), which was more because of the etiologic ambiguity resulting from the Chan et al study design.

Large studies with a risk-estimation denominator of at-risk men suggest that the SOD2 alanine allele is positively associated with prostate cancer,10-12 although so weakly in some studies that the authors concluded no association.13,14 In studies finding a moderate association, it was present for aggressive and nonaggressive disease10,12 but possibly was stronger for the former. The Chan et al3 results are consistent with these results10,12; if the alanine allele is more strongly positively associated with aggressive than nonaggressive disease in a typical, at-risk cohort design, then the RR of aggressive disease would be above 1.0 when using the Chan et al design (Table 2, in which the hypothetical scenario is constructed as are those in Table 1).

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### Table 1. Hypothetical Scenarios Involving an At-Risk Cohort of Men That May Explain the Apparent Positive Association Made by Chan et al3 Between Higher Circulating Selenium Level and Aggressive Prostate Cancer

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Aggressive</th>
<th>Nonaggressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>↑</td>
<td>Null</td>
</tr>
<tr>
<td>B</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>C</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>D</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

**Table 2. Hypothetical Scenario Involving an At-Risk Cohort of Men That May Explain the Apparent Positive Association Made by Chan et al3 Between the Alanine Allele of SOD2 and Aggressive Prostate Cancer**

<table>
<thead>
<tr>
<th>Hypothetical True Direction of Association Between the Alanine Allele and Prostate Cancer</th>
<th>Typical Cohort Design: Denominator Is Men Without Prostate Cancer at Baseline</th>
<th>Chan et al3 Design: Denominator Is Men With Prostate Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR of Total Prostate Cancer</td>
<td>RR of Aggressive Prostate Cancer</td>
<td>RR of Nonaggressive Prostate Cancer</td>
</tr>
<tr>
<td>↑↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>(80 + 79.8)/1,000</td>
<td>(40 + 60)/1,000</td>
<td>2.00</td>
</tr>
</tbody>
</table>

Abbreviation: RR, relative risk.

*↑ signifies an increase in risk of 1.33 in the group with 2 alanine alleles. ↑↑ signifies an increase in risk of 2.0 in the group with 2 alanine alleles.*
†The cohort in this column consists of 2,000 at-risk men, half of whom are in the high-selenium group. In the low-selenium group, 100 men develop prostate cancer, 40% of which is aggressive.
‡The cohort in this column consists of the prostate cancer cases that are diagnosed in the cohort in †.
§Denominator is at-risk men without prostate cancer at baseline.
¶Denominator is at-risk men with prostate cancer at baseline.
pronounced for aggressive disease in the PHS.13 In contrast, men with high selenium had a lower risk of prostate cancer irrespective of the number of alanine alleles they carried.13 This pattern is not unique to selenium, however. An increased risk of aggressive disease was associated with two alanine alleles and low lycopene in the Health Professionals Follow-up Study (HPFS)14 and with two alanine alleles and low lycopene and low total antioxidants in the PHS.13 Regarding effects on nonaggressive disease, there was no clear interaction between antioxidant status and SOD2 genotype in the PHS,13 and it can be inferred that there was no interaction between lycopene and SOD2 genotype or that it possibly was inversely associated in the HPFS.14 The increased risk of aggressive prostate cancer in men with two alanine alleles and low selenium in the study by Chan et al13 is compatible with the results from these at-risk–denominator studies (paralleling the argument depicted in Table 2). But again, the interaction with SOD2 may not be selenium specific.

The only finding in Chan et al13 that is not compatible with the previous studies of the association between selenium and prostate cancer reviewed here1-2,4-14 is the overall increased risk of aggressive disease associated with higher circulating selenium, which was driven by men with none or one alanine allele. Possible contributors to this incompatible result were the Chan et al study design and methodologic limitations discussed by the authors (eg, lack of temporality and a small sample size for evaluating joint effects). The study population, however, had a selenium exposure (eg, distribution comparable to that in US adult men15) and outcome (eg, PSA era) similar to those in some of the other observational studies. Serum selenium in the Chan et al study was higher than in the NPC study16 but lower than in SELECT,1 and the distribution of stage/grade was likely intermediate between the NPC study (which straddled the pre-PSA and PSA era) and SELECT (PSA era, and virtually all patients had T1/T2 and Gleason ≤ 3 + 4 disease). In the NPC study, the inverse association for selenium supplementation was present for both local and advanced disease and was strongest in men with low circulating selenium.16 The null SELECT result implies no association of selenium supplementation with nonaggressive disease. Baseline selenium level associations with outcome have not been evaluated in SELECT,1 so it is unknown whether supplementation in this trial may have decreased prostate cancer risk in men with low baseline selenium, as in the NPC study, and concurrently increased the risk of overall or aggressive disease in men with high baseline selenium, as in the Chan et al study. That selenium may have opposing effects at high versus low exposures is plausible. In the NPC study, baseline plasma selenium and total cancer (all sites) risk were directly associated in the selenium supplement arm and possibly inversely associated in the placebo arm.17 Therefore, what seems to be an anomalous prostate cancer result of Chan et al warrants additional investigation.

