

## CORRESPONDENCE

### Re: Zinc Supplement Use and Risk of Prostate Cancer

Leitzmann et al. (1) recently reported that men who consumed more than 100 mg/day of supplemental zinc or who took supplemental zinc for at least 10 years had an approximately twofold-elevated risk of advanced prostate cancer compared with nonusers. Given these provocative findings, we investigated the relationship between zinc supplement use and the risk of prostate cancer in a recently completed population-based case-control study in Sweden that included 1499 prostate cancer case patients and 1130 control subjects. After granting informed consent, participants completed a questionnaire that assessed possible risk factors for prostate cancer, including supplemental zinc intake. Frequency of intake was recorded as the number of tablets consumed per week and the number of months per year tablets were used; duration of use was recorded as total number of years. This study was approved by the Karolinska Institute and Umeå University Ethics Committees and was funded by the Swedish Cancer Society.

Use of supplemental zinc at least 1 year prior to completion of the questionnaire was reported by 3.4% ( $n = 51$ ) of case patients and 2.5% ( $n = 28$ ) of control subjects. After adjusting for age, we observed no statistically significant difference in the prevalence of supplemental zinc use between case patients and control subjects (odds ratio = 1.3, 95% confidence interval = 0.8 to 2.1). Further multivariate adjustment for possible confounders, including height, body mass index, family history of prostate cancer, smoking status, alcohol intake, and use of other nutritional supplements, did not appreciably affect the results. The association did not vary for risk of localized versus advanced disease (advanced prostate cancer was defined as tumor stage  $\geq 3$ , nodal stage = 1, metastatic stage = 1, differentiation grade = 3,

Gleason score  $\geq 8$ , and/or serum prostate-specific antigen  $\geq 100$ ; localized prostate cancer was defined as case patients not meeting the preceding criteria) or for risk of sporadic versus familial or hereditary disease (familial prostate cancer was defined as case patients with two first- or second-degree relatives with prostate cancer; hereditary prostate cancer was defined as case patients with  $\geq 3$  first- or second-degree relatives with prostate cancer; sporadic prostate cancer was defined as case patients not meeting the preceding criteria). In addition, we observed no statistically significant difference in prostate cancer risk between supplement users and nonusers when supplemental zinc use was categorized by frequency ( $< 1$  tablet/day versus  $\geq 1$  tablet/day), duration ( $< 5$  years versus  $\geq 5$  years), or cumulative exposure ( $< 200$  total tablets versus  $\geq 200$  total tablets, or total tablets measured on a continuous scale).

Overall, our findings differ from those of Leitzmann et al. (1) and Kolonel et al. (2), who reported that greater zinc consumption is associated with an increased risk of prostate cancer. Our results also differ from those of Kristal et al. (3), who reported that supplemental zinc intake is associated with decreased risk of prostate cancer. Rather, the lack of association between zinc supplement use and prostate cancer risk observed in our study is consistent with the null finding reported by Lee et al. (4).

Our study had limited power to detect any association with risk of prostate cancer or to analyze a dose-response relationship in detail because of the low prevalence of supplemental zinc use among the case patients and the control subjects. Recent studies have found that use of complementary medicine, including zinc supplements, is common in men with prostate cancer (5,6). Thus, if the case patients in our study were prompted to use zinc supplements because of early disease, any inverse association between predisease zinc intake and risk of prostate cancer would have been obscured.

Results of further investigations on zinc consumption in prostate cancer development, especially those from large studies with prospectively collected exposure data, should clarify this relationship.

ELLEN T. CHANG  
MARIA HEDELIN  
HANS-OLOV ADAMI  
HENRIK GRÖNBERG  
KATARINA A. BÄLTER

### REFERENCES

- (1) Leitzmann MF, Stampfer MJ, Wu K, Colditz GA, Willett WC, Giovannucci EL. Zinc supplement use and risk of prostate cancer. *J Natl Cancer Inst* 2003;95:1004-7.
- (2) Kolonel LN, Yoshizawa CN, Hankin JH. Diet and prostatic cancer: a case-control study in Hawaii. *Am J Epidemiol* 1988;127:999-1012.
- (3) Kristal AR, Stanford JL, Cohen JH, Wicklund K, Patterson RE. Vitamin and mineral supplement use is associated with reduced risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 1999;8:887-92.
- (4) Lee MM, Wang RT, Hsing AW, Gu FL, Wang T, Spitz M. Case-control study of diet and prostate cancer in China. *Cancer Causes Control* 1998;9:545-52.
- (5) Boon H, Westlake K, Stewart M, Gray R, Fleshner N, Gavin A, et al. Use of complementary/alternative medicine by men diagnosed with prostate cancer: prevalence and characteristics. *Urology* 2003;62:849-53.
- (6) Wilkinson S, Gomella LG, Smith JA, Brawer MK, Dawson NA, Wajsman Z, et al. Attitudes and use of complementary medicine in men with prostate cancer. *J Urol* 2002;168:2505-9.

### NOTES

*Affiliations of authors:* Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (ETC, MH, HOA, KAB); Department of Radiation Sciences/Oncology, Umeå University, Umeå, Sweden (HG).

*Correspondence to:* Ellen T. Chang, ScD, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, SE-171 77 Stockholm, Sweden (e-mail: ellen.chang@med.ki.se).

