Vitamin and Mineral Supplement Use Is Associated with Reduced Risk of Prostate Cancer[1]

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Abstract

This population-based, case-control study in King County, Washington examined supplement use in 697 incident prostate cancer cases (ages 40–64) identified from the Puget Sound Surveillance, Epidemiology and End Results program registry and 666 controls recruited from the same overall population using random-digit dialing sampling. Participants reported their frequency of use of three types of multivitamins and single supplements of vitamins A, C, and E, calcium, iron, and zinc over the 2 years before diagnosis. Logistic regression analyses controlled for age, race, education, family history of prostate cancer, body mass index, number of prostate-specific antigen tests in the previous 5 years, and dietary fat intake. Adjusted odds ratios (95% confidence limits) for the contrast of ≥7/week *versus* no use were as follows: multivitamins, 0.96 (0.73, 1.26); vitamin A, 0.59 (0.32, 1.06); vitamin C, 0.77 (0.57, 1.04); vitamin E, 0.76 (0.54, 1.08); calcium, 1.04 (0.61, 1.78); iron, 0.50 (0.13, 1.76); and zinc, 0.55 (0.30, 1.00). Odds ratios differed little when cases were stratified by stage of disease at diagnosis or by histopathological grade. There were significant dose-response effects for zinc and ordered dose-response trends for vitamins C and E. Overall, these results suggest that multivitamin use is not associated with prostate cancer risk, but use of individual supplements of zinc, vitamin C, and vitamin E may be protective. Further study is needed to investigate the direct role of these dietary supplements, as well as the role of lifestyle variables associated with supplement use, on prostate cancer risk.

Introduction

In the United States, prostate cancer is the most common cancer among men and second only to lung cancer as the leading cause of cancer-related mortality (1). Control of prostate cancer is based primarily on early detection and treatment, because known risk factors for prostate cancer are either not modifiable (increasing age and a family history of prostate cancer) or not well understood (black race). However, there is increasing evidence that dietary patterns and use of dietary supplements are associated with prostate cancer risk (2, 3). Further research on dietary supplements is of considerable importance, because supplementation could be an inexpensive and easily implemented means for primary prevention.

Few epidemiological studies have reported on associations between supplement use and prostate cancer risk (4). The strongest evidence for a protective effect of dietary supplements comes from two large, randomized controlled trials. In the ATBC[3] trial, which tested 50 mg of α-tocopherol and 20 mg of β-carotene for the prevention of lung cancer among smokers, there was an unexpected 30% reduction in prostate cancer incidence among participants randomized to receive α-tocopherol compared to placebo (5). In the Dietary Prevention of Cancer Trial, which tested 100 μg of organic selenium for the prevention of skin cancer, there was an unexpected 60% reduction among prostate cancer incidence in participants randomized to receive the active agent (6). The only other significant finding of supplement use with prostate cancer risk was from the Health Professionals Follow-Up Study, which found an approximate 3-fold *increase* for advanced disease associated with calcium supplementation of greater than 900 mg (7). No associations of supplementation were found in three randomized trials of β-carotene (8–10) or in a cohort study of the elderly examining vitamins A, C, and E (11).

This report gives results from a large population-based case-control study of middle-aged men and examines associations of dietary supplement use with prostate cancer risk.

Participants and Methods

Data are from a subset of participants in a study of risk factors for prostate cancer. Eligible participants were white and black male residents of King County (Seattle) Washington, ages 40–64 years, who were newly diagnosed with histologically confirmed prostate cancer between January 1, 1993, and December 31, 1996. Cases were identified from the Seattle-Puget Sound SEER cancer registry. Only cases with a residential telephone were eligible, because controls were selected using random-digit dialing.

