BJUI
BJU INTERNATIONAL

Effects of selenium status, dietary glucosinolate intake and serum glutathione *S*-transferase α activity on the risk of benign prostatic hyperplasia

Monika Eichholzer*, Astrid Steinbrecher†‡, Rudolf Kaaks‡, Birgit Teucher‡, Jakob Linseisen‡§ and Sabine Rohrmann*‡

**Division of Cancer Epidemiology and Prevention, Institute of Social and Preventive Medicine University of Zurich, Switzerland, †Max Delbrueck Center for Molecular Medicine, Molecular Epidemiology Group, Berlin, ‡Division of Cancer Epidemiology, German Cancer Research Centre, Heidelberg,and §Institute of Epidemiology I, Helmholtz Zentrum München, Neuherberg, Germany*

Accepted for publication 19 April 2012

Study Type – Prognosis (case control)
Level of Evidence 2

OBJECTIVE

- To determine whether geographical differences in the distribution of benign prostatic hyperplasia (BPH) and migrant studies indicate that modifiable factors play a role in the aetiology of BPH. Oxidative stress produced by chronic inflammation could represent one of the causes, and antioxidants, including selenoproteins, may reduce the risk.

SUBJECTS AND METHODS

- Conditional logistic regression was used to examine the associations of serum selenium and selenoprotein P concentrations and glutathione peroxidase activity with respect to the risk of BPH in a case–control study nested in the European Prospective Investigation into Cancer and Nutrition-Heidelberg cohort, including 111 cases and 214 matched controls.
- In addition, dietary glucosinolate intake and the serum glutathione *S*-transferase α concentration was investigated.

RESULTS

- The risk of BPH significantly decreased with an increasing serum selenium concentration; the risk estimate was 0.83 (35% CI 0.69–0.99) per 10 μg/L increase in serum selenium concentration.
- However, no significant association was present for serum selenoprotein P concentration or glutathione peroxidase activity. Risk estimates for BPH decreased with a higher intake of glucosinolates, although the results were not statistically significant.

CONCLUSION

- A low serum selenium concentration may increase the risk of BPH, although the findings reported in the present study need to be confirmed in larger, well-designed epidemiological studies.

KEYWORDS

benign prostatic hyperplasia, cohort study, GPx, GST-α, glucosinolate intake, SePP, serum selenium

What's known on the subject? and What does the study add?
Geographical and ethnic differences in the distribution of BPH and the results of migrant studies indicate that not only age, androgens and genetics, but also modifiable factors may play a role in the aetiology of BPH. Oxidative stress induced by chronic inflammation could be a cause and antioxidants, including selenoproteins, may reduce the risk. The published data related to this topic are scarce and are mainly based on cross-sectional and case–control studies.

In a nested case–control study, we observed a significant inverse association between serum selenium concentrations and the risk of BPH. These results need to be confirmed in larger, prospective epidemiological studies. Prostate enlargement is an increasing health problem as a result of an ageing population in many countries. Modifiable factors may also play a role. In the present study, before this antioxidant can be recommended as a preventive measure.

INTRODUCTION

BPH is a rapidly increasing health problem, particularly as a result of an ageing population in many countries [1]. Geographical and ethnic differences in the distribution of BPH [2] and the results of migrant studies [3] indicate that not only age, androgens and genetics, but also modifiable factors may play a role in the aetiology of BPH. Obesity, diabetes mellitus, physical activity, alcohol intake and vegetable consumption, etc., are considered as potential risk and protective factors,

respectively, although the current literature is limited [1,3–7].

Preliminary findings suggest that aetiological and pathological links could exist between BPH and prostate cancer [8]. For example, inflammation is emerging as a major contributor to the development of both BPH and prostate cancer [8]. In the European Prospective Investigation into Cancer and Nutrition (EPIC)-Heidelberg Study, we observed a decreased risk of prostate cancer (odds ratio [OR], 0.89; 95% CI, 0.79–1.01) per 10 μg/L increase of serum selenium [Se] concentration) [9]. The risk of prostate cancer decreased significantly over quartiles of total glucosinolate intake (multivariate hazard ratio [fourth vs first quartile], 0.68; 95% CI, 0.48–0.97; $P_{trend} = 0.03$) [10]. Moreover, the glutathione *S*-transferase α (GST-α) serum concentration was significantly inversely associated with glucosinolate intake, as well as with prostate cancer risk [11].