DOI: 10.1093/jnci/djh206

### RESPONSE

We read with interest the letter by Chang et al. reporting no association between zinc supplement use and the risk of prostate cancer in a Swedish case-control study. By comparison, our results (1) suggest that high intake of supplemental zinc is associated with an increased risk of advanced prostate cancer. There are several possible explanations for these discrepant findings. The proportion of subjects in our study with zinc supplement exposure was greater than that in the Swedish study. For example, only 2.5% of the base population in the Swedish study reported using zinc

supplements, whereas 25% of the subjects in our study reported using zinc supplements. In addition, it is likely that the doses of zinc consumed by subjects in the Swedish study were largely compatible with the recommended dietary allowance of 11 mg/day of zinc for men, an intake level that is not associated with an increase in prostate cancer risk (1). By comparison, our study included 4374 men whose zinc intake exceeded the current recommended dietary allowance by at least twofold. Furthermore, it is possible that the duration of zinc supplement use is critical for an increase in prostate cancer risk. In our study, 6177 men reported consistent use of zinc supplements for 10 years or longer. Finally, the apparent adverse effect of zinc supplement use that we observed was restricted to cases of advanced prostate cancer.

To further address the relationship between high doses and long duration of zinc supplement use and the risk of advanced prostate cancer, we present data on intake and duration of supplemental zinc use in combination (Table 1). The risk of advanced prostate cancer was higher among men with the highest intake and the longest duration of zinc supplement use than among nonusers. By comparison, zinc supplement use for fewer than 10 years was not statistically significantly related to the risk of advanced prostate cancer, even at doses exceeding the recommended dietary allowance. These data suggest that the use

of high doses of zinc supplements for a long time (consistent with long-term zinc toxicity) may be required to increase the risk of advanced prostate cancer.

The findings reported by Chang et al. showing a lack of association between supplemental zinc use and risk of prostate cancer do not rule out the possibility of an association between advanced prostate cancer and excessive intakes of supplemental zinc for at least a decade. Zinc effects are likely to vary by dose, as suggested by circumstantial evidence showing that both insufficient and surplus amounts of zinc are associated with undesirable metabolic effects potentially related to prostate cancer. For example, it is recognized that zinc deficiency causes a decline in immunologic competence (2), whereas high intakes of supplemental zinc are also associated with an impaired immune response (3). Future studies designed to address the effects of both long-term zinc deficiency and long-term zinc oversupply should clarify the association between zinc intake and prostate carcinogenesis.

MICHAEL F. LEITZMANN  
EDWARD GIOVANNUCCI

## REFERENCES

- (1) Leitzmann MF, Stampfer MJ, Wu K, Colditz GA, Willett WC, Giovannucci EL. Zinc supplement use and risk of prostate cancer. *J Natl Cancer Inst* 2003;95:1004-7.

- (2) Frost P, Chen JC, Rabbani I, Smith J, Prasad AS. The effect of zinc deficiency on the immune response. *Prog Clin Biol Res* 1977;14:143-53.  
(3) Chandra RK. Excessive intake of zinc impairs immune responses. *JAMA* 1984;252:1443-6.

## NOTES

*Affiliations of authors:* Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD (MFL); Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (EG).

*Correspondence to:* Michael F. Leitzmann, MD, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, 6120 Executive Blvd., EPS-MSC 7232, Bethesda, MD 20892 (e-mail: leitzmann@mail.nih.gov).

DOI: 10.1093/jnci/djh207

**Table 1.** Multivariable relative risk of prostate cancer in relation to the level and duration of supplemental zinc use at baseline in the Health Professionals Follow-up Study\*

Level and duration of supplemental zinc intake	Total prostate cancer	Multivariable RR (95% CI), organ-confined prostate cancer	Advanced prostate cancer
Nonusers	1.0 (referent)	1.0 (referent)	1.0 (referent)
Users			
1-24 mg/day			
1-4 years	0.95 (0.83 to 1.09)	0.99 (0.83 to 1.18)	0.75 (0.52 to 1.08)
5-9 years	0.76 (0.49 to 1.18)	0.71 (0.39 to 1.28)	1.49 (0.59 to 3.77)
≥10 years	0.98 (0.64 to 1.49)	0.86 (0.48 to 1.54)	1.75 (0.69 to 4.48)
25-74 mg/day			
1-4 years	1.02 (0.85 to 1.24)	0.93 (0.72 to 1.21)	1.14 (0.69 to 1.87)
5-9 years	1.03 (0.76 to 1.38)	0.92 (0.62 to 1.39)	1.78 (0.90 to 3.49)
≥10 years	0.93 (0.64 to 1.36)	0.59 (0.32 to 1.09)	2.63 (1.32 to 5.23)
≥75 mg/day			
1-4 years	0.96 (0.69 to 1.31)	0.74 (0.46 to 1.18)	1.58 (0.79 to 3.16)
5-9 years	1.06 (0.68 to 1.67)	0.93 (0.49 to 1.73)	1.15 (0.35 to 3.75)
≥10 years	1.27 (0.82 to 1.99)	0.87 (0.43 to 1.74)	2.91 (1.25 to 6.77)

\*RR = relative risk adjusted for current age, time period, body mass index at age 21, height, pack-years of smoking in the previous decade, family history of prostate cancer, vigorous physical activity, regular aspirin use, and intakes of total energy, dietary calcium, supplemental calcium, fructose, supplemental vitamin E, tomato-based foods, fish, red meat, and  $\alpha$ -linolenic acid; CI = confidence interval.