Re: Zinc Supplement Use and Risk of Prostate Cancer

Leitzmann et al. (1) reported that the use of zinc supplements in high amounts (i.e., >100 mg/day) or for a prolonged time (i.e., ≥10 years) was associated with an increased risk of developing advanced prostate cancer. Several issues concerning their study need to be addressed. First, the $P_{\text{trend}}$ (i.e., <.003) that was reported tested whether the relative risk of advanced prostate cancer was the same among the four dose groups and the nonusers. However, no $P$ values were reported for pair-wise comparisons of each dose group with the nonusers. Although the $P_{\text{trend}}$ provides information about the differences among all groups, it does not provide the statistical comparison of each zinc-user group with the nonuser group, which is necessary to support the main conclusion of the report. In addition, the 95% confidence interval (i.e., 1.06 to 4.95) that was reported for the relative risk of advanced prostate cancer for men who consumed more than 100 mg of zinc per day versus men who consumed no zinc can indicate only that the $P$ value was less than .05. However, if one were to adjust for multiple comparisons, for example, by using the common Bonferroni correction for each of the four dose groups versus nonusers, a $P$ value of less than .0125 would be required for statistical significance. Therefore, the difference between the greater than 100 mg of zinc per day group and the nonuser group reported by Leitzmann et al. (1) might not, in fact, be statistically significant.

Second, the small sample size is of concern. Leitzmann et al. (1) report only 10 advanced prostate cancer cases among the group of men who consumed 101 mg or more of supplemental zinc per day and only 11 cases among the group that consumed 75–100 mg of supplemental zinc per day. We used a chi-square test to compare the proportion of advanced prostate cancer cases among the men who consumed more than 100 mg zinc/day (10 cases of 412 men) with that among the men who did not consume supplemental zinc (317 cases from the total population of 35 121 men). The expected frequency of advanced prostate cancers in men who used zinc was less than 5, which fails to satisfy the requirement for the validity of a large-sample analysis [e.g., see (2)]. The expected frequency for the extended users (23/412) was also less than 5. The small number of advanced prostate cancer cases causes concern about the reliability of the conclusion regarding relative risk because the conclusion depends on the assumption of large sample approximation in calculating standard errors and confidence intervals [e.g., see (3)].

The 20%–25% lower relative risk values of some zinc-user groups reported by Leitzmann et al. (1) seemingly indicate a possible protective effect of zinc, as has been reported in another study (4). Unfortunately, Leitzmann et al. (1) do not discuss or refer to any of several published studies [see (5) for review] that report results that conflict with their findings. Discussion of these divergent results would make apparent the complexity and current lack of unanimity regarding this extremely important issue. The absence of such a discussion leads the readers to the erroneous assumption that the Leitzmann et al. report (1) is the sole and incontrovertible study.

In addition, two important relationships should be recognized in regard to all of these studies. First, high cellular zinc levels have been shown to impede the malignant activities of neoplastic prostate cells (6). This finding suggests that treatments to increase cellular zinc accumulation may prevent the development and progression of prostate cancer. Second, ingestion of high levels of zinc decreases the intestinal absorption and assimilation of zinc, which ultimately affects the circulating and tissue levels of zinc (7). Any direct effect of zinc on the normal or malignant prostate cells is dependent on the plasma level of zinc and its uptake by these cells, not simply on the ingested level of zinc. These parameters need to be considered in the analysis and interpretation of any potential effects of dietary zinc on the development and progression of prostate cancer.
Epidemiologic studies have produced contradictory results that lead us to conclude that the effect of dietary zinc on prostate cancer is not only complex but is confounded by unknown factors. Thus, Leitzmann and colleagues are correct to conclude that this association warrants further investigation. Presently, any definitive conclusions about the effects, either beneficial or harmful, of zinc supplementation on prostate cancer risk are, in our view, premature and unfounded. The resolution of this important issue requires well-controlled prospective studies of the efficacy of zinc alone and in combination with other supplements, along with basic research studies to elucidate the mechanisms by which zinc affects normal and malignant prostate.

**REFERENCES**


(6) Costello LC, Franklin RB. The intermediary metabolism of the prostate: a key to understanding the pathogenesis and progression of prostate malignancy. Oncology 2000;59:269–82.


**NOTES**

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DOI: 10.1093/jnci/djh045

**RESPONSE**

We respond briefly to the points raised by Costello et al. concerning our paper on zinc supplement use and the risk of prostate cancer (1). First, Costello et al. suggest that we should have provided P values for the pair-wise statistical comparisons of each zinc-user group with the nonuser group and used the Bonferroni correction for multiple comparisons. However, the standard method of providing estimates of disease risk according to distinct levels of an exposure in epidemiologic studies is the relative risk with its corresponding 95% confidence interval, and not the P value (2). We recognize that there is a difference of opinion regarding the adjustment for multiple comparisons: We do not believe that a uniform adjustment of the critical level of statistical significance for the P value is the best approach in this circumstance (2) because our study does not represent a multiple-inference situation.

Second, Costello et al. express concern about our small sample size at the highest level of zinc intake. We acknowledge that our risk estimate for men who consumed more than 100 mg/day of supplemental zinc (relative risk = 2.29) is somewhat imprecise as indicated by its wide confidence interval (95% confidence interval = 1.06 to 4.95). However, Costello et al. do not dispute the highly statistically significant positive tests for trend for level of supplemental zinc intake (P_trend = .003) and duration of supplemental zinc use (P_trend < .001) that remained statistically significant even after we excluded nonusers of zinc supplements from the analysis. The test for trend used in our study is a robust overall test for statistical significance that takes into account the entire range of supplemental zinc intake. Moreover, the Cox proportional hazards regression model used in our analysis (3) is not characterized by large sample-approximation requirements, as is the contingency table approach proposed by Costello et al.

Third, Costello et al. state that we failed to refer to published studies that conflict with our findings. On the contrary, we referred to six studies that reported results on zinc and prostate cancer that were not in agreement with our results (4–9), including two important studies by Costello’s group (4,5) showing that high cellular zinc levels inhibit prostate cancer cell growth. In fact, our initial motivation to examine the zinc–prostate cancer hypothesis was based on study results suggesting that zinc protects against prostate carcinogenesis (4–9). Somewhat to our surprise, we observed an increased risk of advanced prostate cancer associated with high-dose and long-term use of zinc supplementation. The apparent 25% decrease in risk of advanced prostate cancer among men reporting 1–24 mg/day of supplemental zinc intake was not statistically significant after adjusting for potentially confounding variables. Unfortunately, we could not discuss the epidemiologic literature on zinc and prostate cancer in detail within the context of a brief communication, but we did acknowledge potential alternative explanations for our findings (e.g., confounding).

Fourth, Costello et al. argue that any analysis and interpretation of the potential effects of dietary zinc on prostate cancer should include a consideration of circulating or cellular levels of zinc. We acknowledge the importance of the simultaneous exploration of the various mechanistic pathways through which zinc may modify prostate carcinogenesis. Thus, we agree with Costello et al. that readers should not conclude that our study is the definitive study on zinc and prostate cancer. Quite the contrary: It is the first study that provides prospective data on the relationship between long-term intake of high doses of zinc and the risk of prostate cancer. We hope our findings stimulate future progress toward understanding the complex interactions between zinc levels (dietary, serum, and tissue) and prostate carcinogenesis.

**REFERENCES**


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DOI: 10.1093/jnci/djh046