Published in final edited form as:
Cancer Causes Control. 2009 July ; 20(5): 691–698. doi:10.1007/s10552-008-9282-y.

Vitamin and Mineral Use and Risk of Prostate Cancer: The Case-Control Surveillance Study

Yuqing Zhang[2], **Patricia F. Coogan**[1], **Julie R. Palmer**[1], **Brian L. Strom**[3], and **Lynn Rosenberg**[1]

[1] Slone Epidemiology Center at Boston University

[2] Clinical Epidemiology Research and Training Unit, Department of Medicine, Boston University School of Medicine

[3] Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, Center for Education and Research on Therapeutics, and Division of General Internal Medicine of the Department of Medicine, University of Pennsylvania School of Medicine

Abstract

Background—Many studies have evaluated the association between vitamin and mineral supplement use and the risk of prostate cancer, with inconclusive results.

Methods—The authors examined the relation of use of multivitamins as well as several single vitamin and mineral supplements to the risk of prostate cancer risk among 1,706 prostate cancer cases and 2,404 matched controls using data from the hospital-based Case-Control Surveillance Study conducted in the United States. Odds ratios (OR) and 95% confidence intervals (CI) for risk of prostate cancer were estimated using conditional logistic regression model.

Results—For use of multivitamins that did not contain zinc the multivariable odds ratios of prostate cancer were 0.6 for 1–4 years, 0.8 for 5–9 years, and 1.2 for 10 years of more, respectively (p for trend =0.70). Men who used zinc for 10 years or more, either in a multivitamin or as a supplement, had an approximately 2-fold (OR=1.9, 95% CI: 1.0, 3.6) increased risk of prostate cancer. Vitamin E, beta-carotene, folate, and selenium use were not significantly associated with increased risk of prostate cancer.

Conclusion—The finding that long-term zinc intake from multivitamins or single supplements was associated with a doubling in risk of prostate cancer adds to the growing evidence for an unfavorable effect of zinc on prostate cancer carcinogenesis.

Keywords

case-control study; multivitamin; prostate neoplasm

Introduction

Prostate cancer is the most common malignancy among men in the United States other than non -melanoma skin cancer and accounts for one third of all male cancers (1). The American Cancer Society estimated that approximately 220,000 new cases of prostate cancer were diagnosed in men in 2007, and about 27,000 men died of this disease (2). Except for age, race, nationality, family history of prostate cancer, and insulin growth factor, few risk factors have been identified (3). Approximately 30% of men aged 20 years or older in the United States reported taking vitamin or mineral supplements regularly in the previous month, making it the third largest over -the -counter drug class used (4). High prevalence of multivitamin and mineral use has also been reported by other investigators (5), and use is common among children (6).

Despite the widespread and long -term use of multivitamins and minerals, there is little evidence that such use has beneficial effects on the occurrence of chronic diseases, including cancer (7).

Many studies have examined the relationship between vitamin and mineral supplement use and the risk of prostate cancer (8–28). Results from prospective cohort studies suggest that use of multivitamins was either associated with an increased risk of prostate cancer (17) or weakly associated with prostate cancer mortality (20). However, results from a case-control study failed to confirm this (10). In a randomized trial of vitamin and mineral supplements, prostate cancer risk was reduced among vitamin users with normal baseline prostate specific antigen levels, but there was no effect among men with elevated levels at baseline (21). Evidence about the effects of single vitamin or mineral supplements is also conflicting (8–16,20,22–24,26–28). One clinical trial (9) and two observational studies (10,22) found that the use of vitamin E supplements was inversely associated with the risk of prostate cancer but other studies showed no association (11,13–16,27). In one study the use of zinc supplements was associated with reduced risk of prostate cancer (10), but others have found a positive association of zinc use with an increased risk of prostate cancer (8,12,23,28). The effect of dietary folate intake on prostate cancer risk was not consistent (24–26).

