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Plasma selenium concentration and prostate cancer risk: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)^{1–3}

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ABSTRACT

Background: Some evidence indicates that a low selenium intake may be associated with an increased risk of prostate cancer.

Objective: The aim of this study was to investigate the association of plasma selenium concentration with subsequent prostate cancer risk and to examine this association by stage and grade of disease and other factors.

Design: A nested case-control study was performed among men in the European Prospective Investigation into Cancer and Nutrition (EPIC). The association between plasma selenium concentration and prostate cancer risk was assessed in 959 men with incident prostate cancer and 1059 matched controls.

Results: Overall, plasma selenium concentration was not associated with prostate cancer risk; the multivariate relative risk for men in the highest fifth of selenium concentration compared with the lowest fifth was 0.96 (95% CI: 0.70, 1.31; *P* for trend = 0.25). There were no significant differences in the association of plasma selenium with risk when analyzed by stage or grade of disease. Similarly, the association of selenium with risk did not differ by smoking status or by plasma α - or γ -tocopherol concentration.

Conclusion: Plasma selenium concentration was not associated with prostate cancer risk in this large cohort of European men.

INTRODUCTION

The possible role of selenium in cancer prevention has been the subject of great interest, largely because it is a key component of the antioxidant enzyme glutathione peroxidase, although it also has many other potentially anticarcinogenic properties, including effects on DNA repair, apoptosis, and effects on the immune system (1). Much experimental evidence indicates that high doses of selenium supplementation can inhibit carcinogenesis in many tissue types (1), including prostate cancer (2–5).

The most important food sources of selenium in countries such as the United Kingdom are cereals, meat, and fish (6). However, the selenium content of plant foods varies widely between regions (7), because it is largely determined by the amount of selenium in the soil. Some ecological data have suggested that

cancer mortality rates may be inversely correlated with the selenium concentration in forage crops (8) and with estimated dietary selenium intake (9). A randomized controlled trial, designed to test whether selenium supplementation reduced the recurrence of skin cancer, found that supplementation with 200 μg Se/d was associated with a significant 63% reduction in prostate cancer incidence, which was particularly evident among men with a low baseline selenium concentration (10, 11). A meta-analysis of 20 epidemiologic studies reported that prostate cancer cases have, on average, a lower endogenous selenium concentration than controls, as measured in plasma, serum, or nails (12). However, the results from recent prospective studies are inconclusive; some have reported a reduced risk of total prostate cancer (13–15) or aggressive disease (16, 17), although others have found no significant association (18–21).

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There is also interest in whether selenium interacts with other antioxidants, such as vitamin E, to reduce prostate cancer risk. A clinical trial conducted in Linxian, China, found that supplementation with selenium in combination with α -tocopherol and β -carotene was associated with a reduced risk of total cancer and gastric cancer, although there were too few prostate cancers to evaluate this separately (22). Nonetheless, evidence from *in vitro* studies indicates that selenium can accentuate the inhibitory effect of vitamin E on cell growth in prostate cancer cell lines (23, 24) and the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a randomized placebo-controlled trial, was specifically designed to test the efficacy of selenium and α -tocopherol, both individually and combined, in prostate cancer prevention (25). However, few observational studies have examined the combined effect of prediagnostic endogenous selenium and α - and γ -tocopherol concentrations on prostate cancer risk (15, 17, 19, 21).

The aim of this study was to investigate the association between plasma selenium concentration and prostate cancer risk among 959 men with incident prostate cancer and 1059 matched controls in the European Prospective Investigation into Cancer and Nutrition (EPIC). A secondary aim was to evaluate this association by stage and grade of disease and to examine the joint association of plasma selenium concentrations and α - and γ -tocopherol on prostate cancer risk.

SUBJECTS AND METHODS

Study population

The EPIC recruitment procedures and collection of questionnaire data, anthropometric measurements, and blood samples are

Murcia, Spain, and CIBER en Epidemiología y Salud Pública, Barcelona, Spain (M-JT); the Public Health & Health Planning Directorate, Asturias, Spain (LR); the Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University Hospital, Umeå, Sweden (PS); the Department of Public Health and Clinical Medicine, Umeå University Hospital Nutritional Research, Umeå, Sweden (GH); the MRC Centre for Nutritional Epidemiology in Cancer Prevention and Survival, Department of Public Health and Primary Care, Cambridge, United Kingdom (SB); the Department of Gerontology, University of Cambridge, Cambridge, United Kingdom (K-TK); the International Agency for Research on Cancer–WHO, Lyon, France (NS, SR, and PB); and the Department of Epidemiology and Public Health, Imperial College London, London, United Kingdom (ER).