Besides other reactions, chronic inflammation promotes the production of various reactive oxygen species. Oxidative stress induces cell proliferation and apoptosis or necrosis, depending on the concentrations of reactive oxygen species and the cell type [12]. Normally, reactive oxygen species are neutralized by a complex system of multiple types of antioxidants (i.e. enzymatic and non-enzymatic antioxidants). Catalase, superoxide dismutase and glutathione peroxidase (GPx) are the main enzymatic antioxidants [13,14]. Se is a key component of GPx; it not only increases the activity and/or concentration of GPx, but also the concentration of selenoprotein P (SePP) and other selenoproteins [9,15–18]. Glucosinolates, which are mainly found in cruciferous vegetables, can be broken down to isothiocyanates and indoles. Different mechanisms, such as the induction of antioxidant and detoxification genes and the inhibition of proinflammatory reactions, are proposed for these breakdown products [19–21]. GST-α, a phase II enzyme, is involved in the detoxification of chemical carcinogens and in cell defence mechanisms against oxidative stress [22]. Published data related to the hypotheses that an adequate Se status, a high intake of glucosinolates and high GST-α serum concentrations, respectively, may reduce the risk of BPH are scarce or missing [4,13,23–25].

Thus, in a case–control study nested in a German prospective cohort study, the EPIC-Heidelberg cohort [26], we examined the association between the risk of BPH and Se status (total serum Se and SePP concentrations, as well as serum GPx activity); in addition, glucosinolate intake and the serum GST-α concentration were investigated in relation to the risk of BPH.

SUBJECTS AND METHODS

STUDY POPULATION

The study population consisted of men from the EPIC-Heidelberg cohort, which contributes to the European EPIC cohort. Study participants were recruited at random from the general population in Heidelberg, Germany, and the surrounding communities between 1994 and 1998. At recruitment, women were aged 35–65 years and men were aged 40–65 years. The final cohort comprised 25 540 participants (i.e. 38% of those originally invited) [26].

During the baseline examination, questionnaires and interviews were used to obtain information on diet, lifestyle, socioeconomic status and medical history. Anthropometric measures were taken in the study centre, where a 30-mL blood sample was drawn from 95.8% of study participants [27]. Blood samples were aliquoted into 0.5-mL straws of serum, plasma, buffy coat and erythrocytes, respectively, and stored in liquid nitrogen at −196 °C.

Active follow-up of the EPIC-Heidelberg participants is conducted to collect (amongst other factors) information on the occurrence of major chronic diseases. In the follow-up questionnaires, the study participants were asked to report the diagnosis of a benign tumour and surgeries. Reports of 'prostate enlargement', 'BPH' and 'prostate adenoma', as well as 'TURP' and 'prostate surgery', were verified by either pathology or medical records by a trained physician. Between September 1997 and September 2004, 182 participants had reported a diagnosis of BPH, of which 111 were confirmed as incident cases with available serum samples and without a diagnosis of cancer (except for non-melanoma skin cancer). For each case, two controls (eight case sets with only one control) were selected from subjects who had not reported BPH, who had no prevalent or incident cancer diagnosis (besides non-melanoma skin cancer), who did not report an increased PSA level in the third follow-up questionnaire, and who had a biological sample available. Cases and controls were matched by age (±5 years) and the time of recruitment (±0.5 years). The analytical dataset included 111 cases and 214 controls.

All participants provided their written informed consent, and the study was approved by the ethics committee of Heidelberg Medical School.

MEASUREMENT OF GPX ACTIVITY, AND SERUM SE, SERUM SEPP AND SERUM GST-α CONCENTRATIONS

Serum GPx activity was determined with Ransel RS 505 kits (Randox, Crumlin, UK) based on the ultraviolet method of Paglia and Valentine [28]. The intra-assay coefficient of variation was 2.7%. The inter-assay coefficients of variation for the four measurement days were in the range 1.3–2.4%. Total serum Se concentration was determined in triplicate by dynamic reaction cell-inductively coupled plasma field mass spectrometry on an Elan 6100 DRC plus (SCIEX Perkin-Elmer, Beaconsfield, UK) as described by Sieniawska *et al.* [29]. The detection limit was set at 0.02 μmol/L (1.58 μg/L); the inter-assay coefficient of variation was in the range 3.0–6.2% and the intra-assay coefficient of variation was in the range 2.9–4.4%. The SePP concentration was measured by an immunoluminometric sandwich assay [30] with a luminometer (LB952T, Berthold, Bad Wildbach, Germany). Each sample was measured in triplicate, and the mean SePP concentration was calculated. As a result of a loss of antigenicity of the standard solutions during storage, a random sample of serums covering each of the different measurement days was re-analyzed with new standard solutions in a separate assay. Based on these measurements, the concentrations of all samples were calibrated. For quality checks, two control samples were measured in each assay, and intra-day and inter-assay coefficients of variation were <10% for SePP values >0.15 mg/L. The serum GST-α concentration (reflecting GSTA1 and GSTA2 subunits) was determined by enzyme immunoassay with Biotrin HEPKIT®-Alpha

