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ORIGINAL PAPER

Boron intake and prostate cancer risk

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Abstract
Introduction Experimental studies suggest that boron may prevent prostate cancer. Only one small epidemiological study has been conducted of boron, which found that those in the highest quartile of boron intake had less than half the risk of prostate cancer versus those in the lowest quartile.
Methods We evaluated the association between boron intake and prostate cancer within the VITamins And Lifestyle (VITAL) cohort. A total of 35,244 men completed the baseline supplement and food frequency questionnaire (FFQ) in 2000–2002. A boron database was constructed from published sources to estimate boron intake from the FFQ and from multivitamins. A total of 832 men developed prostate cancer from baseline to 31 December 2004.
Results Dietary boron intake and total boron intake from diet plus multivitamins were not associated with prostate cancer risk. The hazard ratio of prostate cancer for those in the highest versus lowest quartile of total boron intake was 1.17 (95% CI 0.85, 1.61). This risk did not vary by prostate cancer stage or Gleason score. Furthermore, none of the foods high in boron content was associated with a decreased risk of prostate cancer.
Discussion This cohort study provides no evidence for a preventive role of boron intake on prostate cancer. Since few studies exist on this topic, future research is needed to better elucidate any role that boron may play in the prevention of prostate cancer.

Keywords Diet · Boron · Minerals · Prostate cancer

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Introduction

Prostate cancer is the most common cancer among US men and ranked second among the underlying causes of death from cancer in US men in 2003 [1]. Increased age, family history of prostate cancer, and African–American race are among the few established risk factors [2]. Dietary studies of prostate cancer are an active area of investigation, because such studies might lead to identification of modifiable risk factors for this common disease [2].

One dietary factor that has been rarely investigated in an epidemiologic study of prostate cancer is intake of boron, despite evidence for a possible effect of boron on prostate cancer provided by a number of laboratory and animal studies. Gallardo-Williams et al. demonstrated that boric acid reduced the growth of seeded prostate tumors in mice, and reduced IGF tissue levels and serum prostate specific antigen (PSA) [3, 4]. Studies by Barranco et al. have provided insight into the cellular mechanisms of boron; specifically, boric acid inhibited cell proliferation in prostate cancer cell lines, without inducing cell death, via a reduction in cyclins A–E [5, 6]. Furthermore, treated cells showed reduced adhesion and migration suggesting less metastastatic potential [6].

In addition, dietary boron has been hypothesized to influence prostate cancer risk via its effects on steroid hormones, and steroid hormones, particularly androgens, are suspected to play a role in human prostate

carcinogenesis [7–11]. Supplemental boron has been found to influence steroid hormones in two small human studies. A study by Naghii et al. [12] supplemented boron to a group of 18 healthy men with 10 mg twice weekly, and after four weeks plasma testosterone did not change significantly while estradiol concentrations increased significantly from 52 to 74 pmol/l. In a study in women, Nielsen et al. [13] also found that boron supplementation increased serum estrogen levels. A possible increase in estradiol is significant because at least two studies have found that increased circulating estradiol [9] or free estradiol [8] are associated with decreased prostate cancer risk. However, a meta-analysis of hormonal predictors of prostate cancer supports testosterone, as a risk factor and found little role for estradiol after adjustment for testosterone [11]. It is possible that boron intake may protect against prostate carcinogenesis by modulating the tumor-promoting effects of androgens via an effect of estrogens [14].

Up to date, only one epidemiologic study of individuals and one ecologic study have been conducted to examine the association between boron intake and prostate cancer. A cross-sectional study conducted by Cui et al. [15] of 95 prevalent prostate cancer cases and 8,720 controls within the Third National Health and Nutrition Examination Survey found that men in the highest quartile of boron intake had half the risk of prostate cancer compared with men in the lowest quartile (OR = 0.46, 95% CI 0.21–0.98). A recent ecologic study supports this finding: Barranco et al. [16] found a correlation of 0.63 between groundwater boron levels and prostate cancer incidence across Texas (US) counties and planning regions.

