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Serum zinc and prostate cancer risk in a nested case-control study: the Multiethnic Cohort

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Abstract

BACKGROUND—Experimental studies have provided evidence that zinc has a protective effect against development and progression of prostate cancer. However, epidemiological studies have reported inconsistent findings. We evaluated the association between prediagnostic serum zinc and prostate cancer risk in a cohort of multiethnic population.

METHODS—This case-control study is nested within the Multiethnic Cohort of African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites in Hawaii and California. The analysis included 392 prostate cancer cases and 783 controls matched on age, race/ethnicity, date/time of blood draw and fasting status. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI).

RESULTS—The mean serum zinc concentrations did not significantly differ between cases (94.9 μg/dl) and controls (93.9 μg/dl). No association was found between serum zinc levels and prostate cancer either overall or by tumor stage/grade. In ethnic-specific analyses, positive associations were found in Japanese Americans (OR for the highest vs. the lowest tertile = 2.59, 95% CI: 1.09–6.17) and Latinos (OR = 2.74, 95% CI: 1.05–7.10), whereas no association was observed in African Americans and whites.

CONCLUSIONS—We found no evidence to support an inverse relationship between serum zinc and prostate cancer risk, and, to the contrary, found a suggestion in the ethnic-specific results of a possible increase in risk; however, blood concentrations of zinc may not adequately reflect the levels in prostate tissue. Further study with a larger sample size, and if possible, with assessment of zinc tissue levels, is warranted to confirm these findings.

Keywords

zinc; prostate cancer; nested case-control study; multiethnic population

INTRODUCTION

Because zinc is highly concentrated in prostatic tissue and is essential to DNA synthesis, immune function, and antioxidant activity, it may be protective against the development and

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progression of prostate cancer [1]. Indeed, experimental data strongly suggest a protective role of zinc against prostate cancer [2]. On the other hand, because zinc is essential for the production of androgens, which have been positively associated with prostate cancer risk, zinc could also be hypothesized to increase prostate cancer risk [3]. Furthermore, circulating zinc levels have been correlated with higher levels of insulin-like growth factor 1 (IGF-1), which are related to prostate cancer development [4]. Unlike experimental studies, epidemiological studies have shown inconsistent results: possible beneficial effects, possible harmful effects, and no effect of dietary and supplemental zinc on prostate cancer risk [1, 2].

Serum zinc is an appropriate biomarker for zinc status, as confirmed by its response to zinc intakes and correct prediction of functional responses to zinc interventions [5]. In this case-control study nested within a large multiethnic cohort, we evaluated the association between prediagnostic serum zinc and subsequent prostate cancer risk. To our knowledge, this is the first report of a prospective analysis of this relation with risk.

MATERALS AND METHODS

Study Population

We carried out a nested case-control study within the Multiethnic Cohort Study, which was established in Hawaii and California between 1993 and 1996 [6]. The study was approved by the review boards of the University of Hawaii and the University of Southern California. More than 215,000 adults aged 45–75 years entered the cohort by completing a 26-page mailed questionnaire on diet and lifestyle factors, which targeted five ethnic/racial groups: African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites. A prospective biorepository was developed primarily between 2001 and 2006 [7], when cohort members who gave informed consent to participate provided a blood and/or urine sample. A total of 67,594 members contributed to the biorepository, of which 31,136 were men.

Selection of Cases and Controls

Identification of incidence prostate cancer cases was accomplished through the tumor registries of the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute covering Hawaii and California. For this nested case-control study, cases were defined as men who were diagnosed with invasive prostate cancer after blood collection up to the time of sample shipment in May 2006: the average length of time between blood collection and cancer diagnosis was 1.9 years. Advanced prostate cancers were defined as all cancers that were regional or metastatic (not in situ or localized). High-grade prostate cancers were based on Gleason score ≥7 (categorized as poorly differentiated). During the follow-up period, 467 eligible prostate cancer cases were identified. For each case, two controls were randomly selected from a pool of potential controls in the biorepository who were alive and free of prostate cancer at the age of the case's diagnosis and who matched the case on location (Hawaii or California), race/ethnicity, birth year (±1 year), date of blood draw (±6 months), time of blood draw (±2 hours), and fasting hours (0 to <6, 6 to <8, 8 to <10, and ≥10 hours). Of 467 cases, 392 had fasting blood samples available for analysis (including 134 advanced or high-grade prostate cancer cases and 248 localized cases without a high-grade tumor). Of their 784 matched controls, one did not have a sample available for analysis. Therefore, 392 cases and 783 controls were included in analyses.