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described in detail elsewhere (26). In brief, standardized questionnaire data on dietary and nondietary variables were collected at recruitment from $\approx 370\,000$ women and 150 000 men across Europe between 1992 and 2000, and a blood sample was collected from $\approx 400\,000$ of these individuals (37% of whom were male; the median date of blood collection was 1995). The present study includes men with a diagnosis of prostate cancer made after blood collection and their matched controls from 8 of the 10 participating countries: Denmark, Germany, Greece, Italy, Netherlands, Spain, Sweden, and the United Kingdom. France and Norway were not included in the present study because these cohorts included only women.

A 30-mL (20 mL in the Umeå, Sweden cohort) blood sample was collected according to a standardized protocol. Filled syringes were kept at 5–10 °C, protected from light, and transferred to a local laboratory for further processing, except those for participants who were recruited through the Oxford center. Here, blood samples were collected throughout the United Kingdom and transported to a laboratory in Norfolk by mail at ambient temperature. Blood fractions (plasma, serum, red blood cells, and buffy coat) were transferred into 0.5-mL straws, which were then heat-sealed and stored in liquid nitrogen tanks at -196 °C , except in Denmark where samples were stored in 1-mL tubes in nitrogen vapor at -150 °C and in Umeå, Sweden, where samples were stored in 1.8-mL plastic tubes in -80 °C freezers.

Follow-up for cancer incidence and vital status

In Denmark, Italy, Netherlands, Spain, Sweden, and the United Kingdom, incident cancer cases were identified through record linkage with regional or national cancer registries. In Germany and Greece, follow-up was based on a combination of methods, which included health insurance records, cancer and pathology registries, and active follow-up through study participants and their next of kin. Data on vital status in most EPIC study centers were collected from mortality registries at the regional or national level in combination with data collected by active follow-up (Greece). For each EPIC study center, follow-up time was accrued until censoring at the date of diagnosis of prostate cancer, death, emigration, other loss to follow-up, or the date at which follow-up ended, defined as the last date at which follow-up data from cancer registries were judged to be complete or the last date of contact in the centers that used active follow-up (closure dates varied between June 1999 and January 2003).

Selection of case and control participants

The case-control dataset used in the current study is an expansion of a dataset established in January 2004 that included 658 cases and their matched controls, derived from a population of 127 811 men that were part of a collaborative analysis of genetic and hormonal factors on prostate cancer (27). For the current analysis, Umeå (Sweden) and Denmark contributed an additional 406 cases for whom a plasma sample was available. Details of the eligibility criteria are described in full elsewhere (28). In brief, cases were selected among men who developed prostate cancer after blood collection and before the end of the study period (defined for each study center by the censoring date or latest end date of follow-up). Participants who had no blood sample available, who had missing information on the date of blood collection or who had a history of another cancer (except

nonmelanoma skin cancer) at the time of blood collection were excluded. Laboratory measurements for the current analysis were available for 959 cases and their matched controls: 288 cases in Denmark, 62 in Italy, 202 in Germany, 9 in Greece, 25 in the Netherlands, 93 in Spain, 200 in Sweden, and 180 in the United Kingdom.

For each case, one male control participant (in Umeå, 2 male control participants) was chosen at random from appropriate risk sets consisting of all cohort members alive and free of cancer (except nonmelanoma skin cancer) at the time of diagnosis of the index case. An incidence density sampling protocol for control selection was used, such that controls could become a case later in time and could also be sampled more than once. Matching criteria included study center, age at recruitment (± 6 mo), time of day of blood collection (± 1 h), and time between blood collection and last consumption of foods or drinks (<3 , $3-6$, and >6 h). All participants gave written consent for future analyses of their blood samples, and the study was approved by the local ethics committees in the participating countries and the ethical review board of the International Agency for Research on Cancer (IARC).