Furthermore, because the emphasis was on recruiting younger men, only a random 75% sample of cases ages 60–64 were recruited. Of 917 cases selected for participation, 753 (82.1%) were interviewed. Reasons for nonresponse were physician refusal to allow contact (2.6%), case refusal (12.5%),

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[3] The abbreviations used are: ATBC, α-Tocopherol, β-Carotene; PSA, prostate-specific antigen; SEER, Surveillance, Epidemiology and End Results program.

inability to locate (1.5%), illness (0.4%), and death (0.2%). Controls were identified using random-digit dialing, frequency matched to cases by age (same 5-year group), and recruited evenly throughout the ascertainment period for cases. Of the 21,116 residential numbers contacted, 94% provided household census data. Of the 1025 eligible men identified, 941 (91.8%) agreed to receive mailed information about the study, and 703 (74.7%) were interviewed. Reasons for nonresponse were refusal (24.2%), loss to follow-up (<1%), and illness (<1%).

Participants completed in-person interviews conducted by trained male interviewers. Information was collected on a broad range of topics, including demographic characteristics, height and weight, family history of prostate cancer, and 5-year history of screening using PSA and digital rectal examination. For cases, all time-sensitive questions used diagnosis date as the reference date. For controls, the reference date was randomly assigned from dates that approximated the distribution of cases' diagnosis date. A calendar of life events was used to enhance recall. Following the interview, participants were given a self-administered food frequency questionnaire and a questionnaire on use of vitamin and mineral supplements and were asked to complete these at home and return them by mail. Vitamin and mineral supplement questionnaires were completed by 697 cases (92.6%) and 666 controls (94.7%). Clinical information was abstracted from the SEER registry. Stage of disease at diagnosis was coded according to the Whitmore-Jewett system (12), and histopathological grade was classified using the Gleason system (13).

The vitamin and mineral supplement questionnaire asked about the frequency and duration of using four types of multivitamins (with minerals, without minerals, stress type, and "not sure what kind") and six individual supplements [vitamins A (retinol, not including β-carotene), C, and E; calcium; iron; and zinc]. The questionnaire did not allow respondents to write in other supplements they may have used. For each type of multivitamin and single supplement, participants reported the frequency of use (never, 1 or less per week, 2–5 per week, 1 per day, 2 or more per day) and duration of use (less than 6 months, ½ year to 1 ½ years, 1 ½ years or more) during the 2 years prior to the reference date. Supplement use was calculated as the average exposure over the 2-year period: weekly use was calculated as 0, 1, 3.5, 7, and 14 times per week corresponding to frequency of use categories, and these were weighted for duration of use using 0.125, 0.5, and 1.0 corresponding to the duration categories. The food frequency questionnaire included 99 food items and 19 questions on food purchasing and preparation used to adjust nutrient calculations (14, 15), and the nutrient database is from the University of Minnesota Nutrient Data System (16).

Unconditional logistic regression was used to calculate odds ratios for risk of prostate cancer associated with each supplement. Associations were adjusted for age (in 5-year groups), race (white *versus* black), family history of prostate cancer (none, second degree only, and first degree), education (≤12, 13–15, 16, and ≥17 years), body mass index the year before diagnosis (<24, 24-<27, 28-<29, ≥30 kg/m^2), number of screening PSA tests in the 5 years before reference date (0, 1–2, 3–4, and ≥5), and dietary intakes of energy and fat (log transformed). Effect modification was examined in two ways. For analyses comparing effects of supplements by stage of disease, polytomous logistic regression was used to model odds ratios for controls *versus* stages A and B and controls *versus* stages C and D simultaneously (17). For analyses examining whether effects differed by fat intake, total fat was dichotomized at the midpoint, and regression models examined the interaction this dichotomous variable with supplement use.

Table 1 Demographic and health-related characteristics of cases and controls

	Cases (n = 697) (%)	Controls (n = 666) (%)
Age (yr)		
40–49	5.7	8.1
50–54	19.7	18.9
55–59	34.6	38.3
60–64	40.0	34.7
Race		
White	94.8	97.9
Black	5.2	2.1
Family history of prostate cancer		
No family history	72.5	84.5
1st degree	18.9	9.8
2nd degree only	8.6	5.7
Education (yr)		
<12	27.7	23.4
13–15	21.5	22.8
16	26.8	27.3
17+	24.0	26.4
Body mass index (kg/m^2)		
≤23	23.5	21.5
24–26	37.4	34.7
27–29	22.1	24.9
≥30	16.9	18.9
PSA tests within previous 5 yr		
None	28.7	67.3
1–2	34.0	19.2
3–4	19.8	8.1
≥5	17.5	5.4
Stage at diagnosis		NA[a]
A	15.2	
B	57.0	
C	17.4	
D	7.7	
Unknown	2.7	

[a] NA, not applicable.

