**Editorial**

Environmental Selenium and Cancer: Risk or Protection?


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One of the joys of epidemiology is the discovery of a new association that has not been previously reported in the literature. In this issue of Cancer Epidemiology, Biomarkers and Prevention (1), Vinceti et al. purport to have observed just such an association between malignant melanoma and exposure to selenium in drinking water from a municipal water supply in Reggio Emilia, a municipality in northern Italy. Unfortunately, the authors ignore the basic issue of the biological plausibility of the association, and either omit or misinterpret a number of articles to support their hypothesis. Thus, this study must be interpreted with extreme caution and considered only a chance association, unless additional information is uncovered that would change our basic understanding of the nutritional essentiality of selenium.

The stated motivation for conducting the study was "a moderate imprecisely measured increased risk of melanoma" in the Nurses Health Cohort and "an increase in mortality from cancer of certain sites, including melanoma" in Reggio Emilia. The 63 nurses in the Nurses Health Cohort with a diagnosis of malignant melanoma had a nonsignificant (P = 0.10) 5% higher toenail selenium level than controls (0.886 versus 0.844 µg/g; Ref. 2). Our previous review of this study identified a number of methodological issues limiting its interpretability; in addition, no adjustment was made for the multiplicity of end points tested, which affects the interpretation of any site-specific P values (3). Regarding the stated excess mortality from melanoma in Reggio Emilia, surprisingly the excess is limited to males in the referenced abstract, and consists of only one case in an earlier publication of cancer mortality rates in Reggio Emilia (4). Furthermore, the authors’ literature review overlooks an earlier case-control study of selenium and melanoma in Germany, a region with a selenium status similar to that of Italy (5). This study with 101 cases observed a significant inverse association with serum selenium levels. The association was the strongest with low selenium levels for lentigo maligna melanoma and superficial spreading melanoma, tumors with typically small initial tumor mass. Although we have previously discussed the limitations of case-control studies of selenium and cancer (6), these issues are less applicable to malignant melanomas with their initially small tumor mass than to other types of cancer. Thus, the prior epidemiological literature does not provide a strong suggestion of an increased risk for malignant melanoma with enhanced selenium status.

The issue of biological plausibility is central and essential to the proper interpretation of this study. Three aspects of this question need to be addressed: (a) is it plausible that an intake of selenium that increases the activity of the selenium-dependent enzyme GSH-Px² and other selenoproteins could have adverse effects? (b) does exposure to inorganic forms of selenium confer a different risk than organic forms? and (c) do Italians respond differently from other populations in their response to increased selenium intake?

First, there is a large body of literature that describes the response of GSH-Px, a component of the cellular antioxidant system, to selenium status. There is a clear dose-response relationship between selenium status measured by intake or biological levels of selenium, and the activity of GSH-Px. The strong linear phase of this association plateaus at blood selenium levels of approximately 100 µg/d, well above the average intake of either the "exposed" or control population in Reggio Emilia.

Selenium, the form of selenium in excess in the water supply of Reggio Emilia, is the further oxidized form of selenide and is known to undergo thiol-dependent reduction to selenide (7) before being incorporated into SeCys in the synthesis of the specific selenium-proteins (8) or being methylated to a variety of excretion products (7). Thomson et al. (9) showed that 200 µg/d of either a high selenium yeast or sodium selenate produced similar levels of GSH-Px activity in both plasma and whole blood in New Zealand women. The activity of two other biologically important selenium-containing proteins, selenoprotein P and thioredoxin reductase, have a similar response to selenium status and would not be maximized at the reported intake of this study population. Selenoprotein P and thioredoxin reductase are involved in the cellular antioxidant system and cell cycling, respectively. A biological model that would be consistent with both the known activity of these selenoproteins and the results of the study by Vinceti et al. would be complex, difficult to construct, and even more difficult to interpret.

Recently, Rafferty et al. (10) showed that both inorganic sodium selenite and organic selenomethionine protected melanocytes from UVB-induced cell death. These results indicate that the effects of inorganic and organic forms of selenium on melanocytes are similar, although the optimal concentration varies. The absence of specific information on the selenium status of cases in the investigation by Vinceti et al. significantly weakens the interpretability of the observed association, as data

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² The abbreviation used is: GSH-Px, glutathione peroxidase.
were not presented to indicate whether the cases actually had higher selenium intakes than controls.

Recent clinical trials (11, 12) support the extensive animal evidence that enhanced selenium intake reduces cancer incidence. Our previously reported cancer prevention trial observed a significant 37% reduction in total cancer incidence, excluding nonmelanoma skin cancer, and eight cases of melanoma occurred in each treatment group. Of particular relevance to the issue of the health benefits of supplemental selenium in Italians are the recently presented results of a colorectal adenoma prevention trial in Genoa. It observed a 46% reduction in the incidence of new adenomatous polyps in patients assigned to receive a nutritional supplement containing 200 μg of selenium (13). In China, a controlled clinical trial using a supplement of 50 μg of sodium selenate, in combination with 25 other vitamins and minerals, resulted in a nonsignificant, 4% lower cancer mortality rate (14). This dose of selenate is similar to the reported excess intake of the exposed cohort in the study by Vinceti et al.; making it unlikely that this dose of selenium has important detrimental effects.

Because the results of our previous cancer prevention trial require confirmation before public health recommendations can be made, we have proposed conducting a large general population cancer prevention trial to definitively test the selenium and cancer hypothesis. Together with leading investigators from six countries (the United States, Denmark, Finland, Holland, Sweden, and the United Kingdom), we have designed the PRECISE trial, Prevention of Cancer with Selenium in Europe and America. As presently designed, the trial would randomize 52,500 subjects to either a placebo or a dose of 100, 200, or 300 μg of selenium/day. It would have the statistical power to detect a 10% change in total cancer incidence and would provide the most definitive information available on the health benefits and safety of enhanced selenium status.

How should the study of Vinceti et al. be interpreted given the large literature on the beneficial health effects of selenium in both animals and humans? Certainly there is a strong statistical association in this study; however, the likelihood of this association being a biological rather than a random effect is exceedingly small given our present knowledge of the essentiality of selenium in human and animal nutrition. The results of clinical trials will ultimately provide the best evaluation of the most optimal intake of selenium to promote human health.

References
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