TABLE 1 Baseline characteristics of cases and controls in the European Prospective Investigation into Cancer and Nutrition-Heidelberg nested case–control study (N = 325)

Characteristic	Controls (*n* = 214)	Cases (*n* = 111)
Age at recruitment (years), mean (SD)	56.3 (5.6)	56.6 (5.7)
BMI (kg/m^2), mean (SD)	27.1 (3.3)	27.3 (3.4)
Waist circumference (cm), mean (SD)	96.8 (9.0)	98.9 (10.8)
Serum selenium (μg/L), mean (SD)	88.8 (14.5)	85.8 (12.3)
Serum SePP (mg/L), mean (SD)	2.88 (0.78)	2.88 (0.79)
GPX activity (U/L), mean (SD)	676.9 (108.7)	693.81 (117.2)
Serum GST-α concentration (ug/L), median (IQR)*	2.6 (2.3–3.0)	2.4 (2.0–2.9)
Smoking status, *n* (%)		
Never	56 (26.2)	35 (31.5)
Former	104 (48.6)	61 (55.0)
Current	54 (25.2)	15 (13.5)
Education, university degree, *n* (%)	70 (32.7)	49 (44.1)
Participation in PSA screening, *n* (%)	121 (56.5)	100 (90.1)
Family history of prostate cancer, *n* (%)	8 (3.7)	7 (6.3)
Cambridge physical activity score, *n* (%)		
Inactive	16 (7.5)	17 (15.3)
Moderately inactive	83 (38.8)	32 (28.8)
Moderately active	61 (28.5)	32 (28.8)
Active	54 (25.2)	30 (27.0)
Alcohol consumption (g/day), *n* (%)		
0–4.9	51 (23.8)	24 (21.6)
5–19.9	67 (31.3)	31 (27.9)
20–59.9	76 (35.5)	44 (39.6)
≥60	20 (9.4)	12 (10.8)
Total glucosinolate intake (mg/day), median (IQR)	7.5 (5.1–11.6)	7.5 (5.2–12.6)
Energy-adjusted GLS intake (mg/day), median (IQR)	7.7 (5.0–11.5)	7.4 (5.1–12.1)
Energy intake (kJ/day), median (IQR)	8 485 (6 769–10 245)	9 017 (7 356–11 098)

**Geometric mean and corresponding 95% CI; participants with GST-α concentrations outside the range covered by the internal standard (0.25–200.00 μg/L) were excluded, resulting in 105 cases and 198 controls.*
BMI, body mass index; GLS, glucosinolates; GPX, glutathione peroxidase; GST-α: glutathione S-transferase α; IQR, interquartile range; SePP, selenoprotein P.

(Biotrin, Dublin, Ireland) in accordance with the manufacturer's instructions. Intra-day and inter-day coefficients of variation were 4.9% and 5.8%, respectively.

DIETARY AND LIFESTYLE DATA, AND INTAKE OF GLUCOSINOLATES

Habitual diet during the previous year was assessed at baseline by validated self-administered semi-quantitative food frequency questionnaires [31,32]. Participants filled in portion size and consumption frequency of 145 food items and the mean daily food consumption for each participant was calculated. The nutrient intake for each participant was computed by linking food consumption data to the German Food Code and Nutrient Data Base (BLS II.3), as well as a database on the glucosinolate content of food established to assess glucosinolate intake in the EPIC-Heidelberg cohort. This database covered 26 individual glucosinolates in 18 different vegetables and condiments [33]. Information on lifestyle and sociodemographic characteristics was assessed at study entry by questionnaires and personal interview.

STATISTICAL ANALYSIS

Baseline characteristics of the study population are given as percentages by case–control status or the mean (SD), except for dietary data (median and interquartile range) and serum GST-α concentration (geometric mean).

Conditional logistic regression was used to compute ORs and corresponding 95% CIs to examine the associations of biomarkers (i.e. serum concentrations of Se, SePP and GST-α and GPx activity with the risk of BPH by tertiles of biomarker concentration). Tertiles were computed based on the distribution among controls. These analyses were stratified by case set (i.e. taking into account matching factors) and were adjusted for smoking (never, former and current) and alcohol consumption (0–4.9, 5–19.9, 20–59.9 and ≥60 g/day). Because the serum GST-α concentration showed a highly skewed distribution, analyses were performed using the log-transformed variable. We excluded participants with a GST-α concentration outside the range covered by the internal standard (0.25–200.00 μg/l); if a case was excluded, the two corresponding controls (in the case set) were also omitted, leaving 303 participants of which 105 were cases. The analyses were further adjusted for alcohol consumption categories and smoking. Additionally taking into account energy-adjusted glucosinolate intake, body mass index, family history of prostate cancer and education did not alter the results and was not considered in the final model.