Results

Table 1 gives distributions of demographic characteristics, family history, PSA use, and stage of disease at diagnosis. As determined by the study design, more than 60% of study participants were under age 60. Fewer than 5% were black and approximately 50% had completed college, consistent with the overall population of the Seattle/King County area. Cases were more likely than controls to have a family history of prostate cancer ($P < 0.001$), be black ($P < 0.003$), and have received PSA screening tests ($P < 0.001$). The majority of cases were stage B, and only 25% were diagnosed with advanced stage C and D disease.

Table 2 gives distributions of supplement use among cases and controls. The most commonly used supplements were multivitamins, used at least daily by 30% of cases and 27% of controls. The most commonly used were multivitamins with minerals (22%), whereas use of multivitamins without minerals (3%), stress types (3%), and type unknown (2%) were rare. Other frequently used supplements were vitamin C, used daily by approximately 21% of participants, and vitamin E, used daily by approximately 14% of participants. Only 5% of participants used zinc, calcium, or vitamin A daily, and only 1% used iron.

Table 3 gives associations of supplement use with prostate

Table 2 Distribution of vitamin and mineral supplement use in cases and controls

Supplement (frequency/week)	Cases (n = 697) (%)	Controls (n = 666) (%)
Multivitamin		
0	54.5	55.7
<1/week	5.6	5.1
1–6/week	9.5	12.5
≥7/week	30.4	26.7
Vitamin C		
0	62.3	58.7
<1/week	6.2	7.7
1–6/week	10.6	11.7
≥7/week	20.9	21.9
Vitamin E		
0	77.6	76.4
<1/week	3.0	3.5
1–6/week	6.2	5.7
≥7/week	13.2	14.4
Zinc		
0	92.4	90.5
<1/week	2.0	2.0
1–6/week	2.3	2.6
≥7/week	3.3	5.0
Calcium		
0	90.7	91.9
<1/week	1.0	1.2
1–6/week	2.4	2.3
≥7/week	5.9	4.7
Vitamin A		
0	92.8	92.0
<1/week	1.1	1.2
1–6/week	2.7	1.8
≥7/week	3.3	5.0
Iron		
0	96.4	96.7
<1/week	1.3	1.7
1–6/week	1.6	0.6
≥7/week	0.7	1.1

cancer risk. Odds ratios are given unadjusted and adjusted for confounding variables. There were no statistically significant associations of multivitamin supplement use with risk, nor were there suggestions of trends across levels of use. Results were similar for each type of multivitamin, and for those with minerals (minerals plus unknown types) and without minerals (without minerals plus stress types; data not shown). There was some evidence of a protective effect of vitamin C. The adjusted odds ratio for those using vitamin C at least daily was 0.77, with an upper 95% confidence limit of 1.04. Similarly, there was some evidence of a protective effect for vitamin E, with an adjusted odds ratio of 0.76 and upper 95% confidence limit of 1.08 for those using vitamin E daily. Although zinc use was rare, there was a borderline statistically significant 45% reduction in risk among those using zinc daily, with a significant test for trend. Analyses of calcium, vitamin A, and iron showed no consistent trends across use categories, although there were nonsignificant decreases in risk associated with daily use of iron and vitamin A.

Table 3 also shows associations of supplement use with prostate cancer risk among the subset of participants who reported using at least one type of single supplement. This analysis is an attempt to control for unmeasured confounding factors that may be associated with both prostate cancer risk and supplement use, because it includes only persons who use supplements. The power to detect significant trends is low because the sample size is reduced to only 620, and none of these trends was statistically significant at $P < 0.05$. However, consistency of results between analyses based on all participants, and this subset of participants provides some assurance that unmeasured confound factors are not affecting results. Results based on supplement users only did not differ markedly for zinc. For vitamin C, estimates of the protective effects were somewhat larger at all levels of use, although these did not reach statistical significance. For vitamin E, the strength of association was reduced at all levels of use, such that daily use was associated with only a modest 14% reduced risk.

