

Selenium Supplementation and Cancer Rates

To the Editor.—Dr Clark and colleagues¹ informed us that while, compared with a placebo, selenium supplements reduced overall cancer morbidity and mortality, they did not reduce all-cause morbidity and mortality. This indicates that selenium increased morbidity and mortality from diseases other than cancer. So that we can adequately inform our patients, Clark et al should tell us what those other diseases are and by how much their morbidity and mortality were increased by the selenium supplements. Patients susceptible to those other diseases may be as much harmed by taking selenium supplements as those susceptible to certain cancers may be helped.

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1. Clark LC, Combs GF Jr, Turnbull BW, et al, for the Nutritional Prevention of Cancer Study Group. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial. *JAMA*. 1996;276:1957-1963.

To the Editor.—The article by Clark et al¹ has very important implications. The results suggest that increased selenium intake results in a substantial reduction in cancer incidence in only 5 years. This is especially remarkable with regard to lung cancer, since the effects of smoking cessation usually require a much longer follow-up.² These results can be due to (1) a true beneficial effect of selenium; (2) random variation, ie, type I error; and (3) an unexplained higher rate in the control group; in other words, the differences are not due to the benefit of selenium, but due to a much higher rate in the control group than would be expected. Unfortunately, the authors do not provide information on age- and sex-specific cancer rates in either group or the age distribution of cancer cases. They report a mean age of 63 years at entry, 75% men, and approximately 8000 person-years of observation. The observed incidence rates, based on approximately 4000 person-years in each group are for lung cancer, 7.8 per 1000 in the control vs 4.25 per 1000 in the intervention; for prostate cancer (men only), 11.9 per 1000 in the control and 4.3 per 1000 in the intervention; and for colorectal cancer, 4.8 per 1000 in the control and 2.0 per 1000 in the intervention.

Using data from the Surveillance, Epidemiology, and End Results (SEER) program (of which men comprised 75%),³ the lung cancer incidence for whites aged 60 to 64 years was 3 cases per 1000 and for those aged 65 to 69 was 4.2 per 1000. These rates are similar to those in the intervention group, but lower than those in the control group. For prostate cancer, the rate for men aged 60 to 64 years was 2.8 in SEER and for those aged 65 to 69 years, 5.7. Again, the rates in the intervention group are more comparable to SEER, and the rates in the control group appear to be high. For colorectal cancer, the rates in SEER were 1.8 for those aged 60 to 64 years and 2.7 for those aged 65 to 69 years. Likewise, the rate in the intervention group is closer to SEER than the rates in the control group. For total cancer, the rates in study by Clark et al appear to be 30 per 1000 in the control group and only 19 per 1000 in the intervention group. Rates for SEER were 13.5 per 1000 for those aged 60 to 64 years and 20.2 per 1000 for those aged 65 to 69 years; again, similar to the selenium intervention group rates. The estimated breast cancer inci-

dence for women of 9 cases per 1000 in the intervention group vs 3 cases per 1000 in the control group is also consistent with a greater rate in the control groups.

It would be important and reassuring to see a comparison of age- and sex-specific cancer incidence rates in the selenium trial for the intervention and control groups as compared with SEER cancer incidence rates. This would help to rule out the possibility that the control events are really more frequent than expected rather than events in the selenium group being less than expected, ie, a treatment effect. This is important before we begin to either recommend selenium intervention or spend large amounts of funds replicating a greater than expected rate in the intervention group.

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1. Clark LC, Combs GF Jr, Turnbull BW, et al, for the Nutritional Prevention of Cancer Study Group. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial. *JAMA*. 1996;276:1957-1963.

2. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. *Br Med J*. 1994;309:901-911.

3. Miller BA, Ries LAG, Hankey BF, et al, eds. *SEER Cancer Statistics Review: 1973-1990*. Bethesda, Md: National Cancer Institute; 1993. National Institutes of Health publication 93-2789.

To the Editor.—I have questions regarding the article by Clark et al.¹ Other selenium studies I have read generally use generic forms of selenium: selenomethionine or sodium selenite. The study by Clark et al¹ uses a commercial product: high-selenium yeast tablets from Nutrition 21. Nutrition 21 manufactures selenium supplements for distribution to health food stores. The use by Clark et al of Nutrition 21 selenium tablets could be interpreted as an endorsement. Already Nutrition 21 distributors are citing the study by Clark et al in sales promotions for Nutrition 21 selenium tablets. An independent chemical supplier could have made up selenomethionine tablets for this study, thereby avoiding commercial involvement.

Many people cannot tolerate even small amounts of yeast. This fact may have caused the gastrointestinal upset that led some of the research subjects to withdraw from the study.

The study by Clark et al states that 200 µg of selenium per day is not likely to have toxic adverse effects. However, how was 200 µg of selenium per day determined to be the optimum therapeutic dose regardless of body weight? Unfortunately, to compare this selenium study by Clark et al with another

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selenium study requires an assumed average dose: I estimate 2.9 µg of selenium per kilogram of body weight per day.

In a study of blood platelet function in humans, Perona² gave 9.9 µg of selenite selenium per kilogram per day for 8 weeks. The authors state that "during and after this experiment, symptoms or signs of intolerance to selenite, either gastrointestinal or neurological, were absent." Because selenite selenium inhibits thromboxane, subjects in this study experienced a 2-fold increase in bleeding time, the same effect as from taking 1 g of aspirin. Unlike aspirin, selenite selenium did not lower levels of prostacyclin, a cardioprotective prostaglandin.