Conditional logistic regression was also used to examine the association of glucosinolate intake with the risk of BPH. Glucosinolate intake was adjusted for energy intake using the residual method [34]. These analyses were further adjusted for the intake of fat, protein and vegetables (all continuous).

Analyses were performed using SAS, version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

The baseline characteristics of the participants in this nested case–control study are summarized in Table 1. Cases with BPH and controls did not differ by age at recruitment and the time of recruitment (matching factors). Cases had a greater probability than controls of having a family history of prostate cancer, having participated in PSA screening, having a university degree, and drinking ≥20 g of alcohol per day, although they had a lower

probability of being current smokers. There were no differences in mean body mass index. Median intake of total energy, fat, protein and vegetables was somewhat higher in cases than in controls.

The results with respect to an association between serum Se and SePP concentrations and GPx activity and the risk of BPH are shown in Table 2. In the fully adjusted model, the risk of BPH decreased statistically significantly with an increasing serum concentration of Se. The OR (95% CI) was 0.83 (0.69–0.99) per 10 μg/L increase in serum Se concentration.

No statistically significant associations were present for the serum concentration of SePP and serum activity of GPx; in addition, the serum GST-α concentration was not associated with the risk of BPH (Table 2).

Table 3 provides data on the association of dietary glucosinolate intake with the risk of BPH. Even though the risk decreased with an increasing intake of glucosinolates, the associations were not statistically significant in the multivariate model (OR, 0.62; 95% CI, 0.31–1.24; top vs bottom tertile; P_{trend} = 0.19). The results obtained for subgroups of glucosinolate intake (i.e. aliphatic glucosinolates and indoles) (data not shown) were not different.

TABLE 2 Association of serum selenium, selenoprotein P (SePP), glutathione peroxidase (GPX) and glutathione S-transferase α (GST-α concentration (in tertiles) with BPH in the European Prospective Investigation into Cancer and Nutrition-Heidelberg nested case–control study (N = 325)

Variable	Cases	Controls	Model 1* OR (95% CI)	Model 2† OR (95% CI)
Serum selenium (μg/L)				
<82.9	49	71	1.00	1.00
82.9–94.0	30	74	0.58 (0.33–1.02)	0.54 (0.30–0.96)
>94.0	32	69	0.66 (0.38–1.16)	0.60 (0.34–1.07)
Continuous (per 10 μg/L)			0.85 (0.71–1.01)	0.83 (0.69–0.99)
			P_{trend} = 0.07	P_{trend} = 0.04
Serum SePP (mg/L)				
<2.58	29	72	1.00	1.00
2.58–3.14	44	70	1.61 (0.89–2.90)	1.56 (0.86–2.84)
>3.14	38	72	1.37 (0.75–2.53)	1.33 (0.71–2.50)
Continuous			1.01 (0.74–1.39)	1.00 (0.72–1.39)
			P_{trend} = 0.95	P_{trend} = 0.99
GPX activity (U/L)				
<625.5	33	71	1.00	1.00
625.5–710.1	32	71	1.00 (0.57–1.75)	1.08 (0.61–1.90)
>710.1	46	72	1.38 (0.79–2.40)	1.43 (0.81–2.51)
Continuous (per 100 U/L)			1.15 (0.93–1.41)	1.14 (0.93–1.41)
			P_{trend} = 0.20	P_{trend} = 0.21
GST-α concentration*				
<1.64	35	66	1.00	1.00
1.64–3.73	43	67	1.19 (0.68–2.11)	1.08 (0.60–1.93)
>3.73	27	65	0.78 (0.42–1.46)	0.72 (0.38–1.39)
Continuous‡			0.92 (0.73–1.16)	0.91 (0.72–1.16)
			P_{trend} = 0.49	P_{trend} = 0.44

**Model 1: taking into account matching factors. †Model 2: additionally adjusted for smoking and alcohol consumption categories. ‡P_{trend} computed using a log-transformed variable.*
OR, odds ratio.