The analyses shown in Table 3 were repeated, stratified by stage of disease at diagnosis. There was no suggestion of different effects among participants with early (stages A and B) and advanced (stages C and D) disease. The adjusted odds ratios (95% confidence limits) for none *versus* ≥7/week were as follows: zinc, 0.65 (0.33, 1.25) and 0.46 (0.15, 1.17); vitamin E, 0.72 (0.48, 1.06) and 0.71 (0.40, 1.22); and vitamin C, 0.77 (0.55, 1.08) and 0.71 (0.44, 1.12) for stages A and B versus stages C and D, respectively. Analyses stratified by grade (Gleason scores 2–7 *versus* 8–10) found somewhat stronger protective effects for zinc in higher-grade disease, although trends were similar in both groups. Analyses also examined whether there were differences in effects of supplementation between participants with low and high fat intakes. In particular, we considered whether effects of the fat-soluble antioxidant vitamin E were more pronounced among persons with high fat intake. There was no evidence of effect modification by fat intake for any supplement (data not shown).

Discussion

In this large population-based case-control study, designed to investigate risk factors for prostate cancer in middle-aged men, we found modest evidence of association between some vitamin and mineral supplements and prostate cancer risk. There were statistically significant protective effects for zinc, borderline although not statistically significant protective effects for vitamin C, and suggestive trends for vitamin E. There was no evidence for associations of multivitamins, calcium, vitamin A, or iron.

These results are only partially consistent with the few previous studies on supplement use and prostate cancer. The estimated 24% reduction in risk associated with vitamin E supplementation is somewhat less than the 32% decrease found in the ATBC trial (5), although the dose of vitamin E found in single supplements is generally 8 times higher than the 50 mg tested in the ATBC trial. There was no evidence that calcium supplementation was associated with elevated risk, either for the total sample or, as reported by Giovannucci *et al.* (7) in those with advanced disease. Furthermore, although Shibata *et al.* (11) reported a relative risk of 1.0 (95% confidence interval, 0.8–1.3) comparing vitamin C users to nonusers, we found a borderline statistically significant finding of a 23% reduction in risk from daily vitamin C use.

The finding of a protective effect for zinc supplementation is consistent with many clinical studies that find much lower tissue zinc concentrations in prostates with cancer compared to those without, as reviewed in Ref. 18. Some studies also find lower plasma zinc concentrations in persons with prostate cancer compared to controls (19, 20), although there are no prospective studies that have examined serum zinc levels and prostate cancer risk. Zinc, which is concentrated in the prostate, is a component of many physiologically active proteins that play a role in regulating apoptosis, transcription, and cellular

Table 3 Odds ratios of prostate cancer associated with use of vitamin and mineral supplements

