

# Does Zinc Supplementation Increase the Risk of Prostate Cancer?

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**I**n the United States, prostate cancer is the most commonly diagnosed cancer in men and the second leading cause of cancer deaths in this population. It is estimated that 220 000 cases of prostate cancer will be diagnosed this year, and this is expected to increase with the expanding geriatric population. The etiology of prostate cancer is multifactorial. Genetic factors are important and contribute to incidence rates that are higher in African Americans than any other racial group. It is also clear that diet plays an important role in modulating the cancer phenotype. There is expanding interest, both in the lay press and the scientific community, in the use of dietary supplements that minimize the initiation and progression of prostate cancer.

The concentration of zinc in the prostate is higher than that of any other soft tissue in the body. Zinc is a necessary component of numerous metalloproteins including those important for DNA synthesis, immune function, and antioxidant activity. It is estimated that 15% of the population uses zinc supplements to exceed the recommended dietary allowance of 11 mg/d for men.<sup>1</sup> A large body of literature supports a protective role for zinc with regard to prostate cancer progression. Zinc has been found to inhibit prostate cancer cell line growth and invasion.<sup>2</sup> In part, this may be through the inhibition of nuclear factor  $\kappa$ B, an antiapoptotic protein.<sup>3</sup> Tissue levels of zinc are consistently lower in prostate cancer specimens when compared with normal specimens.<sup>4,5</sup> This may be due to the down-regulation or inactivation of zinc transporter proteins,<sup>6</sup> a finding also hypothesized to contribute to increased disease in African Americans.<sup>7</sup> Low serum levels of zinc are associated with an increased incidence of prostate cancer,<sup>8-10</sup> although these findings have been contradicted.<sup>11</sup> In recent case-control studies, a weak to moderate protective effect of higher zinc intake was found against prostate cancer.<sup>12,13</sup> Objective data ana-

lyzing zinc levels in toenail clippings demonstrate no statistical difference between patients with prostate cancer and controls and a moderate protective effect for higher zinc concentrations.<sup>14</sup> These data suggest that the risk of prostate cancer may be lower among men with a moderate to higher zinc intake.

However, a recent study involving 46 000 health professionals (the Health Professionals Follow-up Study)<sup>15</sup> found that men who consumed more than 100 mg/d of supplemental zinc had a higher relative risk (2.9-fold) of advanced prostate cancer. This increase in risk was amplified with the long-term intake of zinc supplements for more than 10 years. Supplemental zinc provided 32% of the total zinc intake and was the major source. The reasons behind the increased risk with zinc intake found in this study are unclear. At extremely high levels, more than 150 mg/d, zinc may cause immune dysfunction.<sup>16</sup> Zinc is also correlated with higher levels of circulating insulinlike growth factor I, which are related to prostate cancer development.<sup>17</sup> The men in the Health Professionals Follow-up Study who consumed supplemental zinc also consumed increased levels of other supplements, notably calcium, and were less likely to have a history of prostate cancer screening, both potentially confounding

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factors. The correlation was found only with advanced cancers (ie, with local extension or metastases) and not with organ-confined cancers, which represent the vast majority of diagnosed cancers. This suggests that the effect, if any, may be in the promotion of aggressive cancers. Only 10 of 2127 patients diagnosed as having prostate cancer during the study had advanced cancer and a zinc intake of greater than 100 mg/d. In sum, the health professionals data suggest that high levels of supplemental zinc may contribute to prostate cancer promotion in a small minority of patients. Further validation of this effect is needed.

Because of the Health Professionals Follow-up Study,<sup>15</sup> concern has been generated regarding the use of supplemental zinc in aging men, a group at high risk for prostate cancer development. The recent Age-Related Eye Disease Study (AREDS)<sup>18</sup> found that 80 mg/d of zinc, either alone, as zinc oxide, or as antioxidants and zinc, significantly reduced the risk of progression of age-related macular degeneration (AMD). Age-related macular degeneration is the leading cause of legal blindness in individuals 65 years or older and affects 1.7% to 1.9% of the population. In the AREDS study, zinc appeared to have a synergistic effect in combination with antioxidants. Prior to this study, no proven treatment had prevented or slowed the development of AMD for the 640 000 or more individuals with signs of late AMD.

If zinc supplementation becomes more widely used, should we be concerned about the development or progression of prostate cancer in these individuals? The levels of zinc supplementation used in the AREDS study were lower (80 mg) than those identified in the health professionals study as being a risk factor for prostate cancer. In addition, no increase in prostate cancer was noted in the patients receiving zinc supplementation in the former study. Given the known benefit of zinc for AMD, it is reasonable to prescribe zinc supplementation to patients at risk for progression to AMD. How-

ever, several caveats should be noted pending further data. Because of the increased risk of prostate cancer identified in patients with a supplemental intake of more than 100 mg/d, patients using the AREDS protocol should be warned not to take additional zinc. The routine intake of foods containing high amounts of zinc, such as beef and breakfast cereals, should be monitored. In addition, the consumption of other supplements, especially those containing calcium, should be minimized or avoided. Given the uncertainty regarding the effect of zinc on cancer progression, it may also be reasonable to avoid zinc supplementation in men diagnosed as having prostate cancer or precancerous lesions of the prostate such as high-grade prostatic intraepithelial neoplasia. One interesting aspect of the AREDS study was the finding that in individuals receiving zinc supplementation, there was an increase in hospitalization for genitourinary symptoms (8.6% vs 4.4%;  $P < .001$ ). The reasons for this difference are not clear and will require further study. At this point, lower urinary tract symptoms should not be considered a contraindication.

In conclusion, 80 mg/d of supplemental zinc for the prevention of AMD does not appear to significantly increase the risk of prostate cancer in most patients. A significant body of data suggests that zinc may play a role in inhibiting prostate cancer at the lower levels used in the AREDS study. Given the known morbidity of AMD and the beneficial impact of zinc on this disease, the use of zinc supplementation should be encouraged in elderly patients at risk for macular degeneration.

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