Since multivitamins and minerals are widely used in the United States, and use may start at young ages and last for a long period of time, clarification of their relation to the risk of prostate cancer is important. We examined the use of multivitamins, vitamin E, beta-carotene, folate, selenium, and zinc in relation to prostate cancer risk using data from the hospital-based Case-Control Surveillance Study.

Subjects and Methods

Since 1976, the Case-Control Surveillance Study has been conducted in hospitals located in four centers (Baltimore, Boston, New York, and Philadelphia) (29). Subjects were interviewed in hospital by trained nurse interviewers who used a structured questionnaire to collect information on demographic factors, reproductive and medical history, family history of cancer, and lifetime history of medication use. To reduce the risk of potential selection bias from referrals to the hospital, only patients who lived in areas that were within 50 miles of the hospital were enrolled; to ensure that this criterion was met, the nurse -interviewers were supplied with lists of acceptable ZIP codes.

Histories of drug use were elicited by questions about 42 indications, which included a specific query about use of supplements, herbal medications, and multivitamins. For each episode of use, the medication name and the duration, timing and frequency of use were recorded. After discharge, the patient's diagnosis that led to hospital admission was abstracted from the hospital record; discharge summaries were obtained for all patients and pathology reports for patients with cancer.

Cases

Eligible cases were 1,706 men aged 40–79 years admitted to the participating hospitals in Baltimore, Boston, New York, or Philadelphia, who met the following criteria: 1) a primary diagnosis of prostate cancer confirmed by pathology report and with the initial cancer diagnosis less than 12 months before the current admission; and 2) no other primary cancer or history of cancer with the exception of non -melanoma skin cancer. Subjects with missing information on multivitamin or supplement use were not eligible for inclusion.

Controls

Controls were selected from a pool of 5,971 men aged 40–79 years with no history of cancer with the exception of non -melanoma skin cancer who had been admitted to the hospital for nonmalignant diseases that we considered unrelated to multivitamin use or risk of prostate cancer. Included were patients admitted for infections, traumatic injury, calculus of kidney and ureter, gallbladder disease, musculoskeletal diseases, and diseases of the circulatory system. Subjects with missing information on multivitamin or supplement use were not eligible as potential controls. Potential controls were, on average, appreciably younger than cases, with mean age of 44 years in controls and 62 years in cases, respectively. We matched the potential controls to the cases in a ratio of up to 4:1 on 5-year age group, as well as on study center, year of interview (5-year categories), and race (white, black). The final control series comprised 2,404 men.

Statistical analysis

We divided multivitamin use into five categories: never used or use for less than 1 year, and use for 1–4 years, 5–9 years, 10–14 years, and 15 or more years. We examined the relation of duration of multivitamin use to the risk of total, local (stage I or II tumor confined within the prostate) and advanced (stage III or IV cancer beyond prostate capsule) prostate cancers using conditional logistic regression. We used multivariable conditional logistic regression models to adjust for the matching factors (*i.e.*, age group, study center, year of interview, and race) and for other potential risk factors for prostate cancer: years of education, body mass index, current cigarette smoking, alcohol consumption, and family history of prostate cancer. To further control for potential confounding from age, we also included a continuous term for age in the regression model. To test for a trend across duration of use, we included a term for duration of use in the model.

We used the same approach to assess the effect of the use of specific vitamins and minerals (*i.e.*, vitamin E, beta-carotene, folate, selenium, and zinc) either from a multivitamin tablet or single supplement. We excluded from these analyses multivitamin users who could not specifically name the product.

In each analysis, the reference group comprised men who had never used the index medication or had used it for less than 1 year.

Results

The characteristics of the cases and controls are shown in table 1. The median age was 62 years for prostate cancer cases and 59 for controls. Most subjects were white and had been interviewed in Philadelphia. Compared with the controls, cases were more educated, more likely to have a family history of prostate cancer, and less likely to be obese or to smoke.

