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Zinc Intake From Supplements and Diet and Prostate Cancer

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Laboratory and animal studies suggest a beneficial effect of zinc on prostate cancer. We evaluated the association between dietary and supplemental zinc and prostate cancer within the VITamins And Lifestyle (VITAL) cohort, a study specifically designed to evaluate the impact of dietary supplements and cancer risk. Of 35,242 men who completed the baseline dietary and supplemental questionnaire, 832 men developed invasive prostate cancers between October 2000 and December 2004. Ten-year average intake of supplemental zinc was not associated with a reduced prostate cancer risk overall (adjusted hazard ratio (HR) = 0.82 (95% confidence interval (CI) 0.58–1.14) for >15mg/day vs. nonuse, *P* for trend = 0.44); however, risk of advanced prostate cancer (regionally invasive or distant metastatic, *n* = 123) decreased with greater intake of supplemental zinc (adjusted HR = 0.34, 95% CI = 0.13–1.09 for 10-yr average intake >15 mg/day vs. nonuse, *P* for trend = 0.04). Dietary zinc was not associated with prostate cancer. In this prospective cohort, long-term supplemental zinc intake was associated with reduced risk of clinically relevant advanced disease. This study had limited ability to study early-stage disease because detection of early-stage disease is highly related to having a PSA test, and information on PSA was only available at baseline. Because few other epidemiologic studies have investigated the association between zinc and prostate cancer, and these have not yielded consistent findings, further research is needed.

INTRODUCTION

The incidence of prostate cancer has been increasing worldwide, with the greatest increases in the United States (1). It is the most common cancer other than skin cancer among U.S. men (2). The etiology of prostate cancer is poorly understood; age, family history, and race are among the few established risk factors (3). Therefore modifiable risk factors, including nutrient intake, are under active investigation.

There are several lines of evidence that suggest that zinc may play an important and direct role in the prostate. Studies have found that total zinc levels in the prostate are 10 times higher than in other soft tissues (4,5). Furthermore, adenocarcinoma cells taken from prostate tumors have lost their ability to amass zinc; whereas in normal prostate cells, zinc is highly concentrated intracellularly in glandular epithelium and inhibits mitochondria aconitase resulting in decreased citrate oxidase (6–8). This metabolic effect has implications in altering energy metabolism and adenosine triphosphate production of prostate cells such that lower zinc levels in prostate cells leads to a higher rate of citrate oxidation, which increases the available energy and has been proposed to contribute to carcinogenesis and tumor growth (4,9–11).

Based on results from cellular studies, we hypothesized that prostate cancer risk may be reduced by zinc intake both from supplements and diet. Only a small number of epidemiologic studies have investigated the relationship between prostate cancer risk and zinc intake from supplements (primarily from multivitamin use) (12–14), diet (15–17), and combined diet and supplements (18,19), with highly inconsistent results.

To address this issue, we have prospectively collected detailed measures of zinc intake from diet and supplements, as well as other factors such as demographic and lifestyle characteristics, in a large cohort study. An advantage of our cohort is that it was specifically designed to investigate the association of supplement use with cancer risk and accordingly includes a large proportion of high users of dietary supplements. We have a more detailed exposure assessment than other studies including exact composition of multivitamins and information on use of single zinc supplements. We also collected information on health conditions that may be the indications for taking supplements; in particular zinc, is marketed and sold as a "men's health" or "prostate health" supplement and is often taken by men with benign prostatic hyperplasia (BPH). Finally, we take into account modifiers of zinc absorption (e.g., vegetable intake) in analysis of the zinc and prostate cancer association.

METHODS

Study Participants

Men in this study were participants in the VITamins And Lifestyle (VITAL) cohort study whose primary aim is to

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investigate vitamin and mineral supplementation and cancer risk. Details of recruitment have been published in a previous report by White et al. (20). Briefly, men and women were eligible to participate in the VITAL study if they were aged 50 to 76 yr and living in a 13-county area of western Washington State. Because this study was limited to men, we report here recruitment of men. Using names that were obtained from a commercial list, 195,465 men were contacted by mail. The mailing sent to potential participants included a recruitment letter targeting supplement users and a 24-page questionnaire. Recruitment was conducted from October 2000 through December 2002, during which time 37,382 men (19.5%) completed and returned the VITAL baseline questionnaire. Of these, 2,136 men who reported a history of prostate cancer at baseline were excluded, as were two men subsequently diagnosed with in situ prostate cancer, leaving 35,244 men available for this analysis.

This project was reviewed and approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Data Collection

Baseline data for the VITAL study were obtained from a 24-page, self-administered questionnaire that included items on supplement use, diet, personal characteristics, medical history, and lifestyle factors.

The questionnaire assessed the use of 38 vitamins, mineral, herbal, and other supplements over the 10 yr prior to enrollment into the study. Participants were first asked about their current multivitamins and selected one of 16 common brand names; or if the brand was not listed, they provided dose information on each vitamin and mineral in their brand. For those who used more than one brand over the 10 yr or only used multivitamins in the past, participants selected from another list of brand names (reflecting past market availability). Nutrient composition of multivitamin brands was obtained from the *Physicians Desk Reference for Non-Prescription Drugs* (2001 for current and 1996 for past) or inquiries to manufactures. For past and current multivitamin use, information on years of use over the previous 10 yr and frequency (times per week) of use in those years was also obtained.

