

Dietary boron intake and prostate cancer risk

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Received September 8, 2003; Accepted October 14, 2003

Abstract. Boron affects human steroid hormone levels. Circulating testosterone and estradiol levels have been proposed to modify prostate cancer risk. However, the association between dietary boron intake and the risk of prostate cancer has not been evaluated by any epidemiological study. We explored the association between dietary boron intake and the risk of prostate cancer in the USA. Our analysis was based on data from the third National Health and Nutrition Examination Survey (NHANES III). Cross-sectional case-control study design was employed by comparing boron intake of 95 prostate cancer cases with that of 8,720 male controls. After controlling for age, race, education, smoking, body mass index, dietary caloric intake, and alcohol consumption, increased dietary boron intake was associated with a decreased risk of prostate cancer with a dose-response pattern. The adjusted odds ratio was 0.46 (95% confidence interval: 0.21-0.98) for the highest quartile of boron intake comparing to the lowest quartile (P for trend = 0.0525). The observed association should be interpreted with caution because of the small case sample size and the nature of the cross-sectional study design, but deserve further investigation.

Introduction

The age-adjusted incidence of prostate cancer has been increasing by approximately 3% annually worldwide (1). It is estimated that, among American men during 2003, 220,900 new prostate cancer cases will be diagnosed, accounting for 33% of all new male cancer cases (excluding basal and squamous cell skin cancers) (2). Prostate cancer currently

ranks second, following lung cancer, as the underlying cause of male cancer death in the USA (2). However, the etiology of prostate cancer is poorly understood. Age and race are among the few established risk factors for prostate cancer. It is estimated that white US men aged 75-79 have approximately 130 times the risk of men aged 45-49 and the disease is 66% more common and twice as likely to be fatal among African-Americans compared to Caucasians (3,4). Male hormone levels have been associated with the risk of the disease (4,5). Although the evidence on genetic factors is mounting, epidemiologic studies strongly suggest that environmental factors, particularly diet and nutrition, are important risk factors (5). The effects of nutritional factors such as fat intake, caloric intake, vitamins and minerals have been widely studied. Although results are not consistent, epidemiologic and experimental studies suggest that increased energy intake, particularly from saturated fat, may be associated with greater risk of prostate cancer (6,7). On the contrary, intakes of selenium, lycopene, vitamin A, vitamin D, and vitamin E may have protective effects (8-14). Studies attempting to establish epidemiologic linkages between endocrine factors, body mass index (BMI), smoking, alcohol consumption, and calcium intake and the risk of prostate cancer have been inconsistent (15-18).

Boron is a naturally occurring trace element in the human diet (19). Rich food sources of boron include fruits, nuts, legumes, vegetables, and wine. Coffee, milk, and other beverages, although low in boron, are major contributors in the US due to the large volume of consumption (20). Evidence from animal experiments suggests that boron is essential during the stage of rapid cell replication subsequent to fertilization, and that it ameliorates some adverse effects on bone of vitamin D deficiency (21-23). Dietary boron intakes have been shown to alter human steroid hormone levels (5). Diets deplete in the element has been shown to affect both the immune and nervous systems (24-26). To date, no epidemiologic studies have been conducted to investigate whether excessive or insufficient dietary boron intake is related to the development of diseases. In this study, we utilized the data obtained from the third National Health and Nutrition Examination Survey (NHANES III) to explore the relationship between dietary boron intake and the risk of prostate cancer.

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Key words: boron, prostate cancer, NHANES III

Table I. Association between potential risk or protective factors and prostate cancer.