TABLE 3 Association of glucosinolate (GLS) intake (in tertiles) with BPH in the European Prospective Investigation into Cancer and Nutrition-Heidelberg nested case–control study (N = 325)

	Cases	Controls	Model 1* OR (95% CI)	Model 2† OR (95% CI)
Energy-adjusted GLS intake (mg/day)				
<6.18	42	71	1.00	1.00
6.18–9.86	33	70	0.82 (0.47–1.43)	0.74 (0.42–1.32)
>9.86	36	73	0.83 (0.47–1.48)	0.62 (0.31–1.24)
Continuous (per 10 mg/day)			0.85	0.28
P_{trend}			0.59	0.19

**Model 1: taking into account matching factors. †Model 2: additionally adjusted for intake of fat, protein and vegetables.*
OR, odds ratio.

DISCUSSION

Although the sample size is limited, the present study is one of the few smaller studies testing the hypotheses that Se status, dietary glucosinolate intake and serum GST-α activity are inversely associated with the risk of BPH. We observed a statistically significantly inverse association between serum Se concentration and the risk of BPH, whereas other Se markers were not associated with the risk of disease. The risk of BPH also decreased with increasing glucosinolate intake, although the results were not statistically significant.

The few existing reports on these topics comprise cross-sectional [24] and case–control [13,23,25,35] studies, and only one other study [4] has examined the risk of BPH prospectively. In addition, studies have used different definitions of BPH, such as histological verification, prostate enlargement confirmed by X-ray, weak urine stream, history of non-cancer surgical treatment of the prostate, enlargement reported by patients, and medical diagnosis [36]. The case definition employed in the present study is based on self-reports of BPH diagnosis and BPH surgery, as validated by pathology and medical records.

It is unclear how Se may protect against BPH, although Se may induce apoptosis and inhibit cell growth [37]. Zacchara *et al.* [25] studied Se concentrations in the whole blood, plasma and prostate of 32 prostate cancer cases, 40 patients with BPH, and in a control group of 39 healthy subjects in Poland. They found that Se concentrations in the whole blood and plasma in both groups of patients were statistically significantly lower than in the control group. Mean (SD) plasma Se concentrations were 66.1 (14.4) ng/mL in patients and 73.9 (13.0) ng/mL in controls. More recently, Muecke *et al.* [13] compared whole blood Se concentrations in prostate cancer cases ($n = 24$), patients with BPH ($n = 21$) and in healthy men ($n = 21$) living in northern Bavaria (Germany) with the recommended Se concentration (85–162 μg/L). Whole blood Se concentrations were significantly lower in patients with prostate cancer than in healthy men; for BPH patients, however, no difference could be detected. All study participants had significantly lower whole blood Se concentrations than the recommended concentrations. Based on cross-sectional data from the US Third National Health and Nutrition Examination Survey, Rohrmann *et al.* [24] reported significantly lower serum Se concentrations in older men with LUTS than in controls without symptoms of LUTS who never had non-cancer prostate surgery. LUTS is often caused by enlargement or obstruction secondary to BPH. In addition, men in the lowest quintile of serum Se had a twofold greater probability of reporting LUTS compared to men in the second quintile (OR, 0.46; 95% CI, 0.23–0.89). Rohrmann *et al.* [24] found decreased risks of LUTS in each of the upper four quintiles of serum Se compared to men in the lowest quintile, although there was no decreasing trend. Thus, low serum Se appears to be a risk factor for LUTS, although increasing concentrations above a threshold did not result in further risk reduction. Kristal *et al.* [4] assessed the effect of dietary factors on the incidence of BPH in 4770 participants of the placebo-arm of the Prostate Cancer Prevention Trial (1994–2003) who had not reported a diagnosis of BPH at baseline for a prospective study. No effect of dietary supplement use of Se (i.e. no intervention) on BPH was observed in these US men. Comparing individuals with a Se intake >30 μg from supplements with individuals consuming <10 μg daily showed an OR of 1.01 (95% CI, 0.83–1.25).

In the present study, there was no association of serum GPx activity with the risk of BPH. The study by Zachara *et al.* [25] not only found a lower Se concentration in the whole blood and plasma in BPH patients compared to healthy controls, but also a significantly lower activity of erythrocyte GPx, as well as non-significantly lower plasma GPx activity. In a Turkish study including 26 BPH cases, Aydin *et al.* [35] observed a non-significantly lower activity of erythrocyte GPx compared to 24 age-matched healthy controls. The present study did not establish a statistically significant association between SePP serum concentrations and the risk of BPH. To the best of our knowledge, no other studies have evaluated this association.