The prevalence of multivitamin use standardized by age was similar across various diagnostic categories among the controls. The prevalence of use for a year or more was 22.3% among controls admitted for infections, 18.4% for traumatic injuries, 19.9% for calculus of the kidney or ureter, 21.3% for gallbladder diseases, 22.8% for musculoskeletal diseases, and 20.0% for diseases of the circulatory system, respectively. The corresponding prevalence of use for 10 years or more was 7.7%, 7.3%, 9.1%, 9.7%, 9.6%, and 5.5%, respectively. The prevalence of ever use of zinc was 5.6% among controls admitted for infections, 2.6% for traumatic injuries, 5.1% for calculus of the kidney or ureter, 7.5% for gallbladder diseases, 7.5% for musculoskeletal diseases, and 7.3% for diseases of the circulatory system.

The relation of duration of use of multivitamins and specific vitamins and minerals to the risk of prostate cancer is shown in Table 2. Relative to use for less than a year, the multivariable-adjusted odds ratios (ORs) for prostate cancer were 0.7 for use of multivitamins/minerals for 1–4 years, 1.1 for 5–9 years, and 1.3 for 10 or more years, respectively (p for trend =0.089).

As shown in Table 2, in the analyses that did not adjust for use of other supplements, the OR for 10 or more years of use was 1.5 (95% CI: 1.2, 2.0) for vitamin E, 1.5 (1.0, 2.3) for folate, 2.3 (95% CI: 1.4, 3.7) for zinc, and 2.2 (95% CI: 1.2, 4.2) for selenium. Control for the use of other supplements reduced all of these ORs for 10 or more years of use to 1.2 or less except for those for zinc and selenium, which were 1.9 (95% CI: 1.0, 3.6) and 1.7 (95% CI: 0.6, 4.3), respectively. The OR for 10 or more years of use of beta-carotene was 0.8 (95% CI: 0.4–1.7) before adjustment for other supplements and 0.3 (95% CI: 0.1, 0.8) after adjustment. All p values for trend were greater than 0.05, suggesting that there was no apparent dose-response relationship between use of either multivitamins/minerals or single supplements and the risk of prostate cancer.

Since a previous study reported that an effect of vitamin E on the risk of prostate cancer was mainly found among smokers, we performed stratified analyses according to smoking status and also added an interaction term (*i.e.*, smoking times vitamin E use) in the multivariable regression model. We found that the association of vitamin E with risk of prostate cancer was not modified by current smoking status (p for interaction > 0.83).

Because the ORs for selenium and zinc remained elevated when adjusted for the use of other supplements, we assessed whether their effects were independent of each other. We did this by exploring the effect of zinc use for a year or more among men who had taken selenium for less than a year. Similarly, for selenium we assessed its effect among men who had used zinc for less than a year (Table 3). In these analyses, the OR for use of zinc for 10 years or more remained significantly elevated (OR=2.1, 95% CI: 1.1, 4.1). The comparable OR for selenium users was 1.3 (95% CI: 0.3, 5.7) based on only eight exposed cases and three exposed controls.

Because we found an association of prostate cancer risk with zinc use, we repeated the analyses of multivitamin use after excluding men who used zinc from multivitamins or single supplements for one year or more. As shown in Table 4, the ORs for 10 or more years of use of multivitamins/minerals that did not contain zinc were 1.2 (95% CI: 0.8, 1.9) for all prostate cancer (p for trend = 0.71), 1.5 (95% CI: 0.9, 2.6) for early stage prostate cancer, and 1.0 (95% CI: 0.5, 1.9) for late stage prostate cancer. The difference in the estimates for early and late stage prostate cancer was not statistically significant. The number of zinc supplement users was too small to allow for assessment of its effect according to the stage of prostate cancer.