Factors	Case (%)	Control (%)	Crude OR (95% CI)	Adjusted OR (95% CI) ^a
Age				
<65	18 (16.30)	6,806 (78.05)	1.0	1.0
65-74	45 (48.91)	1,040 (11.93)	19.63 (10.91-35.35)	14.639 (7.75-27.67)
≥75	32 (34.78)	874 (10.02)	16.61 (8.96-30.80)	9.01 (4.49-18.07)
Trend test			P _{trend} <0.0001	P _{trend} <0.0001
Continuous	95 (100)	8,720 (100)	1.08 (1.06-1.09)	1.06 (1.04-1.07)
Race				
White	69 (72.63)	3,295 (37.79)	1.0	1.0
Black	17 (17.89)	2,454 (28.14)	0.33 (0.19-0.56)	0.65 (0.37-1.14)
Mexican-American	7 (7.37)	2,641 (30.29)	0.13 (0.06-0.28)	0.27 (0.12-0.60)
Others	2 (2.11)	330 (3.78)	0.29 (0.07-1.19)	0.50 (0.12-2.08)
BMI				
<25	42 (44.21)	3,266 (37.45)	1.0	1.0
≥25	53 (55.79)	5,454 (62.55)	0.76 (0.50-1.14)	0.61 (0.40-0.92)
Continuous	95 (100)	8,720 (100)	0.95 (0.90-0.99)	0.94 (0.89-0.99)
Education (years)				
≤12	71 (74.74)	6,357 (72.90)	1.0	1.0
>12	24 (25.26)	2,363 (27.10)	1.91 (0.57-1.45)	1.04 (0.63-1.70)
Continuous	95 (100)	8,720 (100)	0.97 (0.92-1.02)	1.00 (0.95-1.06)
Smoking				
Never	27 (28.42)	3,396 (38.94)	1.0	1.0
Current	58 (61.05)	2,634 (30.21)	2.77 (1.75-4.39)	0.61 (0.29-1.30)
Former	10 (10.53)	2,690 (30.85)	0.47 (0.23-0.97)	1.43 (0.89-2.29)
Pack-year	95 (100)	8,720 (100)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Never	27 (28.42)	3,390 (39.12)	1.0	1.0
Light (<40)	59 (62.11)	3,491 (40.28)	2.16 (1.36-3.41)	1.36 (0.85-2.18)
Heavy (≥40)	9 (9.47)	1,785 (20.60)	0.64 (0.30-1.37)	0.76 (0.35-1.66)
Trend test			P _{trend} =0.9560	P _{trend} =0.9072
Caloric intake				
1st quartile	20 (21.05)	1,240 (14.22)	1.0	1.0
2nd quartile	38 (40.00)	2,464 (28.26)	0.96 (0.55-1.65)	0.97 (0.56-1.71)
3rd quartile	18 (18.95)	1,617 (18.54)	0.69 (0.36-1.31)	1.11 (0.57-2.14)
4th quartile	19 (20.00)	3,399 (38.98)	0.35 (0.18-0.65)	1.02 (0.52-2.00)
Trend test			P _{trend} =0.0001	P _{trend} =0.8625
Continuous	95 (100)	8,720 (100)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Alcohol consumption				
Never	28 (29.47)	1,942 (22.27)	1.0	1.0
Former	37 (38.95)	2,222 (25.48)	1.16 (0.71-1.90)	1.19 (0.71-1.98)
Current	30 (31.58)	4,556 (52.25)	0.46 (0.27-0.77)	0.96 (0.55-1.68)
Never	28 (29.47)	1,942 (22.27)	1.0	1.0
Moderate	53 (55.79)	5,260 (60.32)	0.70 (0.44-1.11)	1.06 (0.54-2.09)
Heavy	14 (14.74)	1,518 (17.41)	0.64 (0.34-1.22)	1.09 (0.67-1.78)
Trend test			P _{trend} =0.1281	P _{trend} =0.8127
Continuous	95 (100)	8,720 (100)	1.00 (1.00-1.00)	1.00 (1.00-1.00)

^aAdjusted for covariates in the table.

Materials and methods

This study utilized data from NHANES III conducted between 1988-1994 by the National Center for Health Statistics, Centers for Disease Control and Prevention, US Department of Health and Human Services (27). The survey was designed to provide national estimates of the health and nutritional status of the non-institutionalized civilian population of the US older than 2 months of age. This cross-sectional survey was conducted using a complex, multistage, stratified probability cluster sample design, with oversampling of young children, older persons, non-Hispanic Blacks and Mexican-Americans. The dataset for this analysis was established by merging data files of Household Adult, Examination, and Lab from the NHANES III database that was released in 1997 and subsequently updated. The final dataset was composed of 9,401 male subjects aged 17 and older, among whom 95 prostate cancer patients were identified, 76 of whom had dietary boron intake data. These prostate cancer patients formed the case group. Male adults with no cancer, totally 8,720, formed the control group; 7,450 had dietary boron intake data. Five hundred and eighty-six other cancer patients were excluded from data analysis.