The establishment of an association of Se and the selenoproteins GPx and SePP with the risk of BPH may be complicated by the complex regulatory mechanisms of Se status [15]. Selenoprotein concentrations are a function of Se intake only within a specific range of dietary Se intake. The lack of an effect of additional dietary Se on plasma selenoprotein concentrations may indicate that the Se requirement for selenoprotein synthesis has been met [38]. Optimization of plasma SePP requires the intake of more Se than does the optimization of GPx activity. When optimized at the plateau point, human plasma SePP contains ~0.81 μmol/L and GPx contains ~0.20 μmol/L of Se [39] (i.e. together, ~0.8–1.1 μmol/L [7–9 μg/dL]) [40]. When the plasma Se concentration is >90 μg/L, selenoproteins are considered to be optimized [41].

In populations with high Se intake, such as in the USA, most individuals reach plasma Se concentrations above these critical levels. By contrast, in Europe, where the intake is generally lower than in the USA [13,42], as a result of the lower Se content of the soil [40], the two selenoprotein biomarkers GPx and SePP may not yet reach plateau levels. This may explain some [4,13,25,36], although not all [24], of the results described above. In the present study, inverse associations would be expected between GPx and SePP and BPH because these two selenoproteins may not yet have plateaued. No generally agreed normal values for GPx activity and SePP concentrations are yet established.

Potentially, the associations between GPx activity and SePP concentration, respectively, and the risk of BPH may be modulated by genetic variation in selenoproteins. As previously observed in the EPIC-Heidelberg cohort [9], carriers of the A allele (GA and AA) in rs7579 of the gene for SePP1 had higher serum concentrations of SePP compared to homozygous GG individuals. There was also an overall decreased activity of serum GPx3 ($P = 0.05$) among carriers of the rare homozygote alleles in rs5859 and rs540049 of the gene for SEP15.

In the present study, we found a decreased (not significant) risk of BPH with higher glucosinolate intake. No published data from other epidemiological studies related to this topic have been published so far. However, two studies [4,23] have evaluated the association between BPH and the consumption of cruciferous vegetables. Because glucosinolates are found almost exclusively in cruciferous vegetables, their intake may be used as a proxy for glucosinolate intake [10]. In the study by Kristal *et al.* [4], the intake of at least four servings per week compared to less than one resulted in an OR of 0.88 (95% CI, 0.66–1.16). Similarly, the Australian case–control study by Ambrosini *et al.* [23], comparing the highest quartile of intake with the lowest one, showed an OR of 0.76 (95% CI, 0.52–1.13) for the risk of BPH. Thus, the result with respect to glucosinolate intake and the risk of BPH obtained in the present study is in good agreement with the published data on cruciferous vegetables and BPH.

In an intervention study, a diet rich in cruciferous vegetables increased the serum concentration of GST-α [6]. The present study did not establish an association between serum concentration of GST-α and BPH. No association between glucosinolate intake and the serum GST-α concentration was observed (data not shown).

A strength of the present nested case–control study is its prospective design, with cases being diagnosed during the follow-up of the cohort. Self-reported cases that were diagnosed before recruitment into the present study were excluded from the analysis. The extensive data collection at recruitment allowed the study of associations between intake or serum concentrations of dietary factors and the

risk of BPH, which have not been studied so far, as well as the adjustment of potential confounding factors. However, the sample size of 111 cases in the present study was quite limited. Study power was improved by matching two controls per case and performing analyses stratified by case set. Nevertheless, there may have been insufficient power to detect some associations with small effects. In addition, the presence of BPH in the control group was not excluded by means of a clinical investigation. Such a misclassification would attenuate the odds ratios. The possibility of incomplete and selective follow-up of BPH cases exists; thus, cases and controls could have been selected from subcohorts with different background characteristics. Finally, cases with BPH may have had symptoms for some time before diagnosis and could have changed diet and other lifestyle factors.

In conclusion, we observed a significant inverse association between serum Se concentrations and the risk of BPH and there are plausible mechanisms regarding how a balanced Se status could reduce the risk of BPH. However, the findings of the present study have to be confirmed in well-designed epidemiological studies with clear study endpoints carried out in a population with marginal Se deficiencies.

CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Parsons JK.** Benign prostatic hyperplasia and male lower urinary tract symptoms: epidemiology and risk factors. *Curr Bladder Dysfunct Rep* 2010; **5**: 212–8

2 **Platz EA, Kawachi I, Rimm EB, Willett WC, Giovannucci E.** Race, ethnicity and benign prostatic hyperplasia in the health professionals follow-up study. *J Urol* 2000; **163**: 490–5

3 **Jin B, Turner L, Zhou Z, Zhou EL, Handelsman DJ.** Ethnicity and migration as determinants of human prostate size. *J Clin Endocrinol Metab* 1999; **84**: 3613–9

4 **Kristal AR, Arnold KB, Schenk JM *et al*.** Dietary patterns, supplement use, and the risk of symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. *Am J Epidemiol* 2008; **167**: 925–34

5 **Parsons JK.** Modifiable risk factors for benign prostatic hyperplasia and lower urinary tract symptoms: new approaches to old problems. *J Urol* 2007; **178**: 395–401

6 **Bravi F, Bosetti C, Dal Maso L *et al*.** Food groups and risk of benign prostatic hyperplasia. *Urology* 2006; **67**: 73–9

7 **Untergasser G, Madersbacher S, Berger P.** Benign prostatic hyperplasia: age-related tissue-remodeling. *Exp Gerontol* 2005; **40**: 121–8

8 **Alcaraz A, Hammerer P, Tubaro A, Schroder FH, Castro R.** Is there evidence of a relationship between benign prostatic hyperplasia and prostate cancer? Findings of a literature review. *Eur Urol* 2009; **55**: 864–73

9 **Steinbrecher A, Meplan C, Hesketh J *et al*.** Effects of selenium status and polymorphisms in selenoprotein genes on prostate cancer risk in a prospective study of European men. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 2958–68

10 **Steinbrecher A, Nimptsch K, Husing A, Rohrmann S, Linseisen J.** Dietary glucosinolate intake and risk of prostate cancer in the EPIC-Heidelberg cohort study. *Int J Cancer* 2009; **125**: 2179–86

11 **Steinbrecher A, Rohrmann S, Timofeeva M, Risch A, Jansen E, Linseisen J.** Dietary glucosinolate intake, polymorphisms in selected biotransformation enzymes, and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 135–43

12 **Dragin N, Smani M, Arnaud-Dabernat S *et al*.** Acute oxidative stress is associated with cell proliferation in the mouse liver. *FEBS Lett* 2006; **580**: 3845–52

13 **Muecke R, Klotz T, Giedl J *et al*.** Whole blood selenium levels (WBSL) in patients with prostate cancer (PC), benign prostatic hyperplasia (BPH) and healthy male inhabitants (HMI) and prostatic tissue selenium levels (PTSL) in patients with PC and BPH. *Acta Oncol* 2009; **48**: 452–6

14 **Dinkova-Kostova AT, Talalay P.** Direct and indirect antioxidant properties of inducers of cytoprotective proteins. *Mol Nutr Food Res* 2008; **52** (Suppl. 1): S128–38

15 **Gromadzinska J, Reszka E, Bruzelius K, Wasowicz W, Akesson B.** Selenium and cancer: biomarkers of selenium status and molecular action of selenium supplements. *Eur J Nutr* 2008; **47** (Suppl. 2): 29–50

16 **Peters U, Takata Y.** Selenium and the prevention of prostate and colorectal cancer. *Mol Nutr Food Res* 2008; **52**: 1261–72

17 **Alfthan G, Xu GL, Tan WH *et al*.** Selenium supplementation of children in a selenium-deficient area in China: blood selenium levels and glutathione peroxidase activities. *Biol Trace Elem Res* 2000; **73**: 113–25

18 **Persson-Moschos M, Alfthan G, Akesson B.** Plasma selenoprotein P levels of healthy males in different selenium status after oral supplementation with different forms of selenium. *Eur J Clin Nutr* 1998; **52**: 363–7

19 **Hayes JD, Kelleher MO, Eggleston IM.** The cancer chemopreventive actions of phytochemicals derived from glucosinolates. *Eur J Nutr* 2008; **47** (Suppl. 2): 73–88

20 **Lampe JW, Chen C, Li S *et al*.** Modulation of human glutathione S-transferases by botanically defined vegetable diets. *Cancer Epidemiol Biomarkers Prev* 2000; **9**: 787–93

21 **Hofmann T, Kuhnert A, Schubert A *et al*.** Modulation of detoxification enzymes by watercress: in vitro and in vivo investigations in human peripheral blood cells. *Eur J Nutr* 2009; **48**: 483–91

22 **Andonova IE, Justenhoven C, Winter S *et al*.** No evidence for glutathione S-transferases GSTA2, GSTM2, GSTO1, GSTO2, and GSTZ1 in breast cancer risk. *Breast Cancer Res Treat* 2010; **121**: 497–502

23 **Ambrosini GL, de Klerk NH, Mackerras D, Leavy J, Fritschi L.** Dietary patterns and surgically treated benign prostatic hyperplasia: a case control study in Western Australia. *BJU Int* 2008; **101**: 853–60

