Editorial

See corresponding article on page 406.

# More results but no clear conclusion on selenium and cancer

*Marco Vinceti*[1,2]* *and Kenneth J Rothman*[2,3]

[1]Environmental, Genetic, and Nutritional Epidemiology Research Center (CREAGEN), University of Modena and Reggio Emilia, Modena, Italy; [2]Department of Epidemiology, Boston University School of Public Health, Boston, MA; and [3]RTI Health Solutions, Research Triangle Institute, Research Triangle Park, NC

In this issue of the Journal, Hughes et al. (1) present findings from the well-known EPIC (European Prospective Investigation into Cancer and Nutrition) study that show an increased risk of hepatocellular carcinoma, gallbladder, and biliary tract cancer among those with low serum concentrations of selenium and selenoprotein P (SePP). The authors suggest that the next step ought to be the initiation of randomized field trials in Western Europe of dietary selenium supplementation to reduce the risk of hepatobiliary cancer.

The EPIC study has many strengths, and the results of this new analysis need to be reckoned with. Nonetheless, it is disappointing to see such an august group of investigators present an epidemiologic analysis that incorporates methods that have long been considered inappropriate or suboptimal, such as comparing mean levels of exposure between cases and controls or evaluating statistical interaction (by using product terms in a multiplicative model) instead of biological interaction. Another problem is the lamentable emphasis on whether the associations reported were significant, rather than focusing on their magnitude (2–4). Because they categorized results according to what was significant and what was not, their findings appear to be less internally consistent than they actually are.

Despite these drawbacks, it is clear that Hughes et al. found a moderately strong, inverse association between these cancer sites and both selenium and SePP. Are these associations causal? These findings are the latest in an array of results on selenium and cancer, from trials and nonexperimental epidemiologic studies, that indicate associations both large and small, positive and negative (5). The most recently reported trials indicate no effect or even an excess risk (6). The divergence of results seems to be more than just the play of chance, and calls for an explanation (7). One possibility is uncontrolled confounding. It seems likely that the complicated multicollinearity among dietary nutrients and other variables, such as toxic chemicals, cannot be fully controlled with multivariable models (8, 9). Furthermore, it appears that the confounding problem is more difficult to disentangle for cancer than for cardiovascular disease or diabetes (10). Inadequate control for lifestyle factors, such as smoking, may also be a relevant issue in selenium research, as recently suggested by an elegant study by Beane Freeman et al. (11), which showed that confounding from smoking intensity or duration could explain the inverse association between selenium status and bladder cancer found in some observational studies. The reported association was not seen in a randomized trial (5, 6).

It is worth noting the discrepancy between results from the study by Hughes et al. and the evidence from "low bias" intervention studies, such as those reviewed in Vincenti et al. (5), and specifically that of the Eastern Cooperative Oncology Group (ECOG) 5597, carried out in patients with resected stage I non–small-cell lung cancer (12). In that study, 6 new cases of liver, gallbladder, or bile duct neoplasms were found among 1040 selenium-treated subjects compared with none among the 521 placebo-control individuals. Another limitation of the study by Hughes et al.—one that is shared by most nonexperimental studies on dietary selenium—is the lack of information about selenium speciation. There is growing awareness of the vastly different nutritional and toxicologic effects of the various chemical species of this metalloid (6), mirroring what is currently known about the role of selenoproteins in both preventing and promoting cancer (13).

Given this background, no matter how much weight we assign the present findings, when they are coupled with the existing literature it is a stretch to infer a straightforward causal connection as an explanation for the observed associations. Nevertheless, let us suppose that selenium and SePP do have a causal role in the occurrence of hepatobiliary cancers. Would it then be reasonable to undertake randomized field trials of selenium supplements as a next step, as suggested by Hughes et al.? The cost of a properly conducted randomized field trial is enormous, even for high-incidence endpoints such as prostate cancer, as exemplified by the SELECT (Selenium and Vitamin E Cancer Prevention Trial) study (14), which cost ~$114 million. That study involved >35,000 participants in selenium, vitamin E, and placebo arms, whereas a study planned to discern a 25% decrease in risk of hepatobiliary cancer with conventional power would require on the order of 180,000 participants followed for 10 y, and thus would be so costly as to be infeasible. Furthermore, intervention studies (5, 6) and a natural experiment (15) have pointed to a large array of possible toxic effects of even low-dose chronic overexposure to selenium. These effects include high-grade prostate

*To whom correspondence should be addressed. E-mail: marco.vinceti@unimore.it.