The findings of Chan et al13 and others1,2,4-14 raise questions that may lead to an increased understanding of selenium supplementation in men at risk of prostate cancer. Did selenium supplementation in SELECT reduce the risk of total or high-grade prostate cancer in men with baseline circulating selenium levels as low as in the bottom tertile of the NPC study? Did selenium supplementation in SELECT increase the risk of total or high-grade disease in men with baseline circulating selenium levels as high as in the top quintile of the Chan et al study? If one combined across large observational studies to achieve adequate sample size for phenotype and a wider range between low and high selenium levels, would higher circulating selenium be associated with the risk of prostate cancer that is aggressive or nonaggressive as determined by stage alone, grade alone, both, and both plus PSA level? In SELECT or combined large observational studies, is the selenium effect on (or association with) prostate cancer risk beneficial, detrimental, or null in those groups of men with higher and lower exposure to other antioxidants; higher and lower production or activity of antioxidant enzymes including manganese superoxide dismutase, perhaps as measured by genotype; higher and lower exposure to oxidant sources; and with variously combined exposures to selenium, other antioxidants, antioxidant enzymes, and oxidant sources? Readers should note that the SOD2 interaction with circulating selenium in relation to prostate cancer risk was present for low lycopene and total antioxidants, not just selenium. Furthermore, manganese superoxide dismutase encoded by SOD2 is only one of a large number of antioxidant enzymes. All of these interactions deserve in-depth study. A last question, which probably cannot be resolved by data from epidemiologic studies, is whether lifelong, distant-past, or recent selenium level is critical to supplement effects on prostate cancer risk.

None of the large observational studies or trials addressed the role of selenium in preventing prostate cancer recurrence, nor did Chan et al13 despite their “caution against broad use of selenium supplementation for men with prostate cancer.” Long-term follow-up of prostate cancer patients characterized for selenium levels before, at, and after diagnosis and treatment will be required to address recurrence. Adjusting for stage and grade at diagnosis will be necessary to determine if selenium predicts recurrence independently of these two prognostic factors.

Placing the findings of Chan et al13 and SELECT in the context of the existing literature does not clarify the role of selenium in prostate cancer etiology. Nevertheless, we offer a couple of working hypotheses. Selenium supplementation does not decrease risk except possibly in selenium-deficient populations. Supplementation possibly increases risk of prostate cancer, especially aggressive disease, in selenium-replete men or men with a particular genotype for antioxidant enzymes. These hypotheses and the questions posed above suggest the need for personalized risk prediction. At present, we do not know enough to determine how much selenium any man or woman should receive from the diet or a supplement.

This lack of knowledge supports the common public health recommendation of moderation with respect to supplements for men and women. Furthermore, we should encourage men and women to eat a wide array of foods, maintain normal weight, be physically active, not smoke, and drink in moderation if at all to prevent chronic diseases in general. Unlike the prospect of personalized chemoprevention, this is not new or exciting advice, but it is common sense.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Elizabeth A. Platz, Scott M. Lippman
Data analysis and interpretation: Elizabeth A. Platz, Scott M. Lippman
Manuscript writing: Elizabeth A. Platz, Scott M. Lippman
Final approval of manuscript: Elizabeth A. Platz, Scott M. Lippman

REFERENCES

**CORRECTIONS**

**Author Correction**


In Figures 2E and 2F, the x-axes were erroneously labeled as “Time (months),” whereas they should have been labeled “Time (years).” The authors apologize to the readers for the mistakes.

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**Journal Corrections**


The second author, Scott M. Lippman, was inadvertently omitted from the author list. *Journal of Clinical Oncology* apologizes to the authors and readers for the mistake.

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In Table 3, the second-to-last column was labeled as “Range,” whereas it should have been labeled “95% CI.” Also, in the row labeled “Einhorn favorable prognosis,” the total number of patients was originally given as 19 (Yes) and 88 (No). However, because none of the patients received a favorable prognosis, the data and the accompanying footnote for “Einhorn favorable prognosis” should have been omitted from the table.

In Table A2, the second-to-last column was labeled as “Range,” whereas it should have been labeled “95% CI.” Also, in the row labeled “Einhorn favorable prognosis,” the total number of patients was originally given as 17 (Yes) and 90 (No). However, because none of the patients received a favorable prognosis, the data and the accompanying footnote for “Einhorn favorable prognosis” should have been omitted from the table.

In the Results section, under “Prognostic Factor Analysis”, the second-to-last sentence of the first paragraph was originally given as:

“Cisplatin sensitivity ($P = .52$), Einhorn “favorable prognosis” ($P = .37$), histology (seminoma v nonseminoma), and target carboplatin AUC did not have a significant impact on DFS.”

whereas it should have read:

“Cisplatin sensitivity ($P = .52$), histology (seminoma v nonseminoma), and target carboplatin AUC did not have a significant impact on DFS.”

The online version has been corrected in departure from the print. *Journal of Clinical Oncology* and the authors apologize to readers for the mistakes.

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