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Prevalence of Prostate Cancer in High Boron-Exposed Population: A Community-Based Study

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Abstract We investigated the possible relationship between boron exposure and prostate cancer (PCa) for men living and being employed at boron mines in villages with rich boron minerals. Out of 456 men studied, 159 were from villages with rich boron sources and boron levels in drinking water of >1 mg L^{-1} and these men formed the study group, while 63 from villages with rich boron sources and boron levels in drinking water of <1 mg L^{-1} were enrolled into control group 1. A further 234 subjects from other villages with no boron mines were considered as control group 2. Prostate specific antigen (PSA) levels could be obtained from a total of 423 men. Urinary boron concentration as an indicator of boron exposure in 63 subjects, prostatic volumes by transrectal ultrasonography in 39 subjects, and prostatic biopsies in 36 subjects were obtained for study and control groups. The daily boron exposure was calculated according to urinary boron levels. Although there was no significant difference among the groups in terms of total PSA levels, the number of subjects with tPSA ≥2.5 and tPSA ≥10.0 ng dL^{-1}

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prostatic volumes in men whose prostates were biopsied ($p<0.012$) was significantly lower in the study group as compared with those in the control group 2. These results suggested that high exposure to boron might have an implication within the prostatic cellular processes related to hyperplasia and carcinogenesis, even though we did not find a statistically significant association between PCa and boron exposure.

Keywords Prostatic neoplasm · Epidemiology · Boron intake

Introduction

A few small epidemiological researches based on experimental studies have suggested that boron which is found in nature at trace levels has some beneficial effects on human organisms. Vitamin D, important for bone metabolism, calcium, and magnesium are related directly to boron level; it also affects steroid hormone mechanisms and has some antioxidant effects in postmenopausal women [1]. These are some of the examples of its effects on the human body [2]. In addition, it has been reported that there have been some encouraging results for cancer patients in favor of boron intake [3, 4].

Prostate cancer (PCa) is the most common cancer among males. Increased age, family history and race are some of the established risk factors [5, 6]. Dietary studies of PCa have become an active field of investigation to prevent PCa. Recent results from epidemiological studies based on the relation between PCa and boron as a dietary factor have shown that men who consume higher levels of boron have a lower risk of PCa [4, 7]. Furthermore, it has been reported that groundwater boron concentration levels were inversely correlated with PCa incidence and mortality rates in Texas, USA [8]. The biological plausibility of these observations has been supported by cell culture and animal studies. Gallardo-Williams et al. demonstrated that boric acid reduced the growth of seeded prostate tumors in mice as well as the levels of IGF tissue and prostate specific antigen (PSA) [3]. Similarly, inhibition of cell proliferation was demonstrated in prostate cell lines. Furthermore, reduced adhesion and migration suggesting less metastatic potential were observed in DU-145 PCa cells with boron supplementation [9].

Turkey has large reserves of boron minerals and is one of the important boron-producing countries worldwide. The villages of Iskele, Osmanca, Yeniköy, and Yolbaşı, centered around Bigadiç town in the Balıkesir region of Turkey, are located in an area containing rich boron minerals. Most of the people living in these villages are employed not only in the mining of boron-rich minerals but also in the cultivating of crops, and have been for more than a century. The agricultural products are cultivated in an area where the levels of boron in tap water are unusually high [10, 11]. Therefore, it would be reasonable to investigate the relationship between boron and PCa in the population living there.

Here, we aimed to examine whether there was a possible association between boron exposure and PCa using an ideal region for an objective epidemiological study. We also investigated whether there was a relationship between the prostatic volume and exposed boron levels in the study group. A reduction in PCa incidence among the population with high dietary intake of boron would be consistent with the hypothesis that boron prevents PCa incidence. Urinary boron concentration as an indicator of boron exposure, PSA levels, prostatic volumes by transrectal ultrasonography (TRUS) in eligible subjects and prostatic biopsies were obtained in the appropriate subjects from all groups.