The distribution of multivitamin/mineral use among subgroups of the controls was similar except for traumatic injury, which was slightly lower than other control groups. We performed a sensitivity analysis by excluding controls with traumatic injuries; the results did not change materially. The ORs of prostate cancer were 1.3 (95% CI: 1.0, 1.7) for use of 10 years or more of multivitamins/minerals, 1.3 (95% CI: 0.9, 2.0) for vitamin E, 0.3 (95% CI: 0.1, 0.8) for beta-carotene, 0.9 (95% CI: 0.5, 1.7) for folate, 1.5 (95% CI: 0.8, 3.0) for zinc, and 1.9 (95% CI: 0.7, 5.2) for selenium, respectively.

Discussion

In this hospital-based case-control study, men who used zinc for 10 or more years, either in a multivitamin or as a single supplement, had an approximately two-fold increased risk of prostate cancer. Use of vitamin E, beta-carotene, folate, and selenium were not associated with increased risk of prostate cancer. We found little evidence to support an effect of multivitamins on the risk of prostate cancer.

Evidence on the relation of multivitamin use to the risk of prostate is conflicting (10,17,19, 20). In a population-based case-control study (10), the use of a multivitamin more than 7 times per week was not associated with risk of prostate cancer compared to no use (OR=0.96, 95% CI: 0.73, 1.26); results did not differ by stage of disease or by histological grade. In seven years of follow-up of 454,000 men in the Cancer Prevention Study II cohort (CPS-II), the risk of death from prostate cancer was not associated with use of multivitamins overall; however, mortality was increased by 30% (OR=1.31, 95% CI: 1.04,1.66) among participants who had used multivitamins for 5 or more years (19). In an up-dated analysis of the CPS-II cohort over 18 years of follow-up, the use of multivitamins for 15 or more times/month was weakly and insignificantly associated with prostate cancer mortality (RR=1.07, 95% CI: 0.99,1.15) (20). Multivitamins were not assessed according to the presence or absence of zinc in these studies. In the prospective AARP Diet and Heath Study, Lawson et al (17) found that men reporting use of multivitamins more than seven time per week had a 30% increase in the risk of advanced and fatal prostate cancer compared with never users (RR=1.32, 95% CI: 1.04,1.67). Our results do not confirm the AARP finding of a stronger association of multivitamin use with advanced than with early stage cancer. In the AARP study, an increased risk was more pronounced among men with a family history of prostate cancer or who took individual supplements, including selenium, beta-carotene, or zinc in addition to a multivitamin. The number of men with a family history of prostate cancer in our study was relatively small (n=248); thus we were unable to obtain a robust estimate of the effect of multivitamin use among men with a positive family history.

Findings on the relation of single vitamin or mineral supplements to the risk of prostate cancer are conflicting. Vitamin E has been associated with a decreased risk of prostate cancer (9,15, 30), with a more pronounced effect among smokers (15,18). In the Male Health Professional Study, Chan and colleagues found no association between vitamin E use and risk of total and metastatic or fatal prostate cancer (11). However, among current smokers and recent quitters, those who consumed at least 100 IU of supplement vitamin E per day had a reduced risk (RR=0.44, 95% CI: 0.18–1.07) for metastatic or fatal prostate cancer compared with nonusers. Results from two large prospective cohort studies (13,16), however, did not find an association between vitamin E supplement and risk of prostate cancer, and its effect was not significantly modified by smoking status. In our study, there was no association between vitamin E use and risk of prostate cancer regardless of smoking status. More recently, results from the Selenium and Vitamin E cancer Prevention Trial suggest there was no beneficial effect of either vitamin E or selenium on the prevention of prostate cancer (31).

The few studies that have evaluated the effects of beta-carotene (15,18,27) and selenium (22, 32) on the risk of prostate cancer have been inconclusive. In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial, participants who received beta-carotene had a slightly higher risk of prostate cancer than those who did not receive beta-carotene (27). However, in the Physicians' Health Study, beta-carotene supplementation of 50 mg on alternative days was not associated with risk of prostate cancer (18). We found an inverse association of 10 or more years of beta-carotene supplement use with prostate cancer risk, but there was not a significant trend.