Serum Zinc Assay

Serum samples were thawed and 100 microliters from each was gravimetrically transferred to a pre-cleaned sample tube and digested at 60°C using a sonicator in the presence of 300 microliters of Optima nitric acid (Thermo Fisher, Pittsburgh, PA) and 100 microliters of

Fluka Trace Select hydrogen peroxide (Sigma-Aldrich, St. Louis, M). The digested samples were diluted to 10 milliliters, internal standards were added, and the zinc concentration was quantified using a Plasma Quad III ICP-MS (Thermo Scientific, Waltham, MA) from both the ^{64}Zn and ^{66}Zn stable isotopes. All data are corrected based on the internal standard with zinc concentrations determined by standard comparison. NIST SRM 909b, Level II, Lyophillzed Human Serum (National Institutes of Standards and Technology, Besthesda, MD) was analyzed as a quality control sample with every analysis batch.

Statistical Analyses

Selected characteristics were tested between cases and controls by the t-test for continuous variables and the chi-square test for categorical variables. Subjects were divided into quartiles or tertiles determined by the overall distribution of serum zinc in both cases and controls. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated using conditional logistic regression where matched sets were the strata to account for the matching criteria given above. We entered age at blood draw and fasting hours to account for any possible systematic differences within matched sets, in addition to adjustment for family history of prostate cancer (yes/no), body mass index (BMI, <25, 25–<30, ≥30 kg/m^2), and education (years of schooling), which were found to be related to prostate cancer risk in this cohort [8]. Dose-response was tested using a log-transformed continuous variable. The associations were computed separately for localized (but not high-grade) cases and their matched controls, and for advanced and/or high-grade cases and their matched controls. The assessment of heterogeneity across cancer stage/grade was performed by fitting the simultaneous conditional logistic regressions for localized and advanced cancers and testing for an interaction between event type and serum zinc by a likelihood ratio test. In the ethnic-specific analysis, Native Hawaiians were not included because the number of the cases was too small (n=15). Assessment for heterogeneity across ethnicity was based on likelihood ratio tests comparing conditional logistic models with and without cross-product terms between ethnicity and log-transformed serum zinc levels. Two-sided P values less than 0.05 were considered significant. All analyses were performed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

There was no significant difference in the matching characteristics, or in years of education, physical activity levels, and BMI between cases and controls (Table 1). Cases were more likely to have a family history of prostate cancer, compared to controls. Mean serum zinc concentrations did not differ between cases and controls.

No association was found between serum zinc levels and prostate cancer risk overall (Table 2). Additional adjustment for family history of prostate cancer, BMI, and education did not change the estimates substantially. When we ran the models for localized and advanced or high-grade cases separately, using tertiles, we found no significant relation for either and no evidence of heterogeneity (p = 0.86) (Table 3). In ethnic-specific analyses, however, positive associations were found in Japanese Americans (OR for the highest vs. the lowest tertile = 2.59, 95% CI: 1.09–6.17) and Latinos (OR = 2.74, 95% CI: 1.05–7.10), whereas no association was observed in African Americans and whites; p for heterogeneity was 0.43 across the four ethnic groups, and 0.12 between Japanese Americans/Latinos and African Americans/whites. When we excluded the cases diagnosed within a year of blood draw, the results remained similar; the increased risk was observed in Japanese Americans and Latinos but not in African Americans and whites (p for heterogeneity between Japanese Americans/Latinos versus African Americans/whites = 0.048, data not shown).

DISCUSSION

In this nested case-control study within the Multiethnic Cohort, we found no overall evidence to support an inverse association between serum zinc levels and prostate cancer risk, and, to the contrary, a suggestion in the ethnic-specific analysis of a possible increase in risk in Japanese Americans and Latinos.