Despite the promising finding from the Cui et al. study and supportive data from experimental studies, no subsequent epidemiological study has tested whether boron intake is associated with reduced prostate cancer risk. This is likely due to the fact that boron is not routinely included in nutrient databases, such as the Minnesota Nutrition Data System for Research [17]. In order to address this hypothesis, we collected in a large prospective study detailed measures of dietary intake, including information on foods that are major contributors to dietary boron such as peanut butter and nuts, avocados, apples, red wine, and white wine. The food frequency questionnaire (FFQ) also included water, which is not typically included on FFQs but contributes boron to the diet. We developed a boron database based on published values, and used that to estimate boron intake. We also collected detailed measures of multivitamin use, including information on brand to allow estimates of boron intake from multivitamins. Up to our knowledge, this study is the first prospective study to examine boron intake and incident prostate cancer.

Methods

Study participants

Participants in this study were men in the VITamins And Lifestyle (VITAL) cohort study, whose primary aim is to investigate vitamin and mineral supplementation and cancer risk. Details of recruitment have been reported in a previous study by White et al. [18]. Briefly, men and women were eligible to participate in the VITAL study if they were aged 50–76 and living in a 13-county area of western Washington State. Since this study was limited to men, we here report recruitment of men alone. Using names that were obtained from a commercial list, a total of 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 to December 2002, during which, 37,382 men (19.5%) completed and returned a VITAL baseline questionnaire which passed quality control checks.

Of these, 2,136 men who reported a history of prostate cancer on the baseline questionnaire or who left that section of the questionnaire blank were excluded. Also, two men subsequently diagnosed with prostate cancer classified as “in situ” were excluded 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 sections on supplement use, diet, medical history, physical activity, personal characteristics, and cancer risk factors.

Participants were asked about their current multivitamin use, and selected one of 16 common brand names or indicated his brand was not listed. We also requested information on frequency (times per week) and years of use over the previous 10 years. Ten-year average boron intake from multivitamins was calculated by multiplying frequency of use times years of use times amount of boron in the subject’s multivitamin brand, and was expressed as average intake per day. If the participant indicated his brand was not listed, the boron in Centrum Silver® (150 μg), the most commonly used brand in the cohort, was used. Approximately 60% of all the multivitamin brands found in our supplement questionnaire contained boron, and a total of 16,482 men used a brand that contained boron—corresponding to approximately 90% of our cohort, who used multivitamins.

Diet was assessed by a semi-quantitative FFQ which asks 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 (e.g., low fat versus whole fat) and preparation techniques. Energy intake was estimated by use of the Minnesota Nutrition Data System for Research [17]. Men (n = 2663) were excluded from the dietary calculations if they did not complete all pages of the food frequency section (at least five items per page) or their energy intake was below 800 kcal or above 5,000 kcal. Alcohol intake and frequency of consumption of types of alcoholic beverages were also ascertained from the FFQ, however, participants were only excluded for these variables if they did not complete the FFQ page on beverages.

Since the FFQ analytic program was based on the Minnesota Nutrition Data System for Research which does not contain boron nutrient values, we developed a boron database. Our database was constructed by using previously published values for boron nutrient content of specific food items or food groups [19, 20]. We assigned boron nutrient values to over 340 specific foods that were combined into the 120 food items or food groups. For those few foods (n = 22) with no reported boron nutrient values, we estimated boron content based on boron nutrient values of similar foods. Dietary boron intake was calculated for each subject for each food as frequency times portion size times boron content of the food, and was summed over all foods and expressed as intake per day. Total boron was calculated by summing 10-year average boron intake per day from multivitamin use and dietary boron intake per day.

The remaining parts of the questionnaire covered demographic characteristics, health history, and other potential confounders. These included age at baseline, race, weight, and height. Using weight and height variables, we calculated body mass index (BMI) for each participant, which is defined as kilograms/meters^2. Physical activity was assessed by a one-page form described in detail elsewhere [21]. Average total MET hours per week over the past 10 years was calculated using the years, frequency, and published energy expenditures for different activities [22].

Health information collected at baseline included history of prostate-specific antigen (PSA) testing within the two years prior to baseline, physician-diagnosed benign prostatic hyperplasia (enlarged prostate), and number of first-degree family members who had had prostate cancer.