Materials and Methods

Out of a total of 527 men were initially contacted by the researchers; 265 of them were from the aforementioned villages with rich boron sources, and 262 were from other villages which did not contain any boron mines but were located in the same region (control group 2). Informed consent was obtained from all the individuals in the study after the approval of the Local Ethical Committee. The first group was reclassified according to the boron levels in their drinking water: higher than 1 mg L^{-1} in the villages of Iskele and Osmanca (study group), and between 0.1 and 1 mg L^{-1} in the villages of Yeniköy and Yolbaşı (control group 1). All the subjects from the study and both control groups were over 40 years old and those in the study group had a minimum residency of 5 years for adequate exposure to boron. In the end, a total of 456 men were studied; 159, 63, and 234 of them in the study group, control groups 1 and 2 respectively, as detailed in Table 1.

Prostate Specific Antigen Determination and TRUS and Prostate Biopsy

To examine the effects of prostate specific antigen (PSA) on PCa, PSA levels were accurately determined in the volunteered 423 (133, 62, and 228 subjects in the study group, control group 1, and control group 2, respectively) of 456 subjects enrolled into the study after exclusions of hemolytic samples, faults in transportation or laboratory errors. Serum PSA values were determined using the Hitachi Roche Elecsys 2010 (Party no: 741–0017-Serial no: 1541–02) device and PSA kit (Cobas-Roche Elecsys cat. no: 04.641.655 190).

The TRUS-guided prostatic biopsy was offered to the subjects with a serum PSA level above 2.5 ng mL^{-1} and was applied to 9, 13, and 17 volunteered individuals from the study group, control group 1, and control group 2, respectively, while TRUS-guided prostatic biopsy was performed on only 36 men, as three men refused the biopsy during the procedure.

Subjects previously administered anticoagulant, aspirin and narcotics were excluded from the study. A medical history, including International Prostate Symptom Score, was taken and both routine systemic and urological physical examinations were done. Antibiotic prophylaxis was administered orally using both 500 mg levofloxacin daily and 500 mg ornidazole twice a day before the biopsy procedure, completed over 4 days. Another informed consent for the biopsy procedure was obtained from all subjects. For analgesia, intrarectal and perianal prilocaine plus lidocaine gel were used [12]. The biopsy procedure was carried out with the guidance of 7.5 MHz ultrasound. Eight-quadrant standard

Table 1 The number of men over 40 years old in the study and control groups according to 2008 census data

	Total population >40 years old	Male population >40 years old	Male population included in the study
Iskele and Osmanca (region for study group)	1,092	526	159 (30.2%)
Yeniköy and Yolbaşı (region for control group 1)*	464	204	63 (30.9%)
Mecidiye, Çağış and Çömlekçi (region for control group 2)*	1,292	603	234 (38.8%)

*The mean value of boron levels in drinking water were between 0.3 and 1.0 mg/L in control group 1 and below 0.3 mg/L in control group 2

sampling was applied to all subjects; 18 gauge biopsy needles and automatic biopsy guns (Bard Magnum Biopsy Instrument) were used during the procedure. Prostatic volumes were calculated by classical ellipsoid formula and during the procedure no complications were observed. All the procedures were completed by the same urologist (TM), who was blinded to the identities of the samples regarding the groups in the study. Biopsy samples were fixed in 10% formalin solution and embedded in paraffin blocks. If needed, high molecule weighed immunohistochemical cytokeratin staining was performed.

The Method Used for Estimation of Daily Boron Intake: Urinary Boron Determination

It is well-known that boron is easily absorbed via gastrointestinal epithelial cells through mucous membranes found in the mouth, eyes, vagina, and anus [2]. The concentration of boron in plasma is very low and not very stable; therefore, plasma boron concentration is not a good indicator of the daily intake [13]. In contrast, it is excreted in urine at a rate of 84–90% in humans and animals [14]. Boron determination in urine conducted on 24-h urine samples is a good measure of daily intake. Therefore, urinary boron level is accepted as a good measure of the total body boron intake. For estimation of the daily B exposure, 24-h urine samples were collected from individuals who had healthy kidney filtering functions represented by creatinine clearance levels within the range of 80–125 ml/min. Blood and urine creatinine values were used to calculate the creatinine clearance levels. It has been reported that the B excreted in the urine represented 85% of the daily B exposure [15]. Boron concentration in urine was determined by using inductively coupled plasma optical emission spectrometry (ICP-OES), as described below. Creatinine clearance (CrCl) studies were performed for all the subjects whose daily boron intake was determined; it was calculated using the following formula: "$\mathrm{CrCl}=[U\times V]/C$ (mL min^{-1})"; where, U=urinary creatinine (mg dL^{-1}), V=urine amount/1,440 (mL min^{-1}), and C=serum creatinine (mg dL^{-1}).