Several epidemiologic studies have examined folate in relation to the risk of prostate cancer, with inconclusive findings (24–26,33–35). Of three case-control studies evaluating plasma concentrations of folate in relation to prostate cancer (33–35), two (33,34) found that high circulating folate levels were associated with a small but non-significant increase in risk and one (35) reported no effect of folate on prostate cancer risk. In a large dietary case-control study with 1,294 incident prostate cancer cases, folate intake was associated with a decreased risk of prostate cancer, with an adjusted OR of 0.66 (95% CI: 0.51, 0.85) for the highest *vs.* the lowest quintile of folate intake (26). While there was no effect of dietary intake of folate

on overall prostate cancer risk among the male participants in the CPS-II, high dietary folate intake was marginally associated with reduced risk of advanced prostate cancer (25). In a smaller European case-control study, however, high dietary intake of folate was associated with a non-significant increased risk of prostate cancer (24). In our study, no apparent effect of folate supplement use was found on prostate cancer risk.

In a population-based case-control study of 697 incident prostate cancer cases and 666 controls (10), prostate cancer risk was inversely associated with zinc use. However, in the Health Professionals Follow-up Study (12) use of zinc supplements for 10 years or more was associated with more than a doubling in the risk of advanced prostate cancer (RR=2.3, 95% CI: 1.1, 5.0) compared with nonuse. In a large case-control study (1294 prostate cancer cases and 1451 controls) conduced in Italy, Gallus et al (8) reported that the OR of prostate cancer was 1.56 for men with the highest quintile of dietary zinc as compared with those in the lowest quintile (p for trend =0.04). Two other studies also suggested that zinc intake was associated with an increased risk of prostate cancer (23,28). In the current study, we also observed a 2-fold increased risk of prostate cancer among men who used zinc for 10 or more years. Considering that zinc has long been linked to prostate health, some men with long-standing prostate symptoms may be self-medicating with zinc supplements which may account for, at least in part, these positive findings.

Some studies have suggested that high intraprostatic zinc levels may decrease the risk of prostate cancer by suppression of prostate cancer cell growth (36) or inhibition of tumor cell invasion (37). Studies comparing zinc concentrations in normal and malignant prostate tissue have found that zinc content is 60–70% lower in cancer cells (38). These findings raised the possibility that a high intake of dietary zinc and use of supplement zinc could be efficacious in the prevention of prostate cancer (39). However, other studies have shown that zinc may enhance the activity of telomerase, an enzyme that has been associated with the proliferation of prostate cancer cells (40). An excess of zinc has also been shown to reverse the potential inhibitory effect of biophosphonate on prostate tumor cell invasion (41). Studies have also demonstrated that zinc intake is positively associated with levels of serum insulin-like growth factor (42) and testosterone (43), both of which may be risk factors for prostate cancer (44, 45).

Selection of appropriate hospital controls in a case-control study is a challenge, especially for the evaluation of lifestyle factors like multivitamin use. If hospital patients were less likely to take multivitamins than the general population, an adverse effect of multivitamin use on risk of prostate cancer would be exaggerated. We selected controls from men with diagnoses that we judged to be unrelated to multivitamin use. Results were unchanged in a sensitivity analysis which removed the controls with the lowest prevalence of vitamin and supplement use. Finally, the number of advanced prostate cancer cases in the current study is relatively small, which limited our ability to assess the effect of multivitamin or single vitamin or mineral use on advanced disease.

Important prostate cancer risk factors, such as family history of cancer, were controlled simultaneously in multivariable analysis. The data on multivitamin use were collected in the context of questions about many drug indications, and the participants and interviewers were unaware of the hypotheses at issue; thus, it is unlikely that biased reporting of multivitamin use accounts for the present results.