Experimental evidence supports a role of zinc in protecting prostate cells from malignancies; suggested mechanisms include beneficial effects of zinc on mitochondrial aconitase activity, apoptosis, and protection of DNA integrity [2]. However, epidemiological studies have shown mixed results for zinc intake/status and prostate cancer risk. One cohort study [9] and two case-control studies [10, 11] reported a direct association between high zinc intake from foods or supplements and prostate cancer risk, while one cohort study [12] and one case-control study [13] found an inverse association. One nested case-control study found no association between toenail zinc concentration and prostate cancer risk [14]. A spatial study in the United States showed that increased prostate cancer rates were associated with reduced soil zinc concentrations and elevated use of groundwater that would reflect local soil [15].

In the normal prostate, zinc uptake serves to inhibit citrate oxidation and to induce apoptosis. Impairment of the normal uptake of zinc leads to a reduced prostatic zinc concentration, and prostate tumor growth *in vitro* [16]. Zinc levels in malignant prostate tissue are 62–75% lower than the normal tissue [16]. In addition, prostate cancer patients have lower zinc levels in blood compared to healthy controls [17, 18]. However, these studies measured zinc levels after cancer diagnosis, which could reflect the disease process (reverse causation). In the current study, prediagnostic serum zinc concentrations did not predict the risk of prostate cancer in the overall analysis. The mean serum concentration in the controls (93.9 μg/dl) appears to be comparable to that of a US national sample (93.4 μg/dl, morning fasting blood) [19]. Since only 7.5% of our subjects (5.6% of cases and 8.4% of controls) had a serum zinc concentration below the suggested lower cutoff (74 μg/dl, morning fasting blood, for males aged ≥10 years) [19], we are not able to study effects of low zinc status on prostate cancer development.

We found a suggestive direct association between serum zinc and prostate cancer risk in Japanese American and Latino men, but not in African American and whites. Higher zinc exposure may increase prostate cancer risk by raising testosterone or IGF-1 levels [3, 4]. In the current study, serum zinc concentrations was not correlated with testosterone levels, either overall or by ethnicity. In a previous analysis, IGF-1 levels were associated with an increased risk of prostate cancer in Latino men [20]. However, serum IGF-1 was not correlated with serum zinc among either Latino men or other ethnic groups in our study (data not shown). Further investigation is required to explain the possible direct association between zinc status and prostate cancer risk.

The study's strengths include a prospective design, which minimized the possibility that the disease process affected zinc status in the cases, and participants with diverse racial/ethnic backgrounds. Also, we had information on several potential confounding factors. Nevertheless, there are some limitations to be considered. Although serum zinc is the most commonly used biomarker for zinc status, circulating zinc levels may not accurately reflect cellular zinc status due to tight homeostatic control mechanisms [2]. The time between blood draw and tumor diagnosis was relative short (mean = 1.9 years), and thus preclinical disease might have influence circulating zinc status in some cases. However, when we excluded cases diagnosed in the first year of follow-up, the results remained similar. The majority of the cases had early stage disease which limited our ability to detect an effect of

circulating zinc on tumor progression. Also, the smaller number of cases for race/ethnic specific analysis make the results more tenuous.

CONCLUSION

In conclusion, our overall findings do not support an association of circulating zinc concentrations with prostate cancer risk, although blood levels may not correlate well with zinc levels in prostate tissue. The ethnic-specific results showing a possible increase in risk associated with higher zinc levels in blood warrant further study with a larger sample size.