Information on use of single nutrient supplements and nutrients in mixtures not classified as multivitamins, including zinc, was requested from participants including current and past use, years of use over the previous 10 yr, frequency, and usual dose per day. Supplemental intake per day averaged over the last 10 yr prior to baseline for zinc and other nutrients was calculated as (dose per day) $\times$ (days per week/7) $\times$ (years/10), summed over individual supplements and current and past multivitamins.

Diet was assessed by a semiquantitative food frequency questionnaire (FFQ) that asked about the frequency of consumption over the last year and portion sizes of 120 foods or food groups and included 12 adjustments questions on types of foods and preparation techniques (e.g., use of low fat vs. whole fat foods). The FFQ analytic program is based on nutrient values from the Minnesota Nutrition Data System for Research (21). Participants were excluded from the nutrient calculations if they did not complete all pages of the food frequency section (at least 5 items per page) or their energy intake was below 800 kcal/day or was above 5,000 kcal/day.

The remaining parts of the questionnaire covered demographic characteristics, health history, and other potential confounders. Using self-reported weight and height, we calculated body mass index (BMI) for each participant as kg/m^2. Physical activity was assessed by a 1-page form described in detail elsewhere (22). In brief, participants, reported the number of years in the last 10 during which they undertook each of several types of activities followed by the frequency (days per week) and duration (minutes per day). For moderate/strenuous exercise, participants reported the types of exercise (e.g., running); and for walking, they reported pace. Average total MET hours (kcal energy expenditure per kg body weight) per week over the past 10 yr was calculated using the years, frequency, and published energy expenditures for different activities.

Health information collected at baseline included history of prostate-specific antigen (PSA) testing within the 2 yr prior to baseline, physician-diagnosed BPH, ever having a prostate biopsy, current use of medications commonly prescribed for BPH (finasteride, terazosin, doxazosin, or tamsulosin), and family history of prostate cancer.

Follow-Up of Subjects for Prostate Cancer and Censoring

A total of 832 incidents, invasive prostate cancers, were diagnosed between baseline (2000–2002) and December 31, 2004. We obtained case status, cancer stage, and Gleason score by linking the cohort to the western Washington State Surveillance, Epidemiology and End Results (SEER) cancer registry. This registry ascertains all cancers among those living in the 13 counties of western Washington State via abstraction of information from hospital records, pathology laboratories, and other sources.

We utilized a multistep scheme to link our cohort to the SEER registry. Initially, all potential matches were identified by linking on 9 increasingly broad sets of matching criteria (such as full social security number, last name, and date of birth). Next, each potential match was ranked electronically to decide whether it was "sufficient" (enough data items in common to be considered a match), "insufficient" (too few data items in common to consider a match), or "needing visual inspection" (some data items in common). Matches needing visual inspection were examined using all relevant information from VITAL and SEER files. Finally, for records for which the match was still uncertain, the participant was telephoned directly.

For tumor characteristics, SEER summary stage was categorized as local or regional/distant. Grade was measured by Gleason score and was categorized as 2 to 6 and 7 to 10, corresponding to well-differentiated or moderately differentiated and poorly differentiated cancers, respectively. Because SEER

only implemented this coding scheme in 2003, we re-abstracted Gleason scores from the original SEER reports for cancers diagnosed from 2000 to 2002.

The censored date for each subject was the earliest date of withdrawal from the study (0.02%), death (3.0%), move out of the 13 county catchment area of the SEER registry (3.9%), or December 31, 2004. Deaths were ascertained by linkage to Washington State death files. Moves out of area were identified by linkage to the National Change of Address System and by follow-up letters and phone calls.

Statistical Analyses

Cox proportional hazard models with age as the time variable were used to estimate the relative risk, as measured by hazard ratios, of prostate cancer associated with sociodemographic, medical, and lifestyle characteristics other than zinc intake. To understand the correlates of supplemental zinc intake, unconditional logistic regression models were used to estimate odds ratios for the association between these same characteristics and high 10-yr average supplement zinc intake (>15 mg/day) vs. no use, with adjustment for age as a continuous variable. Cox proportional hazard models were used to estimate the relative risk, as measured by hazard ratios, of prostate cancer associated with various measures of zinc intake from supplements and diet. Age was treated as the time variable, with left truncation at age at baseline and censoring (right truncation) at the censoring events noted above. To address the possibility of medical surveillance bias, a variable identifying self-reported PSA testing within the 2 yr prior to baseline was included in all multivariate models. Potential confounding factors associated with both zinc intake and prostate cancer that were included in the multivariate models were ethnicity/race (White, Black, or other), education (continuous), current multivitamin use (yes–no), and first-degree family history of prostate cancer. After these adjustments, other potential confounders, including servings of vegetables, 10-yr average vitamin E supplement use, 10-yr average selenium supplement use, BPH, and use of finasteride or other drugs for BPH did not modify the β-coefficients hazard ratios for zinc intake by more than 10%. To test for a trend across each category, we modeled a single ordinal categorical variable using categorical medians. In the models presented, there was no evidence that the assumptions of the proportional hazard function were violated.

