

Online article and related content current as of May 13, 2009.

Selenium and Vitamin E Supplementation for Cancer Prevention

Margaret P. Rayman; Gerald F. Combs, Jr; David J. Waters

JAMA. 2009;301(18):1876 (doi:10.1001/jama.2009.625)

LETTERS

Selenium and Vitamin E Supplementation for Cancer Prevention

To the Editor: The Selenium and Vitamin E Cancer Prevention Trial (SELECT) by Dr Lippman and colleagues¹ reported that selenium or vitamin E alone or in combination did not prevent prostate cancer. The negative results of this trial confirm the outcomes in the Nutritional Prevention of Cancer (NPC) Trial for those participants with the highest baseline plasma selenium concentration prior to supplementation with selenized yeast.² The conclusion from both NPC and SELECT should be that daily selenium supplementation will not benefit all persons. Cancer risk reduction with selenium should be expected only in men with low or suboptimal levels prior to supplementation.

A U-shaped dose-response relationship between selenium intake and cancer risk, as suggested by studies in dogs,³ is consistent with the results of SELECT and NPC. At baseline, the average participant in SELECT had selenium status within the trough of the U-shaped curve, ie, not low or suboptimal. After supplementation with 200 µg per day of selenium as selenomethionine, the average SELECT participant achieved selenium levels that far exceeded the high postsupplementation values of men in NPC in the highest baseline-selenium tertile. Those NPC participants experienced no prostate-cancer risk reduction and an almost 3-fold increased incidence of diabetes.^{2,4} In SELECT, there was no reduction in prostate-cancer risk and a statistically nonsignificant increased diabetes incidence. We therefore consider the results of SELECT and NPC to be consistent, not contradictory.

We believe that it is time to move beyond the belief that any particular agent administered at the same dose to all participants will benefit the overall population and instead attempt to individualize cancer prevention.³ Subsets of individuals should be identified who are more likely to benefit from supplementation, such as persons with low selenium concentrations or perhaps those with the selenoprotein-P genotype that is associated with prostate-cancer risk.⁵ This stance is distinct from claiming knowledge of which types of cancer will or will not be prevented by selenium.

Margaret P. Rayman, DPhil m.rayman@surrey.ac.uk Faculty of Health and Medical Sciences University of Surrey Guildford, United Kingdom Gerald F. Combs Jr, PhD Grand Forks Human Nutrition Research Center Agricultural Research Service US Department of Agriculture Grand Forks, North Dakota David J. Waters, PhD, DVM Purdue University Center on Aging and the Life Course West Lafayette, Indiana

Financial Disclosures: Dr Rayman reported receiving grant support from Wassen International, a manufacturer of nutritional supplements, including selenium. Dr Waters reported that he is director of the Murphy Cancer Foundation, a not-forprofit research institute that, in collaboration with Bostwick Laboratories, markets a toenail test for selenium. Dr Waters reported that he has no financial interest in Bostwick Laboratories and no financial relationships with any manufacturers of selenium supplements. Dr Combs reported no disclosures.

- 1. Lippman SM, Klein EA, Goodman PJ, 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(1):39-51.
- 2. Duffield-Lillico AJ, Reid ME, Turnbull BW, et al. Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial. *Cancer Epidemiol Biomarkers Prev.* 2002;11(7):630-639.
- **3.** Waters DJ, Chiang EC, Bostwick DG. The art of casting nets: fishing for the prize of personalized cancer prevention. *Nutr Cancer*. 2008;60(1):1-6.
- 4. Stranges S, Marshall JR, Natarajan R, et al. Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. *Ann Intern Med*. 2007;147(4):217-223.
- **5.** Cooper ML, Adami HO, Grönberg H, Wiklund F, Green FR, Rayman MP. Interaction between single nucleotide polymorphisms in selenoprotein P and mitochondrial superoxide dismutase determines prostate cancer risk. *Cancer Res.* 2008; 68(24):10171-10177.

To the Editor: Dr Lippman and colleagues¹ concluded that "selenium, vitamin E, or selenium + vitamin E (at the tested doses and formulations) did not prevent prostate cancer." We believe that this statement is potentially misleading because the data relate to the effects of *L*-selenomethionine supplementation only in a selenium-replete population. The effects of selenium are species specific, with some forms of selenium having greater anticancer benefit than others,² so the null effect of *L*-selenomethionine supplementation on prostate cancer risk should not be applied to selenium in general.

In addition, the effects are dependent not only on the dose and form of selenium but on the initial baseline selenium status of the population. In a previous study, selenium supplementation was only effective against prostate cancer in volunteers (with a previous history of skin cancer) whose plasma selenium was less than $120 \, \mu g/L$ (to convert to $\mu mol/L$, mul-

GUIDELINES FOR LETTERS. Letters discussing a recent *JAMA* article will have the best chance of acceptance if they are received within 4 weeks of the article's publication date. Letters may have no more than 3 authors. They should not exceed 400 words of text and 5 references. Letters reporting original research should not exceed 600 words and 6 references. They may have no more than 5 authors. All letters should include a word count. Letters must not duplicate other material published or submitted for publication. Letters will be published at the discretion of the editors and are subject to editing and abridgment. A signed statement for authorship criteria and responsibility, financial disclosure, copyright transfer, and acknowledgment is required for publication. Letters not meeting these specifications are generally not considered. Before submitting a Research Letter, please review the Instructions for Authors (http://jama.com/instructions). Letters should be submitted via the *JAMA* online submission and review system at http://manuscripts.jama.com (note: do not include "www" before the URL). For technical assistance, please contact jama-letters@jama-archives.org.

Letters Section Editor: Robert M. Golub, MD, Senior Editor.