Follow-up of subjects for prostate cancer and censoring

A total of 832 incident, prostate cancers were identified in the cohort between baseline and 31 December 2004. We obtained case status, cancer stage, and Gleason score by linking the cohort to the Seattle-Puget Sound Surveillance, Epidemiology and End Results (SEER) cancer registry.

We utilized a multi-step scheme to link our cohort to the SEER registry. Initially, all potential matches were identified by linking on nine 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. Lastly, for records for which the match was still uncertain, the participant was telephoned directly.

For tumor characteristics, SEER summary stage was categorized as local (prostate cancer confined to prostate gland) or regional/distant (prostate cancer spread beyond capsule or outer layer). Grade was measured by Gleason score and was categorized as two to six and seven to ten, corresponding to well- or moderately differentiated cancers and poorly differentiated cancers, respectively. Due to the fact that 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 31 December 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 were used to estimate the relative risk, as measured by hazard ratios, of prostate cancer associated with sociodemographic, medical, and lifestyle characteristics other than boron intake. We calculated Pearson correlation coefficients (R) to estimate the proportion of the variance (R^2) of total boron intake (from diet plus multivitamins) explained by intake of specific foods, food groups, and beverages that are high in boron. Cox proportional hazard models were used to estimate the relative risk, as measured by hazard ratios, of prostate cancer associated with various measures of boron intake from diet, including specific high boron contributors (peanut butter and nuts, avocados, apples, red and white wine) and multivitamins. Age was treated as the time variable, with left truncation for age at baseline. Subjects

were censored (right truncation) at the censoring events noted above.

In order to address the possibility of medical surveillance bias, a variable identifying self-reported PSA testing within the 2 years prior to baseline was included in all multivariate models. Potential confounding factors that were included in the multivariate models were ethnicity/race (White, Black or other), education (categorical), first-degree family history of prostate cancer, alcohol (categorical), energy intake (categorical), fruit intake (categorical), and vegetable intake (categorical). Among those foods that are high boron contributors, we chose to treat fruit and vegetable intake and alcohol intake as potential confounders, because we wanted to separate the effect of boron intake per se from general dietary patterns that may influence prostate cancer risk. To test for a trend across each category we modeled a single ordinal categorical variable, using categorical medians. We also examined models stratified by prior PSA test and by prostate cancer categorized by grade and stage. The significance of interaction of PSA and total boron intake was computed as the p-value for an interaction term between the single "trend" boron intake variable and the dichotomous PSA variable, in a model that included the main effects, as well as the interaction term.

We used tabular and graphical methods to evaluate the validity of the proportional hazards assumption. Schoenfeld residuals were plotted against time to determine whether the slope differed from zero. In the models presented here there was no evidence that the assumptions of the proportional hazard function were violated. Analyses were conducted using STATA version 8.2 (StataCorp, College Station, Texas).

Results

A total of 832 men were diagnosed with prostate cancer during an average follow-up time of 3.3 years. About 84% had local stage disease, while 16% had regional/distant disease. Moderate- to well-differentiated tumors (Gleason score 2–6, 57%) were more common than poorly differentiated tumors (Gleason score 7–10, 43%).

Risk of prostate cancer was higher in Black men (Table 1). Other factors associated with an increased risk of prostate cancer included having had a PSA test within the two years prior to baseline, having benign prostatic hyperplasia, and first degree family history of prostate cancer. Among the lifestyle factors (body mass index, physical activity, smoking) and dietary factors (energy, alcohol, fruit, and vegetable intake) evaluated, none was clearly associated with prostate cancer risk. Current multivitamin use was associated with a slightly elevated risk of prostate cancer.

The estimated median intake of boron from diet in this population was 1,347 μg/day, and the median total boron intake from diet plus multivitamins was 1,389 μg/day. Thus, as shown in Table 2, dietary intake of boron explained 98% of the variance in total boron intake, while the boron in multivitamins only accounted for 2%. Fruit intake and vegetable intake explained 27% and 35%, respectively of the variance in total boron intake. The specific foods that contributed the most to total boron intake were peanut butter and nuts, avocado, apples, red wine and white wine.