We also examined the supplemental zinc and prostate cancer relationship stratified by vegetable intake, dietary zinc intake, and PSA testing and by prostate cancer categorized by grade and stage. Interaction between a dichotomous effect modifier variable and a categorical exposure variable was computed as the P value for an interaction term between the single "trend" variable and the effect modifier in a model that included the main effects as well as the interaction term.

Analyses were conducted using STATA version 8.2 (StataCorp, College Station, TX).

RESULTS

Eight hundred and thirty-two men were diagnosed with prostate cancer during an average follow-up time of 3.5 yr Eighty-four percent had local stage disease, whereas 16% had regional/distant disease. Moderate- to well-differentiated tumors (Gleason score 2 to 6, 56.4%) were more common than poorly differentiated tumors (Gleason score 7 to 10, 42%).

Risk of prostate cancer was higher among Black men, men with a higher education, and men with a PSA test in the 2 yr prior to baseline (Table 1). Other factors associated with an increased risk of prostate cancer included having BPH, use of drugs for BPH, having had a prior prostate biopsy, first degree family history of prostate cancer, and current multivitamin use.

To understand the correlates of supplemental zinc intake, age-adjusted unconditional logistic regression models were used to estimate odds ratios for the association between these same characteristics and high 10-yr average supplement zinc intake (>15 mg/day) vs. no use (data not shown). Zinc supplement use >15 mg/day was used as the cutoff in this analysis and in the ones below because it is above the intake that could be achieved by 10-yr daily use of common multivitamins formulations, which typically contain 15 mg of zinc. High supplemental zinc intake was more common in older, highly educated men and men who had a PSA test in the 2 yr prior to baseline. High use was also more common in men diagnosed with BPH, men who use BPH drugs, and men who had a first degree family history of prostate cancer—possibly because higher doses of zinc are included in supplements that are marketed for men for "prostate health." Men who were overweight or obese and drank alcohol were less likely, whereas those who were physically active and had a high consumption of vegetables were more likely, to have a high 10-yr supplemental zinc intake. Current multivitamin use, 10-yr supplemental vitamin E, and 10-yr supplemental selenium use were strongly correlated with high 10-yr supplemental zinc use.

After adjustment for confounders, we observed a weak, nonsignificant inverse association between 10-yr average supplemental zinc and prostate cancer risk (HR = 0.82 [95% CI = 0.58–1.14] for greater than 15 mg/day vs. no use, P for trend = 0.44) (Table 2). Current single zinc supplement use (from individual supplements and mixtures not classified as multivitamins), years single zinc supplements were taken, amount per day of single zinc supplements, dietary zinc intake, and total zinc intake (diet plus10-yr average supplemental zinc) were not associated with prostate cancer risk.

Vegetable intake modified the association between 10-yr average supplemental zinc and prostate cancer risk (P for interaction = 0.01), with an inverse association between 10-yr supplemental zinc and prostate cancer risk restricted to men with a high intake of vegetables (HR = 0.43) (95% CI = 0.25–0.71) for greater than 15 mg/day vs. no use (Table 3). We also considered potential effect modification of the supplemental zinc and

TABLE 1
Association of sociodemographic, medical, and lifestyle characteristics with prostate cancer among 35,244 men in the VITAL cohort[a]

Characteristics	No Prostate Cancer ($N = 34,412$)		Prostate Cancer ($N = 832$)		Age-Adjusted HR	Age-Adjusted 95% CI
	N^b	%	N^b	%		
Socioeconomic factors						
Age (yr)						
50 to ≤55	8,342	24.2	56	6.7		
55 to ≤60	7,938	23.1	139	16.7		
60 to ≤65	6,443	18.7	185	22.2		
65 to ≤70	5,694	16.6	199	23.9		
70 to ≤77	5,995	17.4	253	30.4		
Race						
White	31,642	93.2	781	94.6	1.0	
Black	421	1.2	17	2.1	1.70	1.05–2.76
Other	1,906	5.6	28	3.4	0.65	0.45–0.95
Education						
High school or less	5,405	15.9	135	16.3	1.0	
Some college	11,910	35.0	291	35.2	1.19	0.97–1.46
> College	16,705	49.1	400	48.4	1.19	0.98–1.45
Prostate-related factors						
PSA test in last 2 yr	24,368	71.8	671	82.5	1.47	1.22–1.76
Prior prostate biopsy	2,816	8.2	169	20.4	2.10	1.77–2.50
Benign prostatic hyperplasia (BPH)	5,386	15.7	222	26.8	1.46	1.24–1.71
Finasteride use	195	0.6	8	1.0	1.21	0.60–2.43
Other drugs for BPH	1,212	3.5	51	6.2	1.36	1.02–1.81
Family history[c]						
0	29,544	87.1	665	80.4	1.0	
1	4,133	12.1	136	16.4	1.51	1.26–1.82
2+	263	0.8	29	3.1	3.35	2.26–4.97
Lifestyle/dietary factors						
BMI (kg/m^2)						
18.5–24.9	9,189	27.5	223	27.4	1.0	
25–30	16,205	48.5	435	53.5	1.15	0.98–1.35
≥30	7,994	23.9	155	19.1	0.89	0.72–1.09
Physical activity (MET h/wk)						
None	5,115	15.1	110	13.4	1.0	
0.1–4	7,215	21.3	164	19.9	1.04	0.82–1.32
4.1–10.5	7,591	22.4	181	22.0	1.08	0.85–1.37
10.51–21.1	6,827	20.1	179	21.8	1.18	0.93–1.50
≥21.1	7,188	21.2	189	23.0	1.16	0.92–1.47
Energy intake (kcal/day)						
0–1,658	7,941	25.0	204	26.4	1.0	
1,659–2,140	7,946	25.0	198	25.6	0.99	0.82–1.21
2,141–2,699	7,963	25.0	182	23.5	0.94	0.77–1.15
≥2700	7,955	25.0	190	24.6	1.02	0.84–1.25
Alcohol use (drinks/month)						
<1	10,669	31.6	235	28.2	1.0	
1–6	12,555	37.2	322	39.5	1.24	1.05–1.48
7–13	5,337	15.8	138	16.9	1.21	0.98–1.49

