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Perspective

Cancer Prevention Research

Is Prostate Cancer Prevention with Selenium All in the Genes?

Perspective on Penney et al., p. 604

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Abstract

This perspective discusses how well-conducted research by Penney et al. (beginning on page 604 in this issue of the journal) contributes to the incremental uncovering of the complex association between selenium and prostate cancer. These investigators' earlier findings and current questions, approaches, and findings regarding selenium for prostate cancer prevention are discussed. This group's work raises the following important inferences: Selenium may prevent poorer-prognosis prostate cancer and its progression to bony metastases and death, but only in men with genetic backgrounds that influence the requirement for selenium. These inferences point toward how to reconcile inconsistent prostate cancer risk results from the two randomized trials of selenium conducted to date. *Cancer Prev Res; 3(5); 576–8. ©2010 AACR.*

In this issue of the journal, Penney et al. report findings from a large, well-conducted, prospective cohort study (1) that continue the incremental uncovering of the complex association between selenium and prostate cancer. As noted in a commentary of 2009, no large observational study or trial had yet investigated whether selenium might prevent prostate cancer recurrence (2). Now in 2010, Penney et al. (1) have done just that and much more.

Therefore, the Penney et al. article (1) carries great interest as we continue to try to reconcile the contradictory findings between the Selenium and Vitamin E Cancer Prevention Trial (SELECT; ref. 3) and the Nutritional Prevention of Cancer (NPC) Study (4, 5), which provided part of the motivation for the conduct of SELECT. The randomized, placebo-controlled NPC trial tested 200 μg/d of supplemental selenium for reducing the risk of recurrent skin cancer (the primary end point) and prostate and other cancers (secondary end points) in 1,312 participants living in geographic areas with low levels of selenium in the soil (4). After 6.4 years of follow-up, prostate cancer risk declined by 63%; risks of lung and colorectal cancers also declined, but the risk of recurrent skin cancer did not in the selenium arm (4, 5). Additional follow-up time and statistical analysis found that the greatest benefit occurred in men who had the lowest circulating selenium levels at baseline (5). The randomized, placebo-controlled SELECT tested 200 μg/d of supplemental selenium, alone or combined with vitamin E, for reducing the risk of prostate cancer (the primary end point) in 35,533 men. SELECT supplements were stopped early, or after about 5.5 years of a planned 12-year intervention, because of the high unlikelihood that further supplementation would change negative/neutral interim findings (3).

Investigators are seeking possible mechanistic and nonmechanistic explanations that could square these apparently disparate chemoprevention trial findings. One possible explanation is that baseline levels of selenium unlikely were as low in the men of SELECT as in NPC participants; supplementation-associated risks might differ between people with at-present and/or lifetime low versus high circulating selenium levels. An analysis restricted to men with low circulating selenium before beginning selenium supplementation has not been conducted in SELECT (3). Another possible explanation is that SELECT was conducted fully in the prostate-specific antigen (PSA) era and the majority of prostate cancers that developed were T_1/T_2 and Gleason sum ≤3+4 (3), whereas the NPC Study straddled the pre-PSA and PSA era; selenium might inhibit the development of aggressive, but not nonaggressive, prostate cancer or might inhibit the continued growth of prostate cancer later in its natural history, including microscopic, undetectable disease. The proportion of diagnosed aggressive prostate cancers is smaller in the PSA than in the pre-PSA era. The work of Penney et al. may help clarify these two possible explanations: They evaluated the association between selenium level and risk of the progression of prostate cancer after its diagnosis (and the risks of overall and aggressive prostate cancer, as discussed later), and they offer a twist on these explanations by evaluating whether the risk associations differed by variation in a gene that encodes a selenium-incorporating protein.

Penney and colleagues published three previous prospective analyses that motivated their currently reported research. Spurred by the exciting findings of the NPC Study, they reported that higher selenium in toenail clippings was associated with a lower subsequent risk of

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higher-stage and/or higher-grade prostate cancer in a case-control study nested in the Health Professionals Follow-up Study; they did not measure toenail selenium for men with lower-stage/lower-grade disease (6). Next, they conducted a case-control study nested in the Physician's Health Study (PHS), the same cohort as in the current article, finding that men with the highest circulating selenium levels had a lower risk of advanced-stage prostate cancer and that this association was stronger in men who had an elevated PSA level at the start of the study (7). (Unavailable when the study started in 1982, PSA levels were measured in stored blood.) Selenium level was not associated with localized disease. Also in the PHS, the investigators observed an interaction between variants in the gene encoding manganese superoxide dismutase (SOD2; an antioxidant enzyme that does not require selenium) and circulating selenium levels (8). Men with 1 or 2 copies of the wild-type valine allele at amino acid 16 and men with 2 copies of the variant alanine allele had a lower risk of total prostate cancer if they were in the top three quartiles of plasma selenium (versus risk in the reference group, who had 1 or 2 copies of the wild-type allele and low plasma selenium). Men with 2 copies of the variant allele who were in the bottom quartile of plasma selenium, however, had a higher risk of total prostate cancer. For aggressive prostate cancer (high stage, high grade, or fatal), the inverse association was even stronger among men with 2 copies of the variant allele and high selenium, and the positive association was even stronger among men with 2 copies of the variant allele and low selenium (8). To summarize these findings, selenium may protect against aggressive prostate cancer (i.e., disease with a poorer prognosis), but possibly only in men with certain genetic backgrounds (e.g., men with reduced antioxidant capacity).