Method: Colorimetric, Jaffe Cinetix

Urinary Boron Determination by ICP-OES, Sample Preparation, and Analysis Method

Three parallel solutions were prepared. Five milliliters of concentrated HNO_3 were added to 5.0 mL urinary sample and the resulting mixture was placed in a microwave oven for the digestion of samples. For this purpose, the temperature of the oven was brought from room temperature to 150°C in 5 min; the temperature was kept constant at 150°C for another 5 min. It was then elevated to 180°C in 5 min and was again kept constant there for another 5 min. After the digestion process was completed, samples were cooled to room temperature and were diluted to 50.0 mL with deionized water in a plastic volumetric flask. Indium was used as an internal standard which was added to all samples and standard solutions so that its final concentration was 10 mg L^{-1}. Parameters for ICP-OES were selected for optimum performance. The wavelengths selected for analyte boron and internal standard indium were 249.733 and 230.606 nm, respectively. Plasma radiofrequency power was 1.4 kW; coolant and auxiliary Ar flow rates were 16 and 0.5 Lmin^{-1}, in turn; nebulizer pressure was adjusted to 35 psi. To introduce the samples to Ar plasma, the peristaltic pump flow rate was adjusted to 1.0 mL min^{-1}; both uptake and rinse periods were selected as 30 s. Integration periods for both signal and background were 1 s.

Student's t test and Kruskall–Wallis one-way ANOVA tests were used in the statistical analysis. A Spearman's non-parametric test was used for two different variables. The rate of

groups was analyzed with chi-square, but when expected values were low, Fisher's exact chi-square tests were used. $p<0.05$ was considered as the cut-off for statistical significance.

Results

General Descriptive Measures of Subjects in this Observational Study

Fifteen men from the study group and 48 men from the two control groups were randomly selected for daily boron intake calculation. The creatinine clearance results were found to be normal in all the participants. The mean values of creatinine clearance were 83.1, 80.0, and 94.0 in the study group, control group 1, and control group 2, respectively. The mean value for daily boron exposure was found to be 6.1 mg day^{-1} in subjects of the study group, while it was 0.88 and 0.64 mg day^{-1} in control groups 1 and 2, respectively, as shown in Table 2. According to boron levels in drinking water, there was a statistically significant difference between the study group and both of the control groups ($p<0.0001$), but no significant difference was detected between control groups 1 and 2 in terms of daily boron exposure ($p<0.883$), as highlighted in Table 3.

Although there was no significant difference among the groups in terms of total PSA levels, prostatic volumes were significantly lower in the study group as compared with those in the control group 2 in men whose prostates were biopsied ($p<0.012$), as detailed in Table 3.

The study group included the smallest number of both subjects with tPSA ≥2.5 and tPSA ≥10.0 ng dL^{-1}, as compared with other groups, although it is not statistically significant.

When the subjects were stratified according to their PSA levels into four groups, as 0–2.5, 2.6–4.00, 4.01–10.00, and >10.00 ng mL^{-1}, no significant difference was observed ($p=0.546$). However, the number of subjects with PSA levels greater than 10.00 ng mL^{-1} was lowest in the study group, as shown in Table 4.