Approximately 16% of subjects did not know the name of the multivitamin they had taken and they were excluded from the analysis of specific vitamins or minerals. Similar to most previous studies, we did not collect data on dietary intake and therefore could not take into account vitamin and mineral intake from food. Finally, our study did not collect information on dosage

of either multivitamins/minerals or single supplements. Thus, we were unable to assess the effect of doses of either multivitamins/minerals or single supplements.

In summary, the present study found that long-term use of multivitamins that did not contain zinc was not associated with increased risk of prostate cancer. Long-term zinc intake from multivitamins or single supplements was associated with a doubling in risk. This finding together with other epidemiologic evidence suggests that that there is an unfavorable effect of zinc use on prostate carcinogenesis.

Acknowledgments

This work was supported by grant CA45762 from the National Cancer Institute. Additional support was provided by Grant FD-U-00082 from the Food and Drug Administration.

Abbreviations

CI
: Confidence interval

OR
: Odds ratio

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Table 1

Characteristics of prostate cancer cases and controls, Case Control Surveillance Study, 1976–2006

Characteristics	Cases (n=1,706)	Controls (n=2,404)
Age (Mean, SD)	61.9 (6.8)	58.9 (7.5)
Race (%)		
White	83.9	77.0
Black	16.1	23.0
Area (%)		
Boston	1.9	5.3
New York	12.3	11.6
Philadelphia	78.4	74.2
Baltimore	7.4	8.9
Years of education (%)		
≤ 12 years	36.1	52.8
13–15 years	17.3	15.6
16 years or more	46.6	31.6
Body Mass Index (kg/m^2) (%)		
< 25	30.5	33.6
25 – 29	50.2	43.4
30+	19.3	23.0
Current smoker (%)	13.4	28.9
Current alcohol drinker (%)	68.6	66.1
Family history of prostate cancer (%)	10.2	3.1

Table 2

The use of multivitamin and specific vitamin and mineral supplements in cases and controls

Preparation used	Disease Status	Duration of Use (years)			
		Never or < 1 yr use	1–4	5–9	10+
Multivitamins	Controls	1900	210	100	194
	Cases	1260	112	95	239
	OR (95% CI [a]	1.0 (ref)	0.7 (0.5, 0.9)	1.1 (0.8, 1.5)	1.3 (1.0, 1.6)
P for trend	0.089				
Vitamin E	Controls [b]	1704	172	75	123
	Cases [b]	1070	102	76	153
	OR (95% CI) [c]	1,0 (ref)	0.8 (0.6, 1.0)	1.4 (1.0, 2.0)	1.5 (1.2, 2.0)
	OR (95% CI) [d]	1.0 (ref)	0.7 (0.5, 1.0)	1.1 (0.7, 1.8)	1.2 (0.9, 1.9)
P for trend	0.798				
Beta-carotene	Controls [b]	2029	17	11	17
	Cases [b]	1338	24	18	21
	OR (95% CI) [c]	1,0 (ref)	1.2 (0.6, 2.3)	2.0 (0.8, 4.8)	0.8 (0.4, 1.7)
	OR (95% CI) [d]	1.0 (ref)	1.4 (0.6, 3.1)	1.3 (0.4, 3.6)	0.3 (0.1, 0.8)
P for trend	0.341				
Folate	Controls [b]	1910	76	35	53
	Cases [b]	1232	54	42	73
	OR (95% CI) [c]	1,0 (ref)	0.9 (0.6, 1.4)	1.6 (1.0, 2.7)	1.5 (1.0, 2.3)
	OR (95% CI) [d]	1.0 (ref)	1.1 (0.6, 1.9)	1.0 (0.4, 2.1)	1.0 (0.5, 1.7)
P for trend	0.414				
Zinc	Controls [b]	1962	58	21	33
	Cases [b]	1260	41	36	64
	OR (95% CI) [c]	1.0 (ref)	0.9 (0.6, 1.5)	2.3 (1.3, 4.4)	2.3 (1.4, 3.7)
	OR (95% CI) [d]	1.0 (ref)	0.9 (0.5, 2.0)	2.5 (0.8, 7.5)	1.9 (1.0, 3.6)
P for trend	0.292				
Selenium	Controls [b]	2005	35	17	17
	Cases [b]	1293	31	31	46