Supplement (frequency/week)	Unadjusted odds ratio (95% confidence limits)	Adjusted odds ratio[a] (95% confidence limits)	*P* value for trend	Adjusted odds ratio[a] (95% confidence limits), supplement[b] users only
Multivitamin				
0	1.00	1.00		
<1/week	1.12 (0.69, 1.82)	1.15 (0.67, 1.98)	0.468	
1–6/week	0.78 (0.54, 1.10)	0.69 (0.46, 1.02)		
≥7/week	1.16 (0.91, 1.49)	0.96 (0.73, 1.26)		
Vitamin C				
0	1.00	1.00		1.00
<1/week	0.76 (0.49, 1.16)	0.73 (0.45, 1.17)	0.071	0.62 (0.32, 1.19)
1–6/week	0.86 (0.60, 1.21)	0.83 (0.56, 1.22)		0.70 (0.39, 1.26)
≥7/week	0.90 (0.69, 1.18)	0.77 (0.57, 1.04)		0.64 (0.37, 1.11)
Vitamin E				
0	1.00	1.00		1.00
<1/week	0.86 (0.47, 1.57)	1.12 (.057, 2.20)	0.118	1.17 (0.59, 2.34)
1–6/week	1.10 (0.68, 1.68)	0.85 (0.51, 1.41)		0.93 (0.55, 1.59)
≥7/week	0.90 (0.66, 1.23)	0.76 (0.54, 1.08)		0.86 (0.57, 1.28)
Zinc				
0	1.00	1.00		1.00
<1/week	1.00 (0.47, 2.19)	0.73 (0.31, 1.71)	0.038	0.82 (0.35, 1.92)
1–6/week	0.88 (0.44, 1.77)	0.79 (0.36, 1.72)		0.81 (0.37, 1.76)
≥7/week	0.65 (0.38, 1.11)	0.55 (0.30, 1.00)		0.59 (0.32, 1.09)
Calcium				
0	1.00	1.00		1.00
<1/week	0.85 (0.30, 2.37)	0.67 (0.22, 2.04)	0.866	0.83 (0.27, 2.49)
1–6/week	1.10 (0.54, 2.24)	1.13 (0.52, 2.45)		1.23 (0.56, 2.70)
≥7/week	1.28 (0.80, 2.08)	1.04 (0.61, 1.78)		1.25 (0.73, 2.17)
Vitamin A				
0	1.00	1.00		1.00
<1/week	0.95 (0.35, 2.59)	1.05 (0.34, 3.18)	0.244	1.16 (0.39, 3.46)
1–6/week	1.50 (0.73, 3.20)	1.46 (0.66, 3.30)		1.56 (0.71, 3.55)
≥7/week	0.66 (0.38, 1.13)	0.59 (0.32, 1.06)		0.67 (0.37, 1.22)
Iron				
0	1.00	1.00		1.00
<1/week	0.78 (0.31, 1.91)	0.52 (0.20, 1.33)	0.700	0.60 (0.23, 1.55)
1–6/week	2.64 (0.90, 9.55)	2.74 (0.82, 10.8)		2.80 (0.85, 10.93)
≥7/week	0.69 (0.20, 2.16)	0.50 (0.13, 1.76)		0.55 (0.15, 1.91)

[a] Controlled for fat, energy, race, age, family history of prostate cancer, body mass index, PSA tests in previous 5 years, and education.
[b] Users of at least one type of single supplement: $n = 312$ cases, $n = 308$ controls.

differentiation (21). Research is needed to investigate whether zinc intake affects prostate tissue zinc concentrations and whether tissue zinc concentrations affect mechanisms potentially related to prostate cancer development.

It is unclear to what extent previous studies on vitamins C and E and prostate cancer are informative about the potential effects of supplementation. Studies of dietary intake are probably not relevant, because the amounts of nutrients obtained from supplements are generally between 2 and 30 times greater than the amounts obtained from foods. Prospective studies based on serum micronutrient concentrations may be informative, but only if significant proportions of the cohorts under study use dietary supplements. There are few prospective studies of serum ascorbate (vitamin C) and α-tocopherol (vitamin E) and prostate cancer risk. In the single prospective study of vitamin C, based on 30 prostate cancer deaths, there was no association of plasma ascorbate concentration with prostate cancer risk (22). Studies of serum α-tocopherol prostate cancer risk are inconsistent, but taken together, they are not strongly supportive of an association (22–27). Protective effects of high serum α-tocopherol levels have been found in subgroup analyses, for example among men over 70 (26), among smokers (22), or in interactions with other nutrients (28). Both vitamin C and E are potent antioxidants, which can protect DNA from damage from reactive oxidants, such as superoxide and hydroxyl radicals (29), and it is possible that high doses obtained from supplements could affect carcinogenesis.