Data on stage and grade at diagnosis were collected from each center, when possible. These data were extracted from pathology reports stored at cancer registries or from medical records stored at the treating hospital, where appropriate. Tumor stage was categorized as localized [TNM staging: tumor (T)-node (N)-metastasis (M) categories T0 or T1 or T2 and N0 or NX and M0, or stage coded in the recruitment center as localized], advanced (T3 or T4, N1+, M1, or some combination of these or stage coded in the recruitment center as metastatic), or unknown. Histologic grade was categorized as low grade (Gleason sum <7 or equivalent; cases coded as well differentiated or as moderately differentiated), high grade (Gleason sum ≥ 7 or equivalent; cases coded as poorly differentiated or as undifferentiated), or unknown.

Laboratory assays

Plasma selenium concentrations were determined by using an Elan DRC^{Plus} inductively coupled plasma mass spectrometer (Perkin-Elmer Sciex, Norwalk, CT) at the MRC Human Nutrition Research Unit, Cambridge, United Kingdom. The limit of detection was set at $0.1 \mu\text{g/L}$. Cases and their matched controls were analyzed in the same batch and all laboratory personnel were blinded to the case-control status of the samples. For quality-control purposes, plasma samples of known selenium concentration were obtained from the interlaboratory comparison program for metals in biological matrices (Institut National de Sante Publique du Quebec). The interbatch variation was assessed by the analysis of pooled plasma samples across 25 batches (mean: $78.8 \mu\text{g/L}$; CV: 4.8%). The accuracy of analysis ($\pm 5\%$) during each batch was assessed through the measurement of the interlaboratory comparison program samples and the pooled plasma samples as well as a separate blood plasma reference material of known selenium concentration contained within each batch ($81 \mu\text{g/L}$; ClinChek plasma control lyophilized for trace elements). Plasma concentrations of α - and γ -tocopherol were measured by using HPLC at the IARC, as described elsewhere (29).

Statistical analysis

Differences in baseline characteristics between cases and controls were compared by using conditional logistic regression for categorical variables and a generalized paired t test for continuous variables, where weights were apportioned according to the number of controls within each matched set (30). Plasma selenium concentration was logarithmically transformed for all statistical analyses to approximate a normal distribution. Analysis of covariance was used to investigate geometric mean differences in selenium concentration among the controls by baseline characteristics, with adjustment for study center and laboratory batch. Tests for trend were obtained by scoring the categories 1, 2, 3, ... as required.

Odds ratios as estimates of relative risk (RR) of prostate cancer in relation to plasma concentrations of selenium were calculated by using conditional logistic regression models. Plasma concentrations were categorized into fifths with cutoffs based on the quintiles of the distribution among the controls from all cohorts combined. The test for trend was assessed by including the logarithm of plasma selenium concentration as a continuous variable in the model. The effects of potential confounders, other than the matching criteria that are controlled for by design, were examined by including additional terms in the logistic regression models: BMI (in kg/m^2 ; in fourths), smoking status (never, past, or current), alcohol intake (<8 , $8-15$, $16-39$, or ≥ 40 g/d), physical activity (index of combined recreational, household, and occupational physical activity: inactive, moderately inactive, or active), marital status (married or cohabiting, unmarried, or not cohabiting), and education level (primary school or equivalent, secondary school, or university degree or equivalent). For most of these variables, $<5\%$ of values were unknown, and these were included in the analyses as a separate category. Likelihood ratio chi-square tests were used to examine the heterogeneity of the trends in prostate cancer risk with the logarithm of plasma selenium concentration between categories of tumor stage (localized or advanced), histologic grade (low or high), time between blood collection and diagnosis (<4 or ≥ 4 y), age at blood collection (<60 or ≥ 60 y), and country of recruitment (8 countries). Because smoking status was the same within many case-control pairs and a conditional logistic regression analysis would have led to a considerable loss of power, an unconditional logistic regression model was used to examine the association of plasma selenium concentration with prostate cancer risk by smoking status, with adjustment for recruitment center, age at blood collection, BMI, alcohol intake, physical activity, marital status, and education level. The combined association of selenium and α - and γ -tocopherol concentrations with prostate cancer risk was assessed by categorizing the micronutrients into thirds according to the distribution among the controls and including an interaction term in the model. All P values presented are 2-sided, and $P < 0.05$ was considered statistically significant. Analyses were performed with STATA software (version 9; Stata Corp, College Station, TX).