Pathological Findings

Totally, 36 out of 85 men whose initial PSA levels were greater than 2.5 ng mL^{-1}, were subjected to the biopsy procedure; nine, 12, and 15 individuals from the study group,

Table 2 Boron levels in drinking water in targeted places and the daily boron exposures in sample population ($p<0.05$)

Groups (n)		Boron levels in drinking water (mg L^{-1})	Daily Boron Exposure (mg day^{-1}±SD (n))
Study group (159)	Iskele (134)	1.42–6.51	6.1±3.0 (15)
	Osmanca (25)	1.72–3.97	
Control group 1 (63)	Yeniköy (44)	0.07–0.41	0.88±0.72 (17)
	Yolbaşı (19)	0.69–0.91	
Control group 2 (234)	Çağış	0.03–0.2	0.64±0.7 (31)
	Çömlekçi	ND	
	Mecidiye	ND	

ND not detected (limit of detection is 0.02 mg/L)

Table 3 The mean values of boron exposure, prostate volumes, PSA values and histopathological results of all groups

	Age±SD	Daily boron exposure (mg day^{-1}±SD)	Prostatic Volume[a] (mL±SD (*n*))	tPSA (ng dL^{-1}±SD)	tPSA ≥2.5 ng dL^{-1} (%)	tPSA ≥10.0 ng dL^{-1} (%)	Cancer (%)	PIN (%)
Study group	59.4±12.8	6.1±3.0	23.2±4.5 (9)	1.60±1.6	22 (16.5)	1 (0.8)	1 (12.5)	1 (12.5)
Control group 1	59.5±9.6	0.88±0.72	29.0±9.2 (13)	2.40±4.1	17 (27.4)	2 (3.2)	2 (15.4)	–
Control group 2	58.4±10.3	0.64±0.7	35.6±12.3 (17)	1.89±2.9	41 (18)	6 (2.6)	2 (13.3)	2 (13.3)
p value	0.6	<0.0001[c]	0.012[d]	0.18	0.170[b]	0.397[b]	Insufficient data for statistics	

There were no statistical differences between the study group and control group 1 and between the two control groups.

tPSA total prostate-specific antigen, *PIN* prostatic intraepithelial neoplasia

[a] TRUS-guided in 39 men

[b] Chi-square test

[c] No difference in groups 2 and 3 ($p=0.883$)

[d] There was a statistical difference only between the study group and control group 2 in according to prostate volume

Table 4 The number of subjects in study group, control groups 1 and 2 according to different tPSA ranges

	n (% of total in a group)				
	PSA=0–2.5	PSA=2.5–4.0	PSA=4.0–10.0	PSA >10.0*	Total
Study group	111 (83.5)	13 (9.8)	8 (6)	1 (0.8)	133 (100)
Control group 1	45 (72.6)	10 (16.1)	5 (8.1)	2 (3.2)	62 (100)
Control group 2	187 (82)	23 (10.1)	12 (5.3)	6 (2.6)	228 (100)
Total	343 (81.1)	46 (10.9)	25 (5.9)	9 (2.1)	423 (100)

*$p<0.005$, $p=0.546$

control group 1, and control group 2 in turn, accepted the biopsy. We found only five prostatic adenocarcinoma cases in the histological examination. Out of them, one subject was in the study group and four subjects were in the control groups. Prostatic intraepithelial neoplasia was detected in three cases; one of the patients was in the study group, and two patients were in control group 2, as detailed in Table 3. All cancers had Gleason grade 6 (3+3)/10. No statistical analysis was done because of insufficient number of subjects in the groups.

Discussion

The region studied has ideal charcateristics for this type of research due to the presence of boron mines. Significant differences in boron exposure may be observed in locations in rather close proximity. These differences are believed to be originated from the boron content of the drinking water available to the study region (Table 2). In our study group, boron exposure was found to be 6.1±3.0 mg/day. In our previous studies using the same part of Turkey, daily boron exposure in men were found to be 6·77 mg/day (SE, 0·47) [15] and 6.48 mg/day (SE, 0.12) [16]. The result obtained in the present study is very close to the previous findings as stated above. Therefore, chronic boron exposure in mining region is validated. On the other hand, boron exposure is not high for the control groups where the drinking water boron content is lower than 1.0 mg L^{-1} [15, 16].