Dietary boron intake was estimated for study subjects who completed one day of dietary recall in the NHANES III, using the Boron Nutrient Database generated by Food Research, Inc. of Costa Mesa, CA (Rainey *et al*, unpublished data). Boron intake was analyzed first as a continuous variable. Then it was categorized into quartiles and analyzed as a polytomous indicator variable for trend tests and as dummy variables for odds ratios for each category of intake. The boundaries used to categorize boron intake were first quartile, median, and third quartile of boron intake according to the distribution of boron intake in the control group.

Demographic and potential confounding factors for prostate cancer included age, race-ethnicity, education, smoking status, BMI, caloric intake, and alcohol consumption. The age used in analysis was the age at initial diagnosis for cases and the age at the time of the dietary survey for controls. Age was analyzed first as a continuous variable and then as a categorical variable, in three categories: younger than 65, 65-74 and 75 years of age or older. Race-ethnicity was divided into four categories: non-Hispanic White, non-Hispanic Black, Mexican-American, and Others, and was analyzed as dummy variables. Education was first analyzed as a continuous variable (years of education completed), and then as a categorical variable, dichotomized into those with a high school education or less (≤ 12 years of schooling) and those with more than a high school education (> 12 years of schooling). Smoking status was divided into three categories: never, former, and current smokers. Pack-years of smoking was analyzed as a continuous variable, and then categorized as never, light (< 40 pack-years) and heavy smokers (≥ 40 pack-years). Alcohol consumption was first divided into three categories: never, former, and current drinker. It was also categorized into never, moderate (< 5 drinks per day), and heavy (≥ 5 drinks per day). Finally, alcohol consumption was analyzed as a continuous variable. Body mass index (BMI) was analyzed first as a continuous, then as a binary variable, with persons with BMI ≥ 25 considered overweight and persons with BMI < 25 considered as reference. Caloric intake was analyzed as a continuous

variable first and then as a categorical variable with quartiles. Because of the limited sample size, other nutrition factors were analyzed separately with boron intake to evaluate potential confounding effects.

Data analyses were performed with the Statistical Analysis Software (SAS). First, descriptive statistics on all variables were generated to examine distributions of values, to check for outliers, and to assess the extent of missing data. Second, associations between prostate cancer and potential confounding factors such as age, race, education, smoking, BMI, caloric intake, and alcohol consumption were explored. Third, the association between boron intake and prostate cancer was examined with or without controlling for those potential confounding factors. An unconditional logistic model was employed to assess the associations between prostate cancer and those factors.

Results

The associations between potential risk or protective factors and prostate cancer were explored initially (Table I). Age is confirmed as a risk factor for prostate cancer. The crude odds ratio (OR) for the continuous variable was 1.08 [95% confidence interval (CI): 1.06-1.09]. After adjusting for other factors listed in Table I, the OR of age decreased slightly to 1.06 (95% CI: 1.04-1.07), indicating there is a 6% increase of prostate cancer risk with each one year increment of age. This is consistent with previous studies (3). Earlier studies also indicated that Blacks experienced a higher risk than Whites (18). However, no obvious difference was found in this study, perhaps due to the limited number of black male cases. Higher BMI appeared to be inversely related to prostate cancer with an adjusted OR of 0.61 (95% CI: 0.40-0.92). No obvious relationship was found between prostate cancer and education, smoking, dietary caloric intake, and alcohol consumption in univariate and multivariate analyses.