24 **Rohrmann S, Smit E, Giovannucci E, Platz EA.** Association between serum concentrations of micronutrients and lower urinary tract symptoms in older men in the Third National Health and Nutrition Examination Survey. *Urology* 2004; **64**: 504–9

25 **Zachara BA, Szewczyk-Golec K, Tyloch J *et al*.** Blood and tissue selenium concentrations and glutathione

peroxidase activities in patients with prostate cancer and benign prostate hyperplasia. *Neoplasma* 2005; **52**: 248–54
26 **Boeing H, Korfmann A, Bergmann MM.** Recruitment procedures of EPIC-Germany. European Investigation into Cancer and Nutrition. *Ann Nutr Metab* 1999; **43**: 205–15
27 **Kroke A, Bergmann MM, Lotze G, Jeckel A, Klipstein-Grobusch K, Boeing H.** Measures of quality control in the German component of the EPIC study. European Prospective Investigation into Cancer and Nutrition. *Ann Nutr Metab* 1999; **43**: 216–24
28 **Paglia DE, Valentine WN.** Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase. *J Lab Clin Med* 1967; **70**: 158–69
29 **Sieniawska C, Mensikov R, Delves H.** Determination of total selenium in serum, whole blood and erythrocytes by ICP-MS. *J Anal Atomic Spectrom* 1999; **14**: 109–12
30 **Hollenbach B, Morgenthaler NG, Struck J *et al*.** New assay for the measurement of selenoprotein P as a sepsis biomarker from serum. *J Trace Elem Med Biol* 2008; **22**: 24–32
31 **Bohlscheid-Thomas S, Hoting I, Boeing H, Wahrendorf J.** Reproducibility and relative validity of food group intake in a food frequency questionnaire developed for the German part of the EPIC project. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol* 1997; **26** (Suppl. 1): S59–70
32 **Bohlscheid-Thomas S, Hoting I, Boeing H, Wahrendorf J.** Reproducibility and relative validity of energy and macronutrient intake of a food frequency questionnaire developed for the German part of the EPIC project. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol* 1997; **26** (Suppl. 1): S71–81
33 **Steinbrecher A, Linseisen J.** Dietary intake of individual glucosinolates in participants of the EPIC-Heidelberg cohort study. *Ann Nutr Metab* 2009; **54**: 87–96
34 **Willett W.** *Nutritional Epidemiology*, 1st edn. New York: Oxford University Press, 1998
35 **Aydin A, Arsova-Sarafinovska Z, Sayal A *et al*.** Oxidative stress and antioxidant status in non-metastatic prostate cancer and benign prostatic hyperplasia. *Clin Biochem* 2006; **39**: 176–9
36 **Parsons JK.** Lifestyle factors, benign prostatic hyperplasia, and lower urinary tract symptoms. *Curr Opin Urol* 2011; **21**: 1–4
37 **Willis MS, Wians FH.** The role of nutrition in preventing prostate cancer: a review of the proposed mechanism of action of various dietary substances. *Clin Chim Acta* 2003; **330**: 57–83
38 **Yang G, Zhu L.** Human selenium requirements in China. In Combs G, Levander O, Spallholz J, Oldfield J eds, *Selenium in Biology and Medicine*, New York: AVI, 1987: 589–607
39 **Hill KE, Xia Y, Akesson B, Boeglin ME, Burk RF.** Selenoprotein P concentration in plasma is an index of selenium status in selenium-deficient and selenium-supplemented Chinese subjects. *J Nutr* 1996; **126**: 138–45
40 **Standing Committe on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine.** *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington, DC: National Academy Press, 2000
41 **Xia Y, Hill KE, Li P *et al*.** Optimization of selenoprotein P and other plasma selenium biomarkers for the assessment of the selenium nutritional requirement: a placebo-controlled, double-blind study of selenomethionine supplementation in selenium-deficient Chinese subjects. *Am J Clin Nutr* 2010; **92**: 525–31
42 **Rayman MP.** The importance of selenium to human health. *Lancet* 2000; **356**: 233–41

Correspondence: Sabine Rohrmann, Division of Cancer Epidemiology and Prevention, Institute of Social and Preventive Medicine University of Zurich, Hirschengraben 84, CH-8001 Zürich, Switzerland.
e-mail: sabine.rohrmann@ifspm.uzh.ch

Abbreviations: **EPIC**, European Prospective Investigation into Cancer and Nutrition; **GPx**, glutathione peroxidase; **GST-α**, glutathione *S*-transferase α; **Se**, selenium; **SePP**, selenoprotein P.