RESULTS

This study includes 959 patients with prostate cancer, which was diagnosed from the time of blood collection until the end of follow-up and 1059 matched controls. The median age at blood collection was 61 y (range: 43–76 y). There were no large differences between cases and controls, although cases had a

TABLE 1

Characteristics of prostate cancer cases and control participants

Characteristic	Cases (<i>n</i> = 959)	Controls (<i>n</i> = 1059)	<i>P</i> value ¹
Age [<i>n</i> (%)]			
<50 y	26 (2.7)	39 (3.7)	—
50–54 y	140 (14.6)	155 (14.6)	—
55–59 y	286 (29.8)	315 (29.7)	—
60–64 y	361 (37.6)	401 (37.9)	—
65–70 y	77 (8.0)	79 (7.5)	—
≥70 y	69 (7.2)	70 (6.6)	0.77
Weight (kg) ^{2,3}	80.1 ± 11.3	81.1 ± 11.9	0.03
Height (cm) ^{2,3}	173.6 ± 6.9	173.8 ± 6.9	1.00
BMI (kg/m ²) ^{2,3}	26.6 ± 3.3	26.9 ± 3.6	0.02
Smoking [<i>n</i> (%)] ⁴			
Never	306 (32.6)	318 (31.5)	—
Former	408 (43.5)	406 (40.3)	—
Current	224 (23.9)	284 (28.2)	0.02
Alcohol consumption [<i>n</i> (%)] ⁴			
<8 g/d	325 (34.8)	381 (37.7)	—
8–15 g/d	187 (20.0)	209 (20.7)	—
16–39 g/d	249 (26.7)	232 (22.9)	—
≥40 g/d	173 (18.5)	189 (18.7)	0.58
Physical activity [<i>n</i> (%)] ⁴			
Inactive	194 (21.5)	179 (18.8)	—
Moderately inactive	317 (35.2)	306 (32.1)	—
Active	390 (43.3)	469 (49.2)	0.02
Marital status [<i>n</i> (%)] ⁴			
Married or cohabiting	499 (88.8)	572 (88.3)	0.83
Not married or cohabiting	63 (11.2)	76 (11.7)	—
Educational attainment [<i>n</i> (%)] ⁴			
Primary or equivalent	349 (37.8)	406 (40.4)	0.23
Secondary	332 (36.0)	376 (37.4)	—
Degree	242 (26.2)	224 (22.3)	—
Selenium (μg/L) ⁵	70.6 (69.7, 71.5)	71.9 (71.0, 72.7)	0.49
Cases only			
Time to diagnosis [<i>n</i> (%)]			
<2 y	173 (18.0)	—	—
2 to <4 y	269 (28.1)	—	—
4 to <6 y	291 (30.3)	—	—
6 to <8 y	153 (16.0)	—	—
≥8 y	73 (7.6)	—	—
Year of diagnosis ⁶	2000 (1994–2005)	—	—
Age at diagnosis (y) ²	64.8 ± 5.7	—	—
Stage [<i>n</i> (%)]			
Localized	480 (50.1)	—	—
Advanced	203 (21.2)	—	—
Unknown	276 (28.8)	—	—
Grade [<i>n</i> (%)]			
Low grade	442 (46.1)	—	—
High grade	283 (29.5)	—	—
Unknown	234 (24.4)	—	—

¹ *P* values are from a generalized paired *t* test (for continuous variables) or conditional logistic regression matched by case-control set (categorical variables), as appropriate.

² Mean ± SD.

³ Unknown for 16 participants.

⁴ The calculations of percentages exclude missing values (not shown in the table).

⁵ Geometric mean (95% CI).

⁶ Median (range).

slightly lower weight and BMI, were less likely to smoke, and were less physically active than controls (**Table 1**). Plasma selenium concentration ranged from 23 to 198 μg/L, and the geometric mean concentration was similar between prostate cancer

cases and their matched controls (71.9 and 70.6 μg/L, respectively; *P* = 0.49).