Table II presents the results of dietary boron intake and its relationship with prostate cancer. It was shown that prostate cancer cases had a lower dietary boron intake than controls. The boundaries of the 1st, 2nd and 3rd quartiles of dietary boron intake were 0.52, 0.86, and 1.36 mg/day for cases and 0.62, 1.00, and 1.54 mg/day for controls, respectively. To explore the relationship between dietary boron intake and the risk of prostate cancer, three stages of data analyses were conducted. First, boron intake was analyzed as a continuous variable in the model when adjusting for potential confounding factors listed as footnotes of Table II. This resulted in an adjusted OR of 0.76 (95% CI: 0.52-1.10). Second, boron intake was categorized into quartiles according to the distribution of controls in the same model and was analyzed as dummy variables with the lowest quartile considered as the reference group. The adjusted ORs of the 2nd, 3rd, and 4th quartile categories were 0.61 (95% CI: 0.32-1.16), 0.59 (95% CI: 0.30-1.16), 0.46 (95% CI: 0.21-0.98), respectively. These results showed that the highest dietary boron intake was inversely related to prostate cancer, when compared to the lowest quartile. Finally, the trend test was performed to evaluate the dose-response relationship between dietary boron intake and the risk of prostate cancer. The adjusted P-value for trend was 0.0525, showing a monotonic trend.

Table II. Dietary boron intake and risk for prostate cancer.

	Case (%)	Control (%)	Crude ORs (95% CI)	Adjusted ORs (95% CI) ^a
1st quartile	25 (32.89)	1,897 (25.46)	1.0	1.0
2nd quartile	18 (23.68)	1,847 (24.79)	0.74 (0.40-1.36)	0.61 (0.32-1.16)
3rd quartile	18 (23.68)	1,850 (24.83)	0.74 (0.40-1.36)	0.59 (0.30-1.16)
4th quartile	15 (19.74)	1,856 (24.91)	0.61 (0.32-1.17)	0.46 (0.21-0.98)
Trend test			$P_{\text{trend}}=0.1445$	$P_{\text{trend}}=0.0525$
Continuous	76 (100)	7,450 (100)	0.83 (0.62-1.11)	0.76 (0.52-1.10)

^aAdjusted for age (continuous variable), race (dummy variables), education (binary variable: high education/no high education), smoking (dummy variables: never, current, former smoking), BMI (binary variable: overweight/not-overweight), caloric intake (continuous variable), and alcohol consumption (continuous variable).

Discussion

There are extensive and consistent observations that high fruit and vegetable intakes are associated with decreased risks of many cancers. A case-control study by Cohen *et al* observed that consumption of a diet high in vegetables, particularly cruciferous vegetables, is associated with a reduced risk of prostate cancer (28). Another multi-center case-control study showed that certain categories of vegetables might protect against prostate cancer (29). Others have attempted to identify substances in vegetables and fruits that provide this protective effect against prostate cancer. Although results are not always consistent, there are some interesting observations. Lycopene, the carotenoid found in tomatoes, has been reported to be protective; α -tocopherol supplementation has shown a protective effect in one intervention study; and vitamin D has been shown to be protective in a prospective study (30). The present study shows that boron, which is abundant in fruits, vegetables, nuts, and legumes, may reduce the risk of prostate cancer. The potential significance of the inverse association is strengthened by the dose-response relationship between dietary boron intake and prostate cancer. Efforts were made to adjust for potential confounding factors such as age, race-ethnicity, education, smoking, BMI, total caloric intake, and alcohol consumption when exploring the association between boron intake and the risk of prostate cancer.

The biological plausibility of the inverse relationship between boron intake and prostate cancer risk falls into four areas: steroid hormones, metabolic regulation, antitumor metabolites, and the regulation of cell proliferation. Testosterone is the major hormonal regulator of prostate growth and function (4,5). A great number of case-control studies have assessed the relationship between circulating testosterone and estradiol level and the risk of prostate cancer. Bosland (5) has reviewed the data and concluded that most studies found an association between an increased ratio of testosterone to 4 α -dihydrotestosterone (DHT) and increased risk of the disease. The relationship with 17 β -estradiol (E2) is somewhat weaker (5). Dietary boron intakes have been shown to alter human steroid hormone levels. Naghii and Samman (31) supplemented boron to a group of 18 healthy males with 10 mg twice per