We did not observe significant associations of dietary boron, total boron (diet plus boron from multivitamins), peanut butter and nut intake, apple intake, and avocado intake with prostate cancer risk, after adjustment for education, race, family history of prostate cancer, PSA testing, and general dietary factors (energy, vegetable, fruit and alcohol intake) (Table 3). However, there was a significant positive association between white wine intake and prostate cancer risk (adjusted HR for >1.5 servings/week versus none = 1.30, 95% CI 1.02–1.65, p for trend = 0.02). Furthermore, we found a borderline significant positive association between red wine intake and prostate cancer risk (p for trend = 0.06).

As shown in Table 4, it appeared that men who did not have a PSA test in the 2 years prior to baseline had an increased risk of prostate cancer associated with increasing boron intake (p for trend = 0.04), while among men who had had a PSA test, there was no association. However, this degree of effect modification was not significant (p for interaction = 0.11). The association between total boron and prostate cancer did not differ when cases where stratified by Gleason score or cancer stage (adjusted HR's for highest versus lowest quartile of total boron intake: 1.31 (95% CI 0.86–1.98) for prostate cancer with Gleason score 2–6; 0.99 (95% CI 0.60–1.63) for Gleason score 7–10; 1.16 (95% CI 0.82–1.65) for local stage; 1.17 (95% CI 0.53–2.60) for regional/distant stage; all p for trend > 0.05).

Discussion

In this study, dietary boron intake and total boron from diet plus multivitamin supplements were not significantly associated with prostate cancer risk. In addition, we did not observe any significant associations between intake of specific foods rich in boron, except for white and red wine, which were positively associated with prostate cancer risk. Our results do not support the strong protective association of boron on prostate cancer reported by Cui et al. [15]. Their study used one-day dietary recall to estimate boron intake, which may result in measurement error, and was based on a small number of cases (n = 95). Furthermore,

Table 1 Association of sociodemographic, prostate-related, and lifestyle characteristics with prostate cancer among men in the VITAL cohort

Characteristics	No prostate cancer (n = 34,412)		Prostate cancer (n = 832)		Age-Adjusted HR[b]	Age-Adjusted 95% CI[b]
	n[a]	%	n[a]	%		
Socioeconomic factors						
Age (years)						
50–54	8,342	24.2	56	6.7		
55–59	7,938	23.1	139	16.7		
60–64	6,443	18.7	185	22.2		
65–69	5,694	16.6	199	23.9		
70–76	5,995	17.4	253	30.4		
Marital status: Not married	5,708	16.8	128	15.5	0.98	0.81–1.18
Education						
<College	5,405	15.9	135	16.3	1.00	
Some college	11,910	35.0	291	35.2	1.19	0.97–1.46
College graduate	16,705	49.1	400	48.4	1.19	0.98–1.45
Race						
White	31,642	93.2	781	94.6	1.00	
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
Prostate-related factors						
PSA test in last two years	24,368	71.8	671	82.5	1.47	1.22–1.76
Benign prostatic hyperplasia	5,386	15.7	222	26.8	1.46	1.24–1.71
Family history of prostate cancer[c]						
0	29,544	87.1	665	80.4	1.00	
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						
Body Mass Index (kg/m^2)						
18.5–24.9	9,189	27.5	223	27.4	1.00	
25–29.9	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-hours/week)						
None	5,115	15.1	110	13.4	1.00	
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
10.6–21	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
Cigarette smoking						
Never	13,211	39.0	303	37.0	1.00	
Current	3,103	9.2	62	7.6	0.92	70–1.20
Former, quit ≤10 years ago	2,565	7.6	47	5.7	0.80	0.59–1.09
Former, quit >10 years ago	14,968	44.2	407	49.7	0.98	0.85–1.14
Energy intake (kcal/day)						
0–1658	7,941	25.0	204	26.4	1.00	
1659–2140	7,946	25.0	198	25.6	0.99	0.82–1.21
2141–2699	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 intake						
None or <1/month	10,669	31.6	235	28.2	1.00	
1/month–<1/day	12,555	37.2	322	39.5	1.24	1.05–1.48