For cases, the median age at cancer diagnosis was 65 y (range: 47–82 y). The median time between blood collection and cancer

TABLE 2Geometric mean (95% CI) selenium concentrations in controls by age and lifestyle factors¹

Characteristic	No. of subjects	Selenium $\mu\text{g/L}$	<i>P</i> value ²
Country			
Denmark	288	69.9 (57.8, 84.6)	
Germany	202	66.2 (56.1, 78.1)	
Greece	9	63.2 (51.3, 77.9)	
Italy	62	72.1 (60.7, 85.6)	
Netherlands	25	71.0 (58.8, 85.7)	
Spain	93	74.6 (63.1, 88.2)	
Sweden	200	76.1 (61.9, 93.6)	
United Kingdom	180	76.3 (64.7, 90.0)	<0.0001 ³
Age at blood collection			
<50 y	39	76.9 (72.3, 81.7)	
50–54 y	155	73.1 (70.9, 75.4)	
55–59 y	315	72.2 (70.7, 73.7)	
60–64 y	401	72.3 (70.9, 73.7)	
65–69 y	79	69.5 (66.5, 72.7)	
≥70 y	70	65.5 (61.3, 70.0)	0.006
BMI			
<24.34 kg/m ²	262	71.2 (69.7, 72.7)	
24.34–26.35 kg/m ²	258	72.8 (71.2, 74.4)	
26.36–28.70 kg/m ²	252	72.9 (71.3, 74.5)	
≥28.71 kg/m ²	275	70.2 (68.7, 71.6)	0.36
Smoking			
Never	318	72.0 (70.6, 73.4)	
Former	406	72.8 (71.5, 74.1)	
Current	284	69.1 (67.7, 70.6)	0.001 ³
Alcohol consumption			
<8 g/d	381	70.4 (69.1, 71.8)	
8–15 g/d	209	72.3 (70.6, 74.1)	
16–39 g/d	232	72.9 (71.2, 74.6)	
≥40 g/d	189	70.3 (68.4, 72.2)	0.61
Physical activity			
Inactive	179	72.4 (70.5, 74.4)	
Moderately inactive	306	70.6 (69.2, 72.1)	
Active	469	70.8 (69.7, 72.0)	0.26
Marital status			
Married or cohabiting	572	70.7 (69.8, 71.8)	
Not married or cohabiting	76	68.6 (65.9, 71.4)	0.15 ³
Education level			
Primary or equivalent	406	71.1 (69.9, 72.4)	
Secondary	376	71.8 (70.5, 73.1)	
Degree	224	73.1 (71.4, 74.9)	0.08

¹ Data are based on ANOVA, with adjustment for age, laboratory batch, and recruitment center, where appropriate.² *P* values are based on a test of trend, by scoring each category as 1, 2, 3,...as required, unless otherwise stated.³ *P* values are based on a test of heterogeneity.

diagnosis was 4.3 y (range: 0.1–15.1 y), with the shortest follow-up time in Greece (median: 2.6 y) and the longest follow-up time in Sweden (9.2 y). The stage of disease at diagnosis was known for 683 cases (71%); of these, 480 (70%) were localized and 203 (30%) were advanced. Tumor grade at diagnosis was available for 725 cases (76%); of these, 442 (61%) were low grade (Gleason sum <7 or equivalent) and 283 (39%) were high grade (Gleason sum ≥7 or equivalent; Table 1). Sixty-seven percent of localized cases were also classified as low grade and 65% of advanced cases were also classified as high grade.

The mean plasma selenium concentration varied by ≈20% between countries, with the lowest concentrations in Germany

and Greece and the highest concentrations in the United Kingdom and Sweden. Age was inversely associated with plasma selenium concentration; men aged ≥70 y had a 15% lower plasma selenium concentration than did men aged < 50 y (*P* for trend = 0.006). Current smokers had a 4–5% lower plasma selenium concentration than did never smokers and former smokers (*P* for heterogeneity = 0.001). No association was found between BMI, alcohol intake, physical activity, marital status, or education level and plasma selenium concentration (Table 2).

Overall, plasma selenium concentration was not associated with prostate cancer risk. The RR for men in the highest fifth of selenium concentration compared with the lowest fifth was 1.00

TABLE 3

Relative risks (RRs) (95% CIs) of prostate cancer by fifths of plasma selenium concentration

Selenium concentration ($\mu\text{g/L}$)	Cases/controls	RR (95% CI)	
		Unadjusted ¹	Adjusted ²
<62.0	229/212	1.00 ³	1.00 ³
62.0–68.5	179/212	0.80 (0.60, 1.05)	0.81 (0.61, 1.07)
68.6–75.0	192/212	0.87 (0.65, 1.16)	0.85 (0.63, 1.14)
75.1–84.0	172/212	0.85 (0.64, 1.14)	0.82 (0.61, 1.10)
≥ 84.1	187/211	1.00 (0.74, 1.36)	0.96 (0.70, 1.31)
<i>P</i> for trend ⁴	—	0.48	0.25

¹ Cases and controls were matched on recruitment center, age at recruitment, time of day of blood collection, and time between blood collection and last consumption of foods or drinks.