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TABLE 1
(Continued)

Characteristics	No Prostate Cancer ($N = 34,412$)		Prostate Cancer ($N = 832$)		Age-Adjusted HR	Age-Adjusted 95% CI
	N^b	%	N^b	%		
14–27	3,574	10.6	78	9.6	0.97	0.75–1.26
≥28	1,614	4.8	43	5.3	1.27	0.92–1.76
Vegetable intake (serving/day)						
0–1.2	7,929	25.1	155	20.4	1.0	
1.21–1.8	7,889	25.0	186	24.4	1.13	0.91–1.39
1.81–2.5	7,873	24.9	218	28.7	1.25	1.01–1.53
>2.51	7,869	24.0	202	26.5	1.15	0.93–1.42
Current multivitamin use						
No	16,231	47.2	333	40	1.0	
Yes	18,173	52.8	499	60	1.25	1.09–1.43
10-yr avg. supplemental vitamin E (mg/day)[d]						
None	16,986	49.6	352	42.4	1.0	
0–37.4	5,756	16.8	165	19.9	1.27	1.05–1.52
37.41–200	5,756	16.8	151	18.2	1.12	0.93–1.36
201–1,500	5,748	16.8	162	19.5	1.09	0.91–1.32
10-yr avg. supplemental selenium (mcg/day)[d]						
None	19,026	55.5	415	50.1	1.0	
0–11	7,456	21.8	182	22.0	1.03	0.86–1.23
11.1–22.5	2,727	8.0	92	11.1	1.47	1.17–1.84
22.51–400	5,070	14.8	139	16.8	1.11	0.92–1.35

[a]Abbreviations are as follows: VITAL, VITamins And Lifestyle study; HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; BMI, body mass index; MET, metabolic equivalent.

[b]Numbers do not add up to total number due to missing data: For all variables, missing data is <5%, with the exception of income (15.5% of no prostate cancer participants and 18.6% of cases), calories (7.6% of no prostate cancer participants and 7.0% of cases), and dietary vegetable intake (8.3% of no prostate cancer participants and 8.5% of cases).

[c]Number of first-degree relatives with prostate cancer.

[d]10-yr average vitamin E and selenium includes individual vitamin E or selenium supplements and multivitamins.

prostate cancer association by dietary zinc. Ten-year average supplemental zinc intake was associated with a reduction in prostate cancer risk in those men who consumed above the median intake of dietary zinc (>13.2 mg/day), whereas it was not associated with prostate cancer in those men who consumed less than the median of dietary zinc intake; however, this interaction was not significant (P for interaction = 0.13). Report of a PSA test in the two years prior to baseline did not alter the zinc and prostate cancer association.

Associations between 10-yr supplemental zinc and prostate cancer did not vary by tumor grade (Table 4). However, although there was no association of supplemental zinc intake with risk of localized prostate cancer, there was a significant inverse trend of 10-yr supplemental zinc use and risk of prostate tumors classified as regional/distant (HR = 0.34) (95% CI = 0.13–1.09) for greater than 15 mg/day vs. no use (P for trend = 0.04).

DISCUSSION

In this large, population-based cohort study, we observed that 10-yr average intake of supplemental zinc was associated with a small, nonstatistically significant reduced risk of prostate cancer overall. However, risk of advanced prostate cancer (regionally invasive or distant metastatic) decreased significantly with greater intake of supplemental zinc. Dietary zinc and total zinc intake (diet plus 10-yr average supplemental zinc) were not associated with prostate cancer risk.