day. After 4 weeks plasma testosterone levels were unchanged, but estradiol concentrations increased from 52 to 74 pmol/l (31). In women, boron supplementation has produced mixed results. Nielsen and colleagues supplemented women receiving a low magnesium diet with boron (3 mg/day) for 16 days and observed a significant increase in both serum testosterone and 17 β -estradiol (32). In a follow-up study with normal Mg intakes, they only observed increases in 17 β -estradiol, and it was limited to women receiving estrogen therapy (33). Independent studies by Volpe *et al* (34) and Beattie and Peace (35) reported no effect of boron on either testosterone or 17 β -estradiol.

Several biological functions of boron are now understood at the molecular level. Although no molecular function has been identified for boron in animals, cell wall rigidity in plants depends on the formation of rhamnogalacturonan II (RG-II), a pectic polysaccharide, that is covalently cross-linked through cis-diols of apiosyl residues by a borate ester (36,37). RG-II accounts for about 20% of the ethanol-precipitable polysaccharides in red wine and is the predominant polysaccharide in fruit drinks. The ability of boric acid to bind to hydroxyl groups of serine and NAD explains its ability to inhibit serine proteases and dehydrogenases (38,39). Several potential boric acid binding sites are involved in prostate cancer. The conversion of 5 α -dihydrotestosterone (DHT) to 3 α ,17 β androstenediol by 3 β hydroxysteroid dehydrogenase type II presents two potential binding sites, the diol product and the dehydrogenase coenzyme. Prostate serum antigen (PSA), a serine protease, is also a potential site for direct boration.

Another potential mode of action is through the synthesis or activation of metabolites that regulate growth. Tartrolon, boromycin, and aplasmomycin are antibiotics synthesized by bacteria and each contains a single boron atom (40-42). Tartrolons act by inhibiting DNA, RNA, and protein synthesis, while boromycin and aplasmomycin disrupt membrane permeability. Although there are no known metabolites in vertebrates that contain boron, it is required for cell division in zebrafish and embryogenesis in *Xenopus*, and it also stimulates the release of α TNF in rats (21,43-45).

There were certain limitations to this study, which, if addressed in future research, could further elucidate the

relationship between boron intake and prostate cancer. First, because this is a cross-sectional survey measuring boron exposure and prostate cancer simultaneously, temporal ambiguity can not be excluded. Second, a 1-day dietary recall was used to estimate boron intake, which may provide limited estimates of the dietary intakes of study subjects, considering daily variation and seasonal changes (46). Third, from the data, we found that only 25% of prostate cancer patients were diagnosed less than 1 year before interview; most of the patients were prevalent cases. It is possible that the disease might have caused patients to change their diets and, as a result, their intake of boron. If patients did change their diets after diagnosis, it was likely they increased their intake of vegetables and fruits. If this were the case, the true beneficial effect of dietary boron preventing prostate cancer would have been underestimated in our study. Fourth, the small sample size of the case group (n=76) may have resulted in reduced power of the study, and it may have limited our ability to measure the association precisely. We attempted to adjust for additional nutritional variables, such as dietary fat, fiber, serum lycopene, and vitamin E in addition to the adjusted variables in the logistic regression model. However, because of limited sample size, the confidence intervals for odds ratios of boron intake included null value, although the point estimates for high intake of boron were still protective.

Our study, demonstrating that dietary boron intake is inversely related to prostate cancer, suggests that higher boron intake might have a beneficial effect on prevention of prostate cancer. The observed association should be interpreted with caution because of the small case sample size and the nature of the cross-sectional study design, but deserves further investigation.

Acknowledgements

We thank the National Center for Health Statistics as the original data source. This study is supported in part by the NIH National Institute of Environmental Health Sciences, National Cancer Institute, Department of Health and Human Services, Grants ES06718, CA77954, CA09142, CA16042, and CA 42710, by awards from CapCURE, an award from Carolan foundation, a seed Grant from University of California-Los Angeles Jonsson Comprehensive Cancer Center Foundation, and the Weisman Fund.

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