First published online July 13, 2016; doi: 10.3945/ajcn.116.139469.

cancer, type 2 diabetes, and amyotrophic lateral sclerosis (6). The possibility of these adverse effects raises worrisome ethical questions about long-term administration of selenium to humans.

Thus, despite the renewed interest in selenium raised by this provocative report, the results should be considered critically and skeptically before raising expectations of a meaningful benefit from selenium supplements. We need to remind ourselves of the divergent literature, the complex relation between selenium species and human diseases (16), and the disappointment that resulted when intervention studies deflated the hope raised by earlier epidemiologic studies that selenium would reduce the risk of several other cancers (6, 7).

Neither of the authors declared a conflict of interest.

## REFERENCES

1. Hughes DJ, Duarte-Salles T, Hybsier S, Trichopoulou A, Stepien M, Aleksandrova K, Overvad K, Tjønneland A, Olsen A, Affret A, et al. Prediagnostic selenium status and hepatobiliary cancer risk in the European Prospective Investigation into Cancer and Nutrition cohort. Am J Clin Nutr 2016;104:406–14.
2. Greenland S, Senn SJ, Rothman KJ, Carlin JB, Poole C, Goodman SN, Altman DG. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. Eur J Epidemiol 2016;31:337–50.
3. Rothman KJ. Disengaging from statistical significance. Eur J Epidemiol 2016;31:443–4.
4. Wasserstein RL, Lazar NA. The ASA's statement on p-values: context, process, and purpose. Am Stat 2016;70:129–33.
5. Vinceti M, Dennert G, Crespi CM, Zwahlen M, Brinkman M, Zeegers MP, Horneber M, D'Amico R, Del Giovane C. Selenium for preventing cancer. Cochrane Database Syst Rev 2014;3:CD005195.
6. Jablonska E, Vinceti M. Selenium and human health: witnessing a Copernican revolution? J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 2015;33:328–68.
7. Vinceti M, Crespi CM, Malagoli C, Del Giovane C, Krogh V. Friend or foe? The current epidemiologic evidence on selenium and human cancer risk. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 2013;31:305–41.
8. Freudenheim JL. Study design and hypothesis testing: issues in the evaluation of evidence from research in nutritional epidemiology. Am J Clin Nutr 1999;69(Suppl):1315S–21S.
9. Sempos CT, Liu K, Ernst ND. Food and nutrient exposures: what to consider when evaluating epidemiologic evidence. Am J Clin Nutr 1999; 69(Suppl):1330S–8S.
10. Potter JD. Nutritional epidemiology—there's life in the old dog yet! Cancer Epidemiol Biomarkers Prev 2015;24:323–30.
11. Beane Freeman LE, Karagas MR, Baris D, Schwenn M, Johnson AT, Colt JS, Jackson B, Hosain GM, Cantor KP, Silverman DT. Is the inverse association between selenium and bladder cancer due to confounding by smoking? Am J Epidemiol 2015;181:488–95.
12. Karp DD, Lee SJ, Keller SM, Wright GS, Aisner S, Belinsky SA, Johnson DH, Johnston MR, Goodman G, Clamon G, et al. Randomized, double-blind, placebo-controlled, phase III chemoprevention trial of selenium supplementation in patients with resected stage I non-small-cell lung cancer: ECOG 5597. J Clin Oncol 2013;31:4179–87.
13. Hatfield D, Carlson BA, Tsuji P, Tobe R, Gladyshev VN. Selenium and cancer. In: Collins JF, editor. Molecular, genetic, and nutritional aspects of major and trace minerals. Academic Press, Elsevier. In press.
14. Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, Parnes HL, Minasian LM, Gaziano JM, Hartline JA, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2009;301:39–51.
15. Vinceti M, Ballotari P, Steinmaus C, Malagoli C, Luberto F, Malavolti M, Giorgi Rossi P. Long-term mortality patterns in a residential cohort exposed to inorganic selenium in drinking water. Environ Res 2016;150: 348–56.
16. Vinceti M, Burlingame B, Fillippini T, Naska A, Bargellini A, Borella P. The epidemiology of selenium and human health. In: Hatfield D, Schweizer U, Gladyshev VN, editors. Selenium: its molecular biology and role in human health. 4th ed. New York: Springer Science+Business Media; 2016. In press.