There have been only a few prior epidemiological studies of supplemental zinc and prostate cancer, and these have had

TABLE 2
Association of zinc intake from supplement use and diet assessed at baseline with prostate cancer among 35,244 men in VITAL cohort[a]

Zinc Intake	No Prostate Cancer ($N = 34,412$)		Prostate Cancer ($N = 832$)		Multivariate Adjusted HR[c]	Multivariate Adjusted 95% CI
	N[b]	%	N[b]	%		
Single zinc supplement use						
None	30,272	88.4	729	88.4	1.0	1.0
Past	844	2.5	19	2.5	0.80	0.49–1.30
Current	3,133	9.2	79	9.2	0.88	0.69–1.11
Single zinc supplement duration (yr)						
None	30,278	89.0	729	88.7	1.0	
1–3	1,497	4.4	35	4.3	0.86	0.61–1.23
4–6	897	2.6	23	2.8	0.91	0.59–1.39
7–9	406	1.2	5	0.6	0.35	0.13–0.93
10	962	2.8	30	3.7	1.04	0.71–1.51
P trend					0.34	
Single zinc supplement amount (mg/day)						
None	30,278	89.0	729	89.9	1.0	
15	1,497	4.4	32	4.0	0.76	0.53–1.09
30	769	2.3	17	2.1	0.77	0.47–1.26
60	818	2.4	27	3.3	1.13	0.76–1.67
100	244	0.7	6	0.7	0.88	0.39–1.67
P trend					0.60	
10-yr average supplemental zinc (mg/day)[d]						
None	13,472	39.3	285	34.5	1.0	
0.1–7.5	8,168	23.9	185	22.4	0.85	0.64–1.14
7.51–15	8,343	24.4	239	28.9	0.91	0.67–1.25
15.1–80	4,264	12.5	118	14.3	0.82	0.58–1.14
P trend					0.44	
Dietary zinc (mg/day)						
0–10	7,932	25.0	213	27.5	1.0	
10.1–13.2	7,964	25.0	180	23.3	0.84	0.68–1.02
13.21–17.2	7,947	25.0	199	25.7	0.98	0.81–1.20
17.21–70.0	7,962	25.0	182	23.5	0.92	0.75–1.12
P trend					0.73	
Total zinc (mg/day)[e]						
0–13.3	7,927	25.0	181	23.5	1.0	
13.31–19.7	7,945	25.1	165	21.4	0.93	0.75–1.17
19.71–27.6	7,901	25.0	208	27.0	1.02	0.81–1.29
27.61–152	7,892	24.9	216	28.1	0.98	0.77–1.25
P trend					0.95	

[a]Abbreviations are as follows: VITAL, VITamins And Lifestyle study; HR, hazard ratio; CI, confidence interval.

[b]Numbers do not add up to total number due to missing data: For all variables, missing data is <5%, with the exception of dietary zinc (7.6% of no prostate cancer participants and 7.0% of cases), and total zinc (8.0% of no prostate cancer participants and 7.5% of cases).

[c]Multivariate HRs adjusted for education, race, family history, prostate-specific antigen test within the 2 yr prior to baseline, and current multivitamin use.

[d]10-yr average supplemental zinc includes individual zinc supplements and multivitamins.

[e]Total zinc = dietary zinc + 10-yr average supplemental zinc.

TABLE 3
Association of 10-yr average supplemental zinc use assessed at baseline with prostate cancer among 35,244 men in VITAL cohort stratified by vegetable intake, dietary zinc, and PSA test[a]

Zinc Use	No Prostate Cancer		Prostate Cancer		Multivariate Adjusted HR[c]	Multivariate Adjusted 95% CI	*P* Interaction
	N[b]	%	*N*[b]	%			
Above median of vegetable intake (>1.8 servings/day)							
10-yr average zinc (mg/day)[d]							
None	5,749	37.7	143	34.3	1.0		
0.1–7.5	3,633	23.2	96	23.0	0.61	0.39–0.95	
7.51–15	4,035	25.8	123	29.5	0.59	0.37–0.94	
15.1–80	2,250	14.4	55	13.2	0.43	0.25–0.71	
P trend					0.11		
Below median of vegetable intake(≤1.8 servings/day)							
10-yr avg. zinc (mg/day)[d]							
None	6,537	41.5	118	34.7	1.0		
0.1–7.5	3,851	24.4	73	21.5	1.15	0.76–1.74	
7.51–15	3,701	23.5	99	29.1	1.42	0.91–2.24	
15.1–80	1,676	10.6	50	14.7	1.52	0.93–2.49	
P trend					0.20		
							0.01
Above median of dietary zinc intake (>13.2 mg/day)							
10-yr avg. zinc (mg/day)[d]							
None	6,103	39.7	134	35.4	1.0		
0.1–7.5	3,756	23.9	86	22.7	0.70	0.44–1.09	
7.51–15	3,928	24.4	107	28.2	0.70	0.43–1.12	
15.1–80	2,048	12.0	52	13.7	0.57	0.34–0.96	
P trend					0.21		
Below median of dietary zinc intake(≤13.2 mg/day)							
10-yr avg. zinc (mg/day)[d]							
None	6,281	38.5	133	34.0	1.0		
0.1–7.5	3,788	23.7	85	21.7	1.00	0.67–1.50	
7.51–15	3,865	24.8	117	29.9	1.16	0.75–1.80	
15.1–80	1,899	12.9	56	14.3	1.11	0.69–1.79	
P trend					0.41		
							0.13
PSA test within 2 yr prior to baseline							
10-yr avg. zinc (mg/day)[d]							
None	8,837	36.4	213	31.9	1.0		
0.1–7.5	5,844	24.1	149	22.3	0.87	0.63–1.20	
7.51–15	6,306	26.0	206	30.9	0.97	0.69–1.37	
15.1–80	3,277	13.5	99	14.8	0.86	0.59–1.24	
P trend					0.27		
No PSA test within 2 yr prior to baseline							
10-yr avg. zinc (mg/day)[d]							
None	4,441	46.4	62	44.0	1.0		
0.1–7.5	2,221	23.2	33	23.4	0.79	0.40–1.57	
7.51–15	1,958	20.5	30	21.3	0.67	0.32–1.44	
15.1–80	944	9.9	16	11.4	0.65	0.28–1.48	
P trend					0.17		
							0.57

Abbreviations are as follows: VITAL, VITamins And Lifestyle study; PSA, prostate-specific antigen; HR, hazard ratio; CI, confidence interval.