Considering the above findings,² why did the study by Clark et al find no protection against cardiovascular or cerebrovascular disease? Perhaps 2.9 µg of selenium per kilogram per day cannot produce the same biological effect as 9.9 µg of selenium per kilogram per day.

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1. Clark LC, Combs GF Jr, Turnbull BW, et al, for the Nutritional Prevention of Cancer Study Group. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial. *JAMA*. 1996;276:1957-1965.

2. Perona G, Schiavon R, Guidi GC, Veneri D, Minuz P. Selenium dependent glutathione peroxidase: a physiological regulatory system for platelet function. *Thromb Haemost*. 1990;63:312-318.

In Reply.—We share Dr Herbert's concern regarding the safety of using 200 µg of selenium in a high-selenium brewer's yeast and have been concerned about documenting both adverse and beneficial health effects of selenium supplementation, especially those that could only be identified in a double-blind, placebo-controlled trial. The choice of a nutritional dose diminished the safety issues in the trial and was based on the upper limit of the US Estimated Safe and Adequate Intake of selenium.¹

The trial's Safety Monitoring Committee reviewed the incidence of patient-reported disease and did not identify any significant adverse health events associated with selenium supplementation. The trial eligibility criteria excluded patients with active liver and kidney disease; however, we have not identified any additional groups of patients in the trial who were at particular risk of adverse health events. For safety reasons, pregnant women were also excluded from active participation. While there may be groups of patients that are adversely affected by selenium supplementation, we have no evidence for this.

Dr Kuller suggests several alternative explanations for the results of the trial. He observes correctly that the placebo group has a greater risk of cancer than expected from the SEER data. However, our patients were deliberately chosen and randomized from a high-risk population (for purposes of statistical efficiency); hence, the SEER data are not relevant. The stratified, time-block randomization produced comparable treatment and placebo groups based on the information in our Table 1. Furthermore, all subgroup analyses based on age, tobacco use, clinic site or type, or baseline selenium or vitamin E levels are consistent with the overall results reported in our article.

Regarding the issues raised by Mr Parker, the decision to use a 200-µg dose was influenced by the desire to use a high-selenium food at a nutritional dose, rather than an inorganic form of selenium. When we started the trial in 1983, Nutrition 21 was the only US manufacturer and wholesaler of high-selenium yeast. The only company to manufacture selenomethionine declined our request to use it in human studies.

Our study did not address the issue of whether a 200-µg selenium supplement is the optimal dose for cancer preven-

tion. Nor were we able to vary the dose of the supplement by patient body weight for reasons of practicality. We continue to believe that additional research and clinical trials are necessary before public health recommendations regarding the use of selenium supplements can be formulated. Use of a particular product in this trial does not constitute a commercial endorsement of that product.

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1. Food and Nutrition Board. *Recommended Dietary Allowances*. 9th ed. Washington, DC: National Academy of Sciences; 1980:162-164.

Urinary Incontinence in Elderly Patients

To the Editor.—Despite Dr Resnick's excellent discussion in the Clinical Crossroads article on urinary incontinence,¹ I think the patient's incontinence is much more complex. The voiding record of Mrs S revealed nocturnal enuresis.¹ Burgio et al² found that 2% of community-dwelling older adults had nocturnal enuresis; its prevalence was significantly greater among women compared with men (2.9% vs 1.0%, $P < .001$), and it was associated with poorer therapeutic outcomes, compared with the more common forms of daytime incontinence. These authors also found that enuresis was significantly related to symptoms of congestive heart failure, and subjects with mixed stress and urge incontinence during the day were most likely also to have nocturnal enuresis, compared with those with only 1 type of incontinence. Therefore, enuresis appears to be a special type of incontinence and is not as well understood in older patients.

Even though Resnick argued that vasopressin has little efficacy in elderly patients, vasopressin is important in the balance of nocturnal urinary flow and might be an alternative to treat some older patients with enuresis (eg, those without congestive heart failure). In a case report by Gross and Shua-Haim,³ a patient with refractory urinary incontinence and nocturnal enuresis was responsive to intranasal desmopressin spray, which is a synthetic analogue of vasopressin.

In contrast, other elderly patients with enuresis might not respond to vasopressin. Although the response of vasopressin secretion to an osmolar challenge is markedly increased in older patients, this does not translate into greater water conservation. The renal response to vasopressin generally is diminished with aging and results in decreased ability to produce concentrated urine, similar to acquired nephrogenic diabetes insipidus.⁴ However, these patients might respond to diuretics. Ouslander et al⁵ found that patients taking diuretics had more urine output during the day than at night. Also, thiazide diuretics are used to treat nephrogenic diabetes insipidus.

In addition, frail elderly patients tend to have greater urine volume at night. Ouslander et al⁵ found that nursing home residents produced substantially more urine at night than during the day, with a mean of 54% of total urine excreted at night. Moreover, older patients have many causes of increased urinary losses that might lead to incontinence, such as increased atrial natriuretic factor, suppressed vasopressin by drugs (eg, phenytoin) or diseases (eg, postatrial tachyarrhythmia), and diabetes insipidus.^{4,5} Controlling those factors or using vasopressin (ie, inducing central diabetes insipidus) might improve their enuresis.