Preparation used	Disease Status	Duration of Use (years)			
		Never or < 1 yr use	1–4	5–9	10+
	OR (95% CI)[c]	1.0 (ref)	1.0 (0.6, 1.7)	2.0 (1.0, 4.0)	2.2 (1.2, 4.2)
	OR (95% CI)[d]	1.0 (ref)	1.1 (0.4, 2.9)	0.8 (0.2, 2.6)	1.7 (0.6, 4.3)
P for trend	0.340				

[a] Odds ratios were conditioned by the matching variables (i.e., age strata, study center, year of interview and race) and further adjusted for age, years of education, body mass index, current alcohol drinking, current smoking, and family history of prostate cancer

[b] Men who took multivitamins with unknown names were excluded from the analysis of specific supplements

[c] Odds ratios were conditioned by the matching variables (i.e., age strata, study center, year of interview and race) and further adjusted for age, years of education, body mass index, current alcohol drinking, current smoking, and family history of prostate cancer

[d] Odds ratios were conditioned by the matching variables (i.e., age strata, study center, year of interview and race) and further adjusted for age, years of education, body mass index, current alcohol drinking, current smoking, family history of prostate cancer, and use of other vitamin/mineral supplements

Table 3

Use of zinc and selenium supplements among cases and controls

Mineral supplement use	Cases	Controls	OR*	95% CI
Zinc [a]				
Never or < 1 yr use	1245	1955	1.0	
1–9 years	23	31	1.3	0.7, 2.4
≥10 years	25	19	2.1	1.1, 4.1
Selenium [b]				
Never or < 1 yr use	1245	1955	1.0	
1–9 years	7	4	1.4	0.3, 5.7
≥10 years	8	3	1.3	0.3, 5.7

*Odds ratios were conditioned by the matching variables (*i.e.*, age strata, study center, year of interview and race) and further adjusted for age, years of education, body mass index, current alcohol drinking, current smoking, and family history of prostate cancer

[a]Among men who used selenium (in multivitamins or single supplement) for less than 1 year

[b]Among men who used zinc (in multivitamins or single supplement) for less than 1 year

Table 4

Multivitamin use in relation to the risk of prostate cancer and by stage of prostate cancer

Multivitamin Use*	Controls	Cases	OR (adjusted for matching variables)	Multivariable-adjusted OR†	95% CI
Never or < 1 yr use	1825	1175	1.0	1.0	
1–4	57	25	0.6	0.6	0.3, 1.0
5–9	32	17	0.9	0.8	0.4, 1.5
10+	48	43	1.2	1.2	0.8, 1.9
P for trend [a]				0.71	
Early Stage of Prostate Cancer					
Never or < 1 yr use	1825	705	1.0	1.0 (ref)	
1–4	57	18	0.8	0.8	0.4, 1.5
5–9	32	10	0.8	0.7	0.3, 1.6
10+	48	29	1.2	1.5	0.9, 2.6
P for trend [a]				0.37	
Advanced Stage of Prostate Cancer					
Never or < 1 yr use	1825	306	1.0	1.0 (ref)	
1–4	57	6	0.6	0.6	0.2, 1.3
5–9	32	7	1.3	1.4	0.6, 3.4
10+	48	11	1.0	1.0	0.5, 1.9
P for trend [a]				0.96	

*Excluding men who used zinc from multivitamins or single supplement for one year or more

[a]Odds ratios were conditioned by the matching variables (*i.e.*, age strata, study center, year of interview and race) and further adjusted for age, years of education, body mass index, current alcohol drinking, current smoking, and family history of prostate cancer