[b]Numbers do not add up to total number due to missing data: For all variables, missing data is <5%, with the exception of dietary vegetable intake (8.7% of no prostate cancer participants and 9.0% of cases).

[c]Multivariate HRs adjusted for education, race, family history, PSA-test within the 2 years prior to baseline, and current multivitamin use.

[d]10-yr average supplemental zinc includes individual zinc supplements and multivitamins.

TABLE 4
Association of 10-yr supplemental zinc use assessed at baseline with prostate cancer by stage and grade among 35,244 men in VITAL cohort[a]

10-yr Average Zinc (mg/day)[b]	Grade					
	Gleason Score 2 to 6			Gleason score 7 to 10		
	Cases	Adjusted HR[c]	95% CI	Cases	Adjusted HR[c]	95% CI
None	157	1.0		122	1.0	
0.1–7.5	102	0.88	0.60–1.29	81	0.85	0.55–1.33
7.51–15	137	0.99	0.66–1.50	99	0.85	0.53–1.38
>15	73	0.93	0.60–1.45	43	0.70	0.41–1.19
P trend			0.91			0.21
	Stage					
	Local			Regional/Distant		
	Cases	Adjusted HR[c]	95% CI	Cases	Adjusted HR[c]	95% CI
None	233	1.0		51	1.0	
0.1–7.5	154	0.91	0.67–1.24	31	0.58	0.26–1.28
7.51–15	205	1.01	0.72–1.41	33	0.50	0.21–1.19
>15	107	0.94	0.65–1.34	11	0.34	0.13–1.09
P trend			0.98			0.04

[a] Abbreviations are as follows: VITAL, VITamins And Lifestyle study; HR, hazard ratio; CI, confidence interval.
[b] 10-yr average zinc includes all individual zinc supplements and multivitamins.
[c] Multivariate HRs adjusted for education, race, family history, prostate-specific antigen test within the 2 yr prior to baseline, and current multivitamin use.

divergent findings. In a case-control study, Kristal et al. (12) found a significant inverse association for single zinc supplement use of 7 days/wk compared to no use (OR = 0.55, 95% CI = 0.30–1.00, *P* for trend = 0.04), which was the strongest association of 7 supplements studied. The association was similar when limited to advanced disease (OR = 0.65, 95% CI = 0.33–1.25), but no longer statistically significant. In the Health Professionals Follow-up Study, neither high dose of supplemental zinc nor long duration of supplemental zinc use (from multivitamins and individual supplements) was associated with risk of prostate cancer (13). However, when the analysis was restricted to advanced or fatal prostate cancer, both high dose per day (RR = 2.29, 95% CI = 1.06–4.95 for >100 mg/day vs. none, *P* for trend = 0.003) and long duration (RR = 2.37, 95% CI = 1.42–3.95, for 10+ yr vs. none, *P* for trend < 0.001) were associated with *increased* risk. The only randomized clinical trial to our knowledge with zinc as part of the intervention and with prostate cancer reported as an outcome was the SU.VI.MAX trial, which demonstrated a moderate, nonsignificant reduction in prostate cancer risk (HR = 0.88, CI = 0.60–1.29) after 8 yr of follow-up (14). However, this trial randomized men to either a placebo or a supplement with nutritional doses of vitamin C, vitamin E, β-carotene, selenium, and zinc, so the effect of zinc cannot be separated from the effect of this combination of minerals and vitamins. This trial reported an almost 50% statistically significant risk reduction among men with normal baseline PSA (<3 micro/l) and a borderline statistically significant *increased* risk among those with elevated PSA at baseline, suggesting that this combination may have an adverse effect on already established or faster growing tumors. Our findings of a reduced risk of advanced prostate cancer associated with zinc supplement use are most consistent with those of Kristal et al. (12) and are in direct contrast to those from the Health Professional Study.

Our results exploring dietary zinc intake are consistent with two previous observational studies, which found no association with prostate cancer risk (16,17). These two case-control studies were from geographically distinct locations—Utah (17) and China (16). We found no association between total (dietary plus supplemental) zinc intake and prostate cancer risk, consistent with an observational study by Key et al. (18). In contrast, two case-control studies, one in Hawaii (19) on total zinc intake and one in Italy on dietary intake only (15), found statistically significant increased risks among men consuming the highest amounts of zinc. Studies of blood or toenail measures of zinc status and prostate cancer risk have generally been quite small; two reported a significant decreased risk associated with higher zinc status (23,24), whereas one found no association (25).