Acknowledgments

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References

1. Costello LC, Franklin RB, Feng P, Tan M, Bagasra O. Zinc and prostate cancer: a critical scientific, medical, and public interest issue (United States). Cancer Causes Control. 2005; 16(8):901–915. [PubMed: 16132800]
2. Ho E, Song Y. Zinc and prostatic cancer. Curr Opin Clin Nutr Metab Care. 2009; 12(6):640–645. [PubMed: 19684515]
3. Om AS, Chung KW. Dietary zinc deficiency alters 5 alpha-reduction and aromatization of testosterone and androgen and estrogen receptors in rat liver. J Nutr. 1996; 126(4):842–848. [PubMed: 8613886]
4. Holmes MD, Pollak MN, Willett WC, Hankinson SE. Dietary correlates of plasma insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations. Cancer Epidemiol Biomarkers Prev. 2002; 11(9):852–861. [PubMed: 12223429]
5. Gibson RS, Hess SY, Hotz C, Brown KH. Indicators of zinc status at the population level: a review of the evidence. Br J Nutr. 2008; 99(Suppl 3):S14–23. [PubMed: 18598584]
6. Kolonel LN, Henderson BE, Hankin JH, Nomura AM, Wilkens LR, Pike MC, Stram DO, Monroe KR, Earle ME, Nagamine FS. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am J Epidemiol. 2000; 151(4):346–357. [PubMed: 10695593]
7. Park SY, Wilkens LR, Henning SM, Le Marchand L, Gao K, Goodman MT, Murphy SP, Henderson BE, Kolonel LN. Circulating fatty acids and prostate cancer risk in a nested case-control study: the Multiethnic Cohort. Cancer Causes Control. 2009; 20(2):211–223. [PubMed: 18821021]
8. Park SY, Murphy SP, Wilkens LR, Stram DO, Henderson BE, Kolonel LN. Calcium, vitamin D, and dairy product intake and prostate cancer risk: The Multiethnic Cohort Study. Am J Epidemiol. 2007; 166(11):1259–1269. [PubMed: 17925283]
9. 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(13):1004–1007. [PubMed: 12837837]
10. Zhang Y, Coogan P, Palmer JR, Strom BL, Rosenberg L. Vitamin and mineral use and risk of prostate cancer: the case-control surveillance study. Cancer Causes Control. 2009; 20(5):691–698. [PubMed: 19093214]
11. Gallus S, Foschi R, Negri E, Talamini R, Franceschi S, Montella M, Ramazzotti V, Tavani A, Dal Maso L, La Vecchia C. Dietary zinc and prostate cancer risk: a case-control study from Italy. Eur Urol. 2007; 52(4):1052–1056. [PubMed: 17292532]
12. Gonzalez A, Peters U, Lampe JW, White E. Zinc intake from supplements and diet and prostate cancer. Nutr Cancer. 2009; 61(2):206–215. [PubMed: 19235036]
13. 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(10):887–892. [PubMed: 10548317]

14. Platz EA, Helzlsouer KJ, Hoffman SC, Morris JS, Baskett CK, Comstock GW. Prediagnostic toenail cadmium and zinc and subsequent prostate cancer risk. Prostate. 2002; 52(4):288–296. [PubMed: 12210489]

15. Wagner SE, Burch JB, Hussey J, Temples T, Bolick-Aldrich S, Mosley-Broughton C, Liu Y, Hebert JR. Soil zinc content, groundwater usage, and prostate cancer incidence in South Carolina. Cancer Causes Control. 2009; 20(3):345–353. [PubMed: 18949566]

16. Franklin RB, Feng P, Milon B, Desouki MM, Singh KK, Kajdacsy-Balla A, Bagasra O, Costello LC. hZIP1 zinc uptake transporter down regulation and zinc depletion in prostate cancer. Mol Cancer. 2005; 4:32. [PubMed: 16153295]

17. Aydin A, Arsova-Sarafinovska Z, Sayal A, Eken A, Erdem O, Erten K, Ozgok Y, Dimovski A. Oxidative stress and antioxidant status in non-metastatic prostate cancer and benign prostatic hyperplasia. Clin Biochem. 2006; 39(2):176–179. [PubMed: 16413012]

18. Christudoss P, Selvakumar R, Fleming JJ, Gopalakrishnan G. Zinc status of patients with benign prostatic hyperplasia and prostate carcinoma. Indian J Urol. 2011; 27(1):14–18. [PubMed: 21716879]

19. Hotz C, Peerson JM, Brown KH. Suggested lower cutoffs of serum zinc concentrations for assessing zinc status: reanalysis of the second National Health and Nutrition Examination Survey data (1976–1980). Am J Clin Nutr. 2003; 78(4):756–764. [PubMed: 14522734]

20. Gill JK, Wilkens LR, Pollak MN, Stanczyk FZ, Kolonel LN. Androgens, growth factors, and risk of prostate cancer: the Multiethnic Cohort. Prostate. 2010; 70(8):906–915. [PubMed: 20166103]

TABLE I

Characteristics of Prostate Cancer Cases and Controls in the Multiethnic Cohort Study[a]