There are two important differences between this study and most earlier studies on supplements and prostate cancer risk. First, this study examined risk factors in a relatively low-risk age group. Prostate cancer incidence in ages eligible for this study range between 5 and 500 per 100,000, far lower than rates over 1,000 per 100,000 for men age 65 and over (1). Studies of risk factors in low-incidence groups [for example, in China (30)] may allow more clear identification of environmental exposures related to risk, but it is also possible that cancer in low-incidence age groups is due primarily to inherited susceptibility genes. However, such genes are thought to explain less than 30% of cancers diagnosed in men less that 65 years of age (31). Second, this study controlled for important confounding factors, including prostate cancer screening. Men who receive PSA screening are more likely to have prostate cancer detected (32), and they are also more likely to be better educated, have higher incomes, practice healthful dietary behavior, and use dietary supplements (33, 34). Consistent with these associations, control for covariates increased the magnitude of associations of most supplements with cancer risk.

The most significant limitation of this study was that we

did not collect a comprehensive and detailed history of dietary supplement use. We had no strong *a priori* hypotheses about supplement use when designing this study, and we collected modest amounts of information on supplements to augment nutrient intake estimates based on the food frequency questionnaire. In particular, we did not collect information on all supplements (*e.g.*, selenium), on dose, on use over a longer period prior to cancer diagnosis, or on reasons study participants used each supplement. Thus, our inferences about dose are based on frequency of use rather than actual intake of supplement nutrients. Furthermore, because we do not know the reasons participants chose to use certain supplements, it is possible that health conditions or lifestyle factors association with specific supplements, and not use of supplements *per se*, are associated with reduced prostate cancer risk. Our measure of supplement use was similar to that used in standard dietary assessment questionnaires (35), collecting both frequency and duration of use over a specified time period. In a validation study, Patterson *et al.* (36) found good agreement between supplemental nutrient intake assessed using a similar self-administered questionnaire and intake assessed from an in-person, interviewer-administered supplement inventory. However, it is likely that studies on supplement use and cancer risk could be improved by using supplement inventories, as recommended for prescription drugs (37). In addition, because the induction and latent periods for most cancers are quite long, information should be collected on long-term (*e.g.*, 10-year) supplement use (38). These sources of error in measurement were most likely random, and their effect should be to bias relative risk estimates toward 1.0. It is thus possible that true associations between supplement use and cancer risk are underestimated in our results.

An additional limitation of this study is that control participants may have been a biased sample of men who were more interested in health and more likely to use dietary supplements than the overall population. We completed short telephone interviews of 66 potential controls who chose not to participate in the full study. These men were slightly younger, less well educated, and had lower body mass indexes then controls, suggesting that there was biased nonresponse among eligible controls. One argument against a selection bias strongly affecting results of this study was that there were no associations between supplements and cancer risk for most supplements, including multivitamins. Furthermore, results were consistent when analyses were restricted to cases and controls who used at least one type of single supplement. Still, we cannot rule out selection bias and believe this should be considered when interpreting results. Lastly, because of their lower use of PSA screening, some controls may have had undiagnosed prostate cancer. Although we cannot exclude the possibility of this bias, there are two reasons that it may not strongly affect results. First, the incidence of prostate cancer in the age groups included in this study is very low, so it is unlikely that many control men had undetected disease. Second, when analyses were restricted to cases with stage C and D cancers, which would likely be detected clinically, there were no differences in study results.

Additional research on dietary supplement use and prostate cancer risk is needed. There is heightened interest in chemoprevention using dietary supplements, because of the unanticipated prostate cancer outcomes of two randomized controlled trials (5, 6), and a randomized trial of selenium and α-tocopherol supplements to prevent prostate cancer is under development. However, there is still need for carefully designed observational studies. Cohort studies may be the best approach to answering questions about supplements and cancer risk, because they will allow us to examine exposures to different combinations of supplements at a variety of doses, they avoid the persistent concern of selection bias in case-control studies, and they can collect serum to use as objective measures of supplement use. We believe that it is important to remember the generally negative or entirely unanticipated results of the large, randomized chemoprevention trials using dietary supplements (5, 6, 8–10, 39) and thus to refrain from making public health recommendations for supplement use for prevention of prostate cancer until there is a much broader and more compelling consensus of evidence.

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