Prostatic carcinoma is relatively the most common organ cancer in men in Turkey, as well as in other countries [17]. TRUS-guided prostatic biopsy is accepted as a standard method for histopathological diagnosis [18]. This study is a unique one in that the data are presented for interventional (invasive) investigation of the relationship between boron intake and prostatic carcinoma incidence in men living in a region with high boron exposure. In multiple animal studies and retrospective investigations, it has been revealed that boron has some reliable chemopreventive effects [19, 20]. Gallardo-Williams et al. have indicated that boric acid might inhibit PSA which is a specific tumor marker of PCa. In this animal model, it was demonstrated that supplementing the diet with a low concentration of boron reduced the size of implanted human prostate tumors and levels of the tumor trophic factor, IGF-1 [3]. Cui et al. have reported that dietary boron decreases the PCa risk [4]. Several researches have assessed the relationship between circulatory testosterone and estradiol and the risk of prostatic carcinoma [21]. Dietary boron intake has been shown to alter the steroid hormone levels [22]. On the other hand, the ability of boric acid to bind hydroxyl groups of serine and NAD explains its ability to inhibit serine proteases [23]. PSA is also a potential binding site for direct boric acid.

All of the aforementioned mechanisms involve prevention of PCa with boron only in an experimental field, which may provide a limited estimation for the relationship between dietary intake and PCa. Therefore, in our community, based on the study in a region of high boron exposure, it is reasonable to suggest that regarding PCa prevention, dietary boron intake is related to PSA level which is the specific marker of PCa. However, no significant difference was determined between the study and control groups in terms of serum PSA levels. Although statistical analysis could not be performed, a limited number of men with PSA levels over 2.5 ng mL^{-1} (n=36) were subjected to prostatic biopsy procedure, and a limited number of men with PCa were also diagnosed after the biopsy in the groups. For this reason, we could not reach a conclusion regarding the real relationship between PCa promotion and boron, but we can speculate that fewer patients with PCa were diagnosed in the region where high boron intake was evident.

There are three different satisfactory causative factors for this conclusion; firstly, the small sample size of the case group may have resulted in reduced efficacy of the study, and due to the limited number of PCa cases, it may also have limited our ability to measure the association of low dietary boron level and PCa incidence. Secondly, additional nutritional variables, such as dietary fat, fibers, serum lycopene, and vitamin E have to be adjusted in the logistic regression model. The presence of different heavy or toxic material might also be considered. Thirdly, daily boron intake might not be at the preventive levels in this particular region.

As a result, we have similarly confirmed the previous studies and the results were evaluated with real tissue sampling. Barranco mentioned that boron levels in the prostate could represent the boron level in ground water. It may not represent the total boron intake [8]. It was speculated that the people living in a region of high boron levels, may have been protected from PCa. Since few studies exist on this topic, further research is needed to better elucidate the role of boron in prevention of cancer in men who have different serum boron levels.

On the other hand, prostatic volumes calculated with transrectal ultrasound were significantly lower than those in the control groups. Benign prostatic hyperplasia (BPH) is the most common disease that causes bladder outlet obstruction and consequently severe clinical symptomatology [24]. However, etiology of BPH is not known very well. In our study, it seemed that there was a relationship between prostatic volume and daily boron intake. We are currently investigating this correlation in the same region as a community-based study. Although the boron exposure values are very similar for the two control groups, some difference was found for the prostate volumes. However, the difference was not significant for the two control groups regarding both the daily boron exposure and the mean prostate volume values. For the same parameters, a significant difference was found between the study group and the control group 2 with the lowest boron content in the drinking water. These preliminary results have been obtained with rather low number of subjects and further study on BPH-boron relations are needed for conclusive results.

Conclusions

We investigated a possible relationship between boron exposure and prostate cancer in a community-based study. Although we did not find a statistically significant association between PCa and boron exposure, our results suggest that high exposure to boron may have an implication within the prostatic cellular processes related to hyperplasia and

carcinogenesis. However, large, prospective longitudinal studies are warranted to further clarify this possible relationship between boron exposure and prostate cancer.

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