Table 1 continued

Characteristics	No prostate cancer (n = 34,412)		Prostate cancer (n = 832)		Age-Adjusted HR[b]	Age-Adjusted 95% CI[b]
	n[a]	%	n[a]	%		
1–<2/day	5,337	15.8	138	16.9	1.21	0.98–1.49
2–<3/day	3,574	10.6	78	9.6	0.97	0.75–1.26
3+/day	1,614	4.8	43	5.3	1.27	0.92–1.76
Fruit intake (servings/day)						
0–0.63	7,790	24.7	154	20.2	1.00	
0.64–1.20	8,018	25.4	207	27.1	1.25	1.01–1.54
1.21–2.06	7,973	25.3	209	27.4	1.21	0.98–1.49
>2.06	7,794	24.7	193	25.3	1.19	0.96–1.47
Vegetable intake (servings/day)						
0–1.2	7,929	25.1	155	20.4	1.00	
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
>2.5	7,869	25.0	202	26.5	1.15	0.93–1.42
Multivitamin use						
No	16,231	47.2	333	40.0	1.00	
Yes	18,173	52.8	499	60.0	1.25	1.09–1.43

[a] Numbers do not add up to total number due to missing data: for all variables missing data is <5%, with the exception of energy intake (7.6% of no prostate cancer participants and 7.0% of cases), fruit intake (8.2% of no prostate cancer participants and 8.3% of cases), and vegetable intake (8.3% of no prostate cancer participants and 8.5% of cases)

[b] HR = hazard ratio, CI = confidence interval

[c] Number of first degree relatives with prostate cancer

that study had a cross-sectional design which included prevalent cases, thus the diet of cases may not have been representative of their pre-diagnostic diet.

We have recently reported the relationship of alcohol intake and types of alcoholic beverages to prostate cancer in this cohort [23]. In the analysis presented in this article, we have attempted to separate the effects of the high-boron containing alcoholic beverages from the effect of alcohol per se, by controlling our analyses for total alcohol intake. We observed a significant positive association of white wine and a borderline significant positive association of red wine with prostate cancer risk, similar to the findings in our earlier paper [23], despite the different statistical model and different aim. Although alcohol intake in relation to prostate cancer risk has been well studied [24–28], only three recent studies have examined red and white wine separately as predictors of prostate cancer risk [29–31]. Our findings for white wine are consistent with two [29, 31] of the three studies [29–31]: A large cohort study in the Netherlands found an increased risk of prostate cancer associated with increasing white wine consumption (RR for continuous 5 g increments, 1.20, 95% CI 1.0–1.5) [31], and

Table 2 Pearson correlations (R) of intake of boron-rich foods and boron in multivitamins with total boron intake[a,b] and percent variance of total boron intake explained (R^2) by intake of each food

Intake of:	R	R^2
Boron in multivitamins[c] (μg/day)	0.13	0.02
Dietary boron (μg/day)	0.99	0.98
Vegetable intake (servings/day)	0.52	0.27
Fruit intake (servings/day)	0.59	0.35
Peanut butter & nuts (servings/week)	0.32	0.10
Avocado (servings/week)	0.36	0.13
Apples (servings/week)	0.32	0.10
Red wine (servings/week)	0.44	0.19
White wine (servings/week)	0.34	0.12
Water (servings/week)	0.21	0.04
Coffee (servings/week)	0.17	0.03

[a] Total boron (μg/day) = dietary boron (μg/day) + 10-year average boron from multivitamins (μg/day)

[b] Among 32,288 men with complete data on all variables

[c] 10-year average boron intake from multivitamins (μg/day)

Table 3 Association of boron intake from diet, from boron-rich foods, and total boron intake (from diet plus multivitamins) with prostate cancer among men in the VITAL cohort