Several factors affect zinc absorption. It is well established that zinc absorption is reduced when zinc status is high (26). Therefore, we hypothesized that zinc supplement use would provide the most benefit to those with lower zinc intake; however, our results did not support this. Zinc absorption is also inhibited by phytic acid found in vegetables and grains (27–29). We found an inverse association between supplemental zinc and prostate cancer in those men with high consumption of vegetables, suggesting that supplemental zinc may be beneficial among those who absorb less zinc due to the phytate content of the diet.

Our study had several strengths including a large sample size, a prospective design, detailed assessment of exposure, and the ability to control potential confounders. Assessment of supplement intake included exact composition of multivitamins (one of the major sources of zinc intake), thereby distinguishing between regular multivitamins and those marketed for "men's health" with higher amounts of zinc. A validation study of our supplement assessment for other nutrients showed excellent correlation with supplements recorded at a home visit and with biomarkers of nutrient status (30). Due to the prospective design of our study, any measurement error in the assessment of zinc intake from supplements or diet should not have been differential between cases and controls.

Another strength of our study was our attempt to separate the effects of supplemental zinc per se from the health behavior of taking multivitamin pills. About 80% of men who consume supplemental zinc get it from multivitamins only, and furthermore, a large majority of men who take individual zinc supplements also take multivitamins. Therefore, it is difficult to separate the effect of use of multivitamins from any effect of zinc itself. The increased risk of prostate cancer associated with multivitamin use in this study (Table 1) may be attributed to bias due to a correlation between multivitamin use and PSA screening. The increased risk could also represent a real adverse effect of multivitamins on prostate cancer risk as supported by two recent studies (31,32). We attempted to separate the effect of supplemental zinc from use of multivitamins using three methods: a) we controlled for multivitamin use in all analyses, b) we created an upper category of 10-yr average dose of supplemental zinc that could only be achieved by use of individual supplements or formulations of multivitamins with high zinc (e.g., those marketed for "men's heath") and not by 10-yr daily use of common multivitamin formulations (commonly containing 15 mg zinc), and c) we directly looked at zinc supplement use other than multivitamin use (from individual supplements and other combinations).

Limitations of this study included its primarily White and well-educated population; these factors may affect the generalizability of our results. There also may have been some men that had asymptomatic, undiagnosed prostate cancer leading to inclusion as a "non-case," and this may obscure a potential association between zinc intake and prostate cancer risk. We also had a short follow-up; however, we assessed supplement zinc intake over the last 10 yr prior to baseline, which may be a reasonable period of time relevant to prostate cancer development. Another limitation is that we only had information about previous PSA-testing within 2 yr prior to baseline but not after baseline. Because detection of early-stage prostate cancer is highly dependent on having a PSA test, our finding that zinc supplementation only reduced the risk of advanced disease may be due to the limitation of incomplete control for PSA screening rather that due to a mechanism whereby zinc only slows prostate cancer progression but does not affect initiation.

Although zinc supplements have been promoted as beneficial for "men's health," with implications for a consequent reduction in prostate cancer risk, we did not observe a significant association in this cohort. We did, however, find a significant reduced risk among men who have high vegetable intake (with possible low zinc absorption) and in late-stage prostate cancer. Thus, our results provide partial support for the meaningful biological mechanisms that suggest an important role of zinc in the prostate. If future studies support these results, it may suggest that zinc supplements may be beneficial for some subgroups of men or for the most adverse forms of the disease.

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REFERENCES

1. Matsuda T and Saika K: Comparison of time trends in prostate cancer incidence (1973–1997) in East Asia, Europe and USA, from Cancer Incidence in Five Continents Vols. IV–VIII. *Jpn J Clin Oncol* **37,** 556–557, 2007.
2. Ries LAG, Melbert D, Krapcho M, Mariotto A, Miller BA, et al.: SEER Cancer Statistics Review, 1975–2004. Available at http://seer.cancer.gov/csr/1975-2004/, based on November 2006 SEER data submission, posted to the SEER Web site, 2007.
3. Platz EA and Giovannucci E: Prostate cancer. In: *Cancer Epidemiology and Prevention,* Schottenfeld D and Fraumenis JF (eds.) 3rd ed. New York: Oxford University Press, 2006, pp. 1128–1150.
4. Costello LC, Franklin RB, Feng P, Tan M, and Bagasra O: Zinc and prostate cancer: a critical scientific, medical, and public interest issue (United States). *Cancer Causes Control* **16,** 901–915, 2005.
5. Zaichick V, Sviridova TV, and Zaichick SV: Zinc in the human prostate gland: normal, hyperplastic and cancerous. *Int Urol Nephrol* **29,** 565–574, 1997.
6. Bataineh ZM, Bani Hani IH, and Al-Alami JR: Zinc in normal and pathological human prostate gland. *Saudi Med J* **23,** 218–220, 2002.
7. Huang L, Kirschke CP, and Zhang Y: Decreased intracellular zinc in human tumorigenic prostate epithelial cells: a possible role in prostate cancer progression. *Cancer Cell Int* **6,** 10, 2006.
8. Liang JY, Liu YY, Zou J, Franklin RB, Costello LC, et al.: Inhibitory effect of zinc on human prostatic carcinoma cell growth. *Prostate* **40,** 200–207, 1999.
9. Costello LC and Franklin RB: Novel role of zinc in the regulation of prostate citrate metabolism and its implications in prostate cancer. *Prostate* **35,** 285–296, 1998.
10. Costello LC, Liu Y, Franklin RB, and Kennedy MC: Zinc inhibition of mitochondrial aconitase and its importance in citrate metabolism of prostate epithelial cells. *J Biol Chem* **272,** 28875–28881, 1997.