The next logical step, which Penney et al. took via the study they presently report, was to evaluate the association between single-nucleotide polymorphisms (SNP) in *SEP15*, which encodes a selenoprotein (i.e., a protein containing the amino acid selenocysteine), and prostate cancer risk and progression. Although the function of *SEP15* is not fully characterized, investigators suspect it of influencing cancer risk because it is located in a region of chromosome 1 that often is altered in cancer, it has a reduced expression in cancer compared with normal tissue (including of the prostate), and it contributes critically to apoptosis (9). They also assessed whether the associations between plasma selenium and prostate outcomes differed by *SEP15* genotypes in men participants of the PHS, which began as a clinical trial of aspirin and β-carotene for preventing heart disease and cancer. Blood was collected at the start of PHS in 1982, and the men have been followed as a prospective cohort ever since, which has allowed for many epidemiologic studies on the etiology of chronic diseases. The investigators identified men diagnosed with prostate cancer during the trial. These cases were included in analyses of diagnosed prostate cancer progression to bony metastases or death and of prostate cancer incidence. Cases in the former analysis were followed from their date of diagnosis until the development of bony metastases, death, or the end of follow-up. Each case in the latter analysis was matched to a man who was about the same age, had the same smoking status, did not have a diagnosed prostate cancer before the trial began, and was still alive and at risk for prostate cancer when the matched case was diagnosed. For these cases and controls, the investigators measured plasma selenium and genotyped four haplotype-tagging SNPs (tagSNP) and one putative functional SNP in *SEP15* in blood samples archived in 1982.

The analysis of diagnosed prostate cancer progression to bony metastases or death was a prospective cohort study. Because blood was collected in 1982 and the men were diagnosed with prostate cancer after 1982, their plasma selenium concentrations reflect levels before the baseline for this prospective cohort analysis, which was the time of prostate cancer diagnosis; also, the time between blood draw and prostate cancer diagnosis varied from case to case.

The analysis of prostate cancer incidence was a nested case-control study. The case-control design preserves a key strength of a cohort study, temporality—that exposure information or the material used to assess exposure is collected in the months to years before case diagnosis. Nested case-control studies are more efficient than cohort studies because exposure is measured only for the sampled cases and controls. Despite measuring exposure for only a subset of the participants, the measure of association calculated in the nested case-control study, the odds ratio, is an unbiased estimate of the measure of association that would have been calculated in the cohort (the hazard ratio) when the nested controls are sampled via incidence-density sampling (also called risk-set sampling), which involves selecting as a control an individual who is still under follow-up and at risk for the outcome at the time that each case is diagnosed.

In the analysis of progression to bony metastases or death from prostate cancer, which included ~1,300 men with prostate cancer followed for a median of 10 years, Penney et al. observed that carrying 2 copies of the variant allele for three (rs479341, rs561104, and rs1407131) of the four tagSNPs and the putative functional SNP (rs5859) in *SEP15* was associated with a higher risk of progression or death, compared with carrying 0 or 1 copy of the variant allele. None of the SNPs was consistently associated with prostate cancer incidence in the ~1,300 cases versus ~1,300 matched controls. These results were internally consistent: The variant alleles for the tagSNPs that tend to be inherited along with the putative functional SNP or with each other yielded similar results for progression (positive) and for incidence (null).

Penney et al. then investigated whether the association between plasma selenium and prostate cancer risk and progression differed by *SEP15* genotypes. They evaluated this effect modification because a prior study had indicated that cells transfected with the *A* allele at position 1125 (rs5859) of *SEP15* were less responsive to increasing

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concentrations of selenium in an *in vitro* reporter assay than were cells with the *G* allele; responsiveness for the two alleles was similar, however, at depleted or low selenium levels (10). Possibly consistent with these *in vitro* results, Penney et al. found that higher plasma selenium was associated with a lower risk of prostate cancer progression in men who had 0 or 1 copy of the variant for one of the tagSNPs (rs560114) that can be inherited along with rs5859. Among men who carried 2 copies of the variant allele of rs560114, higher plasma selenium was not statistically significantly associated with progression (although the hazard ratios were above 1.0). Effect modifications by the putative functional SNP and the other tagSNPs were not reported because, it may be presumed, the variant alleles were not sufficiently prevalent to evaluate them for effect modifications. When the analysis was not stratified by rs560114 genotype, higher plasma selenium was not associated with the risk of progression. Shedding light on mechanism and extending their prior work showing interactions between *SOD2* and antioxidants including selenium (8), the investigators found that selenium, but not other antioxidants, measured in plasma interacted with rs560114 in *SEP15* for prostate cancer progression.

Considering the present analyses together with this group's prior high-caliber studies leads to the inference that selenium may prevent the development of prostate cancer with a poorer prognosis and/or may prevent the progression to bony metastases and death in men with prostate cancer, but only in men with certain genetic backgrounds that influence the requirement for selenium. Given these inferences, SELECT investigators of the mechanistic and other factors involved in the selenium-prostate cancer association might consider focusing their next steps on measuring baseline circulating selenium concentrations; genotyping participants for genes that encode selenoproteins, enzymes that require selenium for their catalytic activity, and antioxidant enzymes that do not require selenium but may compensate for low selenium in times of oxidative stress; and on following the prostate cancer cases actively for progression or at least passively for death from prostate cancer. This work may help in identifying men at risk for or diagnosed with prostate cancer who might benefit most, or would not benefit, from supplemental selenium for the prevention of prostate cancer or its progression.

Disclosure of Potential Conflicts of Interest

E.A. Platz collaborates on studies of prostate cancer, but not selenium, with some of the authors of the article by Penney et al. in this issue of the journal.

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