Intake of:	No prostate cancer (n = 34,412)		Prostate cancer (n = 832)		Multivariate adjusted HR[b]	Multivariate adjusted 95% CI[a,b]
	n[a]	%	n[a]	%		
Dietary boron (μg/day)						
0–998	7,959	25.0	186	24.0	1.00	
999–1347	7,963	25.0	182	23.5	0.96	0.76–1.22
1348–1792	7,941	25.0	203	26.2	1.07	0.82–1.40
1793–9004	7,942	25.0	203	26.2	1.10	0.80–1.51
p-trend					0.42	
Peanut Butter & Nuts (svgs/week)						
<0.28	8,372	26.3	189	24.4	1.00	
0.28–<1	10,265	32.3	257	33.2	1.11	0.92–1.35
1–<2.5	5,405	17.0	153	19.8	1.20	0.96–1.50
2.5–21.1	7,757	24.4	175	21.0	0.94	0.75–1.18
p-trend					0.73	
Avocado (svgs/week)						
None	19,079	60.0	77	61.6	1.00	
0.01–<0.3	6,275	19.7	152	19.6	1.00	0.83–1.21
0.3–<0.6	4,277	13.4	96	12.4	0.89	0.71–1.12
0.6–21.1	2,174	6.8	49	6.3	0.93	0.69–1.26
p-trend					0.39	
Apples (svgs/week)						
<0.20	7,985	25.1	160	20.7	1.00	
0.20–<0.7	7,962	25.0	224	28.9	1.24	1.00–1.54
0.7–<1.7	7,889	24.8	215	27.8	1.20	0.96–1.50
1.7–33.5	7,969	25.1	175	22.6	1.01	0.79–1.30
p-trend					0.97	
Red wine (svgs/week)						
None	19,444	57.6	433	53.1	1.00	
<0.5	4,783	14.2	121	14.8	1.12	0.89–1.41
0.5-<2.9	5,732	17.0	162	19.4	1.23	0.98–1.54
2.9–63.2	3,790	11.2	100	12.3	1.23	0.94–1.62
p-trend					0.06	
White wine (svgs/week)						
None	20,960	62.1	59	56.3	1.00	
<0.5	5,523	16.4	150	18.4	1.22	0.99–1.51
0.5–<1.5	3,022	9.0	86	10.5	1.27	0.98–1.95
1.5–63.2	4,244	12.6	126	15.4	1.30	1.02–1.65
p-trend					0.02	
Total boron (μg/day)[c]						
0–1,034	7,969	25.1	175	22.6	1.00	
1,035–1,389	7,952	25.0	193	24.9	1.08	0.85–1.37
1,390–1,837	7,940	24.9	206	26.6	1.16	0.89–1.52
1,838–9,004	7,944	25.0	203	25.8	1.17	0.85–1.61
p-trend					0.31	

[a] Numbers do not add up to total number due to missing data: dietary boron, peanut butter and nuts intake, avocado intake, apple intake, total boron (7.6% of no prostate cancer participants and 7.0% of cases), red wine (2% of no prostate cancer participants and 2.0% of cases), and white wine (2.0% of no prostate cancer participants and 2.0% of cases)

[b] HR = hazard ratio, CI = confidence interval. Multivariate HRs adjusted for age (underlying time variable), education, race, family history of prostate cancer, PSA test within the two years prior to baseline, vegetable intake, fruit intake, alcohol intake, and energy intake

[c] Total boron (μg/day) = dietary boron (μg/day) + 10-year average boron from multivitamins (μg/day)

Table 4 Association of total boron intake (from diet plus multivitamins) with prostate cancer among men in the VITAL cohort stratified by Prostate-Specific Antigen (PSA) test

[a] Total boron (μg/day) = dietary boron (μg/day) + 10-year average boron from multivitamins (μg/day)

[b] HR = hazard ratio of prostate cancer, CI = confidence interval. Multivariate HRs adjusted for age (underlying time variable), education, race, family history of prostate cancer, vegetable intake, fruit intake, alcohol intake, and energy intake

Total boron (μg/day)[a]	No prostate cancer		Prostate cancer		Multivariate adjusted HR[b]	Multivariate adjusted 95% CI[b]	*p*-interaction
	n	%	*n*	%			
PSA test within two years prior to baseline							0.11
0–1,034	5,397	23.8	143	22.7	1.00		
1,035–1,389	5,576	24.6	155	24.6	1.00	0.79–1.26	
1,390–1,837	5,729	25.3	168	26.6	1.03	0.82–1.30	
1,838–9,004	5,936	26.2	165	26.1	0.99	0.79–1.25	
p-trend					0.49		
No PSA test within two years prior to baseline							
0–1,034	2,460	27.9	26	20.5	1.00		
1,035–1,389	2,268	25.7	33	26.0	1.45	0.86–2.45	
1,390–1,837	2,138	24.3	36	28.3	1.61	0.96–2.71	
1,838–9,004	1,943	22.1	32	25.2	1.66	0.98–2.84	
p-trend					0.04		

the Health Professionals Follow-up Study found a small increased risk associated with consuming 2–5.9 g of white wine per day (RR 1.14, 95% CI 0.98–1.33) [29]. These two cohort studies [29, 31] did not find an association between red wine intake and prostate cancer, while a recent population-based case–control study found a significant inverse association [30]. Our finding of an increased risk of prostate cancer associated with alcoholic beverages with high boron content independent of any effect of the total amount of alcohol consumed, and the findings of the prior cohort studies, does not support boron as a potentially protective nutrient.