11. Dakubo GD, Parr RL, Costello LC, Franklin RB, and Thayer RE. Altered metabolism and mitochondrial genome in prostate cancer. *J Clin Pathol* **59,** 10–16, 2006.
12. Kristal AR, Stanford JL, Cohen JH, Wicklund K, and Patterson RE: Vitamin and mineral supplement use is associated with reduced risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* **8,** 887–892, 1999.
13. Leitzmann MF, Stampfer MJ, Wu K, Colditz GA, Willet WC, et al.: Zinc supplementation use and risk of prostate cancer. *J Natl Cancer Inst* **95,** 1004–1007, 2003.
14. Meyer F, Galan P, Douville P, Bairati I, Kegle P, et al.: Antioxidant vitamin and mineral supplementation and prostate cancer prevention in the SU.VI.MAX trial. *Int J Cancer* **116,** 182–186, 2005.
15. Gallus S, Foschi R, Negri E, Talamini R, Franceschi S, et al.: Dietary zinc and prostate cancer risk: a case-control study from Italy. *Eur Urol* **52,** 1052–1056, 2007.
16. Lee MM, Wang RT, Hsing AW, Gu FL, Wang T, et al.: Case-control study of diet and prostate cancer in China. *Cancer Causes Control* **9,** 545–552, 1998.
17. West DW, Slattery ML, Robison LM, French TK, and Mahoney AW: Adult dietary intake and prostate cancer risk in Utah: a case-control study with special emphasis on aggressive tumors. *Cancer Causes Control* **2,** 85–94, 1991.
18. Key TJ, Silcocks PB, Davey GK, Appleby PN, and Bishop DT: A case-control study of diet and prostate cancer. *Br J Cancer* **76,** 678–687, 1997.
19. Kolonel LN, Yoshizawa CN, and Hankin JH: Diet and prostatic cancer: a case-control study in Hawaii. *Am J Epidemiol* **127,** 999–1012, 1988.
20. White E, Patterson RE, Kristal AR, Thornquist M, King IB, et al.: VITamins And Lifestyle cohort study: study design and characteristics of supplement users. *Am J Epidemiol* **159,** 83–93, 2004.
21. Schakel SF, Buzzard IM, and Gebhardt SE: Procedures for estimating nutrient values for food composition databases. *J Food Composition Analysis* **10,** 102–114, 1997.
22. Littman AJ, White E, Kristal AR, Patterson SA, Satia-Abouta J, et al.: Assessment of a one-page questionnaire on long-term recreational physical activity. *Epidemiology* **15,** 105–113, 2003.
23. Aydin A, Arsova-Sarafinovska Z, Sayal A, Eken A, Erdem O, et al.: Oxidative stress and antioxidant status in non-metastatic prostate cancer and benign prostatic hyperplasia. *Clin Biochem* **39,** 176–179, 2006.
24. Whelan P, Walker BE, and Kelleher J: Zinc, vitamin A and prostatic cancer. *Br J Urol* **55,** 525–528, 1983.
25. Platz EA, Helzlsour KJ, Hoffman SC, Morris JS, Baskett CK, et al.: Prediagnostic toenail cadmium and zinc and subsequent prostate cancer risk. *Prostate* **52,** 288–296, 2002.
26. Barrie SA, Wright JV, Pizzorno JE, Kutter E, and Barron PC: Comparative absorption of zinc picolinate, zinc citrate and zinc gluconate in humans. *Agents Actions* **21,** 223–228, 1987.
27. Lonnerdal B: Dietary factors influencing zinc absorption. *J Nutr* **130** (5 Suppl), 1378S–1383S, 2000.
28. Sandstrom B and Cederblad A: Zinc absorption from composite meals. *Am J Clin Nutr* **33,** 1778–1783, 1980.
29. Gonzalez AJ, Lampe J, Peters U, and White E: Correlates of toenail zinc in a free-living population. *Ann Epidemiol* **18,** 74–77, 2008.
30. Satia-Abouta J, Patterson RE, King IB, Stratton KL, Shattuck AL, et al.: Reliability and validity of self-report of vitamin and mineral supplement use in the vitamins and lifestyle study. *Am J Epidemiol* **157,** 944–954, 2003.
31. Lawson KA, Wright ME, Subar A, Mouw T, Hollenbeck A, et al.: Multivitamin use and risk of prostate cancer in the National Institutes of Health-AARP Diet and Health Study. *J Natl Cancer Inst* **99,** 754–764, 2007.
32. Stevens VL, McCullough ML, Diver WR, Rodriguez C, Jacobs EJ, et al.: Use of multivitamins and prostate cancer mortality in a large cohort of US men. *Cancer Causes Control* **16,** 643–650, 2005.