Selenium and Vitamin E Supplementation for Cancer Prevention

To the Editor: The Selenium and Vitamin E Cancer Prevention Trial (SELECT) by Dr Lippman and colleagues¹ reported that selenium or vitamin E alone or in combination did not prevent prostate cancer. The negative results of this trial confirm the outcomes in the Nutritional Prevention of Cancer (NPC) Trial for those participants with the highest baseline plasma selenium concentration prior to supplementation with selenized yeast.² The conclusion from both NPC and SELECT should be that daily selenium supplementation will not benefit all persons. Cancer risk reduction with selenium should be expected only in men with low or suboptimal levels prior to supplementation.

A U-shaped dose-response relationship between selenium intake and cancer risk, as suggested by studies in dogs,³ is consistent with the results of SELECT and NPC. At baseline, the average participant in SELECT had selenium status within the trough of the U-shaped curve, ie, not low or suboptimal. After supplementation with 200 µg per day of selenium as selenomethionine, the average SELECT participant achieved selenium levels that far exceeded the high postsupplementation values of men in NPC in the highest baseline-selenium tertile. Those NPC participants experienced no prostate-cancer risk reduction and an almost 3-fold increased incidence of diabetes.^{2,4} In SELECT, there was no reduction in prostate-cancer risk and a statistically nonsignificant increased diabetes incidence. We therefore consider the results of SELECT and NPC to be consistent, not contradictory.

We believe that it is time to move beyond the belief that any particular agent administered at the same dose to all participants will benefit the overall population and instead attempt to individualize cancer prevention.³ Subsets of individuals should be identified who are more likely to benefit from supplementation, such as persons with low selenium concentrations or perhaps those with the selenoprotein-P genotype that is associated with prostate-cancer risk.⁵ This stance is distinct from claiming knowledge of which types of cancer will or will not be prevented by selenium.

Margaret P. Rayman, DPhil m.rayman@surrey.ac.uk Faculty of Health and Medical Sciences University of Surrey Guildford, United Kingdom Gerald F. Combs Jr, PhD Grand Forks Human Nutrition Research Center Agricultural Research Service US Department of Agriculture Grand Forks, North Dakota

1876 JAMA, May 13, 2009—Vol 301, No. 18 (Reprinted)

David J. Waters, PhD, DVM Purdue University Center on Aging and the Life Course West Lafayette, Indiana

Financial Disclosures: Dr Rayman reported receiving grant support from Wassen International, a manufacturer of nutritional supplements, including selenium. Dr Waters reported that he is director of the Murphy Cancer Foundation, a not-for-profit research institute that, in collaboration with Bostwick Laboratories, markets a toenail test for selenium. Dr Waters reported that he has no financial interest in Bostwick Laboratories and no financial relationships with any manufacturers of selenium supplements. Dr Combs reported no disclosures.

- 1. Lippman SM, Klein EA, Goodman PJ, 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(1):39-51.
- Duffield-Lillico AJ, Reid ME, Turnbull BW, et al. Baseline characteristics and the
 effect of selenium supplementation on cancer incidence in a randomized clinical
 trial: a summary report of the Nutritional Prevention of Cancer Trial. Cancer Epidemiol Biomarkers Prev. 2002;11(7):630-639.
- **3.** Waters DJ, Chiang EC, Bostwick DG. The art of casting nets: fishing for the prize of personalized cancer prevention. *Nutr Cancer*. 2008;60(1):1-6.
- **4.** Stranges S, Marshall JR, Natarajan R, et al. Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. *Ann Intern Med.* 2007;147(4):217-223.
- Cooper ML, Adami HO, Grönberg H, Wiklund F, Green FR, Rayman MP. Interaction between single nucleotide polymorphisms in selenoprotein P and mitochondrial superoxide dismutase determines prostate cancer risk. Cancer Res. 2008; 68(24):10171-10177.

To the Editor: Dr Lippman and colleagues¹ concluded that "selenium, vitamin E, or selenium + vitamin E (at the tested doses and formulations) did not prevent prostate cancer." We believe that this statement is potentially misleading because the data relate to the effects of *L*-selenomethionine supplementation only in a selenium-replete population. The effects of selenium are species specific, with some forms of selenium having greater anticancer benefit than others,² so the null effect of *L*-selenomethionine supplementation on prostate cancer risk should not be applied to selenium in general.

In addition, the effects are dependent not only on the dose and form of selenium but on the initial baseline selenium status of the population. In a previous study, selenium supplementation was only effective against prostate cancer in volunteers (with a previous history of skin cancer) whose plasma selenium was less than $120 \, \mu g/L$ (to convert to $\mu mol/L$, mul-

GUIDELINES FOR LETTERS. Letters discussing a recent JAMA article will have the best chance of acceptance if they are received within 4 weeks of the article's publication date. Letters may have no more than 3 authors. They should not exceed 400 words of text and 5 references. Letters reporting original research should not exceed 600 words and 6 references. They may have no more than 5 authors. All letters should include a word count. Letters must not duplicate other material published or submitted for publication. Letters will be published at the discretion of the editors and are subject to editing and abridgment. A signed statement for authorship criteria and responsibility, financial disclosure, copyright transfer, and acknowledgment is required for publication. Letters not meeting these specifications are generally not considered. Before submitting a Research Letter, please review the Instructions for Authors (http://jama.com/instructions). Letters should be submitted via the JAMA online submission and review system at http://manuscripts.jama.com (note: do not include "www." before the URL). For technical assistance, please contact jama-letters@jama-archives.org.

Letters Section Editor: Robert M. Golub, MD, Senior Editor.

©2009 American Medical Association. All rights reserved.