Our study had several strengths, including a reasonable sample size, a prospective design, and the ability to control in part for prior PSA testing and other potential confounders. It is particularly important to control for PSA testing as it is associated with detection of prostate cancer and with healthful behaviors including higher vegetable and fruit intake [32]. However, our measure of PSA testing (having a PSA test in the two years prior to baseline) is limited in that it is not a precise predictor of PSA testing during the follow-up period after baseline. Thus there may be residual confounding, in which case the true HR's may in fact be less than we observed in Table 3.

We also chose to stratify by PSA testing to investigate if having a prior PSA test modified the association between total boron and prostate cancer risk. Since PSA screening is highly associated with increased prostate cancer diagnosis, risk factors for prostate cancer might be obscured in the screened group, because risk might be primarily dependent on whether a subsequent (post-baseline) screen was obtained. Thus risk factors may appear to be stronger in the non-screened group. We saw some evidence of a stronger relationship of boron intake with prostate cancer in the non-PSA group; however, it was in the opposite direction hypothesized, so this provides no support for a protective effect of boron.

Limitations of this study included its primarily Caucasian, well-educated population that was self-selected. While self-section in a cohort study should not cause selection bias, i.e., men cannot self-select to join the study based on both their boron intake and their future unknown cancer status, it may affect the generalizability of our results to a less healthy population. Men interested in joining this diet-related study may have had healthier diets than the general population. Some evidence suggests that boron is rapidly excreted in the urine, does not accumulate in tissues, and is maintained in a relatively narrow range of concentrations in blood of healthy individuals [33]. Consequently, boron may only play a role in prostate cancer in those individuals who are boron deficient, which was not the case in our study population. The men is this study had a median boron intake of 1,390 per day, which is between the adequate and safe range of intake 1–3 mg/day, and only 25% had estimated intakes below 1000 μg (there is no established Recommended Daily Allowance for boron). The men in the Cui et al. [15] study also appeared to have adequate intakes of boron, although slightly lower than in our study, but it is unlikely that the small difference in intakes could account for the difference in results between that study and ours.

Measurement error in assessment of boron intake from diet and supplements is another potential source of study error. FFQ's have substantial error due to poor subject recall and social desirability bias [34]. FFQ's are also limited by their coverage of foods contributing to intake of a specific nutrient and by the quality of the databases used to convert food intake into nutrient intake. As noted in the introduction, our FFQ covered the major sources of boron, and as noted in the methods, we were able to identify boron

values for almost all the foods on our FFQ from published values [19, 20]. However, these published values are likely to have some error due to, for example, the variation in boron content between samples of the same food or between water sources. Due to the prospective design of our study, any measurement error in the assessment of boron intake should not have been differential between cases and controls.

Another limitation is that we were not able to evaluate the separate effect of boron from supplements on cancer risk. The boron dose commonly found in multivitamins (150 μg/pill) is relatively small compared to boron intake from the diet. As a result, boron from multivitamins only accounted for 2% of the variance of total boron intake. We did not assess boron from individual supplements, as single boron supplements are not readily available and were not included in our questionnaire. Furthermore, we could not separate the effect of use of multivitamins, which contain numerous nutrients, from the effect of boron in multivitamins, because 90% of users of multivitamins used a brand containing boron.

In summary, prior cellular, clinical, and epidemiological studies suggest that that dietary boron may reduce prostate cancer risk. However, in this cohort, dietary boron was not associated with a reduction in prostate cancer risk. Thus, the meaningful biological mechanisms that suggest a role of boron in prostate carcinogenesis did not translate to results from this study. Since, few studies exist on this topic, future studies are needed to better elucidate any role that boron may play in the prevention of prostate cancer.

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