	Cases	Controls	p[b]
n	392	783	—
Age at blood draw[a]	69.1 ± 7.1	68.9 ± 7.2	0.67
Fasting hours prior to blood draw[a]	11.7 ± 4.8	11.9 ± 5.0	0.69
Years of education	13.9 ± 2.8	13.8 ± 3.0	0.73
Body mass index (kg/m^2)	26.7 ± 4.0	27.0 ± 4.1	0.24
METS of activity per day	1.6 ± 0.3	1.6 ± 0.3	0.66
Family history of prostate cancer (%)	13.3	8.6	0.01
Ethnicity (%)[a]			
African American	46.2	46.2	1.00
Native Hawaiian	3.8	3.8	
Japanese American	19.6	19.7	
Latino	15.3	15.3	
White	15.1	14.9	
Serum zinc (μg/dl)	94.9 ± 20.4	93.9 ± 17.6	0.42

Data shown as mean ± SD, unless specified otherwise.

[a]Matching criteria: geographic location (Hawaii or California), race/ethnicity, birth year (±1 year), date of blood draw (±6 months), time of blood draw (± 2 hours), and fasting hours prior to blood draw (0–<6, 6–<8, 8–<10, and 10+ hours).

[b]Tested by t-test (means) and chi-square test (percentages).

TABLE II

Association Between Serum Zinc and Prostate Cancer Risk[a]

	Serum zinc (μg/dl)				P for trend[b]
	≤82.9	82.9–≤92.2	92.2–≤102.5	>102.5	
No. of cases	97	95	97	103	
No. of controls	196	199	198	190	
OR (95% CI)[c]	1.00	0.98 (0.69–1.40)	0.99 (0.69–1.43)	1.13 (0.79–1.62)	0.38
OR (95% CI)[d]	1.00	0.99 (0.69–1.42)	0.99 (0.68–1.43)	1.08 (0.74–1.56)	0.65

[a]Matching criteria were accounted for by conditional logistic regression: geographic location (Hawaii or California), race/ethnicity, birth year (±1 year), date of blood draw (±6 months), time of blood draw (± 2 hours), and fasting hours prior to blood draw (0–<6, 6–<8, 8–<10, and 10+ hours).

[b]Based on a log-transformed continuous variable.

[c]Adjusted for age at blood draw and fasting hours prior to blood draw as continuous variables.

[d]Additionally adjusted for family history of prostate cancer, BMI, and education.

TABLE III

Association Between Serum Zinc and Prostate Cancer Risk by Tumor Characteristics and Race/Ethnicity[a]

	Serum zinc (μg/dl)			P for trend[b]	P for heterogeneity[c]
	≤86.1	86.1–≤98.5	>98.5		
Tumor characteristics					0.86
Localized					
Cases/controls	73/173	88/181	87/162		
OR (95% CI)	1.00	1.38 (0.91–2.09)	1.34 (0.89–2.04)	0.56	
Advanced or high grade					
Cases/controls	44/91	44/88	46/88		
OR (95% CI)	1.00	0.96 (0.57–1.64)	0.95 (0.53–1.71)	0.67	
Race/ethnicity					0.43
African American					
Cases/controls	67/128	51/108	63/126		
OR (95% CI)	1.00	0.87 (0.54–1.40)	0.88 (0.55–1.41)	0.63	
Japanese American					
Cases/controls	19/51	28/62	30/41		
OR (95% CI)	1.00	1.40 (0.65–2.99)	2.59 (1.09–6.17)	0.21	
Latino					
Cases/controls	10/41	27/39	23/40		
OR (95% CI)	1.00	3.27 (1.22–8.79)	2.74 (1.05–7.10)	0.21	
White					
Cases/controls	17/42	23/39	19/36		
OR (95% CI)	1.00	1.27 (0.55–2.93)	1.27 (0.52–3.13)	0.73	

[a]Matching criteria were accounted for by conditional logistic regression: geographic location (Hawaii or California), race/ethnicity, birth year (±1 year), date of blood draw (±6 months), time of blood draw (± 2 hours), and fasting hours prior to blood draw (0–<6, 6–<8, 8–<10, and 10+ hours). The models were adjusted for age at blood draw and fasting hours prior to blood draw as continuous variables, as well as family history of prostate cancer, BMI, and education.

[b]Based on a log-transformed continuous variable.

[c]Based on the likelihood ratio test. P for heterogeneity between Japanese Americans/Latinos and African Americans/whites = 0.12