² Adjusted for BMI, smoking status, alcohol intake, physical activity, marital status, and education level.

³ Reference category.

⁴ Test for linear trend based on the continuous log-transformed variable.

(95% CI: 0.74, 1.36; *P* for trend = 0.48) without adjustment and 0.96 (95% CI: 0.70, 1.31; *P* for trend = 0.25) after adjustment for BMI, smoking status, alcohol intake, physical activity, marital status, and education level (**Table 3**).

The association of plasma selenium concentration with risk according to stage and grade of disease and other factors is shown in **Table 4**. The risk estimates were adjusted for BMI, smoking status, alcohol intake, physical activity, marital status, and education level; however, the unadjusted RRs were similar (data not shown). There were no significant differences in the association of selenium concentration with prostate cancer risk by stage or grade of disease; men in the lowest fifth of selenium concentration had a small increased risk of advanced-stage and high-grade

disease, but there was no evidence of a monotonic inverse trend across categories of increasing concentration, and none of these associations were statistically significant. Selenium concentration was inversely associated with prostate cancer risk for men with a diagnosis <4 y since blood collection and was not associated with risk among men with a diagnosed ≥ 4 y since blood collection. However, these differences were not significantly different. Although there was a higher proportion of advanced-stage disease among cases diagnosed in the first 4 y of follow-up (39%) than in cases diagnosed later (24%), selenium concentration did not vary by time since blood collection to diagnosis (the geometric mean selenium concentration, adjusted for age, batch, and center, in cases diagnosed <4 y and ≥ 4 y since recruitment

TABLE 4Multivariable-adjusted relative risks (95% CIs) for prostate cancer by fifth of plasma selenium concentration, subdivided by various factors¹

	Quintile of plasma selenium concentration ($\mu\text{g/L}$)					<i>P</i> for trend ²	<i>P</i> for heterogeneity ³
	<62.0	62.0–68.5	68.6–75.0	75.1–84.0	≥ 84.1		
Stage of disease							
Localized	1.00 ⁴	0.73 (0.48, 1.11)	0.79 (0.51, 1.20)	0.67 (0.43, 1.03)	1.00 (0.63, 1.58)	0.79	
Cases/controls (<i>n</i>)	116/101	77/100	99/116	83/122	105/120		
Advanced	1.00	0.67 (0.36, 1.25)	0.57 (0.30, 1.09)	0.70 (0.35, 1.37)	0.62 (0.32, 1.21)	0.13	0.36
Cases/controls (<i>n</i>)	59/46	42/46	33/42	33/37	36/45		
Grade of disease							
Low	1.00 ⁴	0.97 (0.65, 1.46)	0.94 (0.60, 1.47)	0.89 (0.56, 1.40)	1.22 (0.75, 2.00)	0.90	
Cases/controls (<i>n</i>)	107/111	92/104	87/99	72/94	84/94		
High	1.00	0.59 (0.32, 1.09)	0.55 (0.31, 0.98)	0.67 (0.37, 1.19)	0.73 (0.40, 1.31)	0.06	0.13
Cases/controls (<i>n</i>)	69/49	46/61	53/66	55/69	60/75		
Time between blood collection and diagnosis							
<4 y	1.00 ⁴	0.63 (0.41, 0.96)	0.88 (0.56, 1.37)	0.68 (0.43, 1.08)	0.66 (0.40, 1.09)	0.03	
Cases/controls (<i>n</i>)	123/103	85/106	95/85	69/77	60/69		
≥ 4 y	1.00	0.94 (0.63, 1.40)	0.79 (0.53, 1.19)	0.90 (0.60, 1.35)	1.19 (0.77, 1.82)	0.87	0.07
Cases/controls (<i>n</i>)	106/109	94/106	97/127	103/135	127/142		
Age at blood collection							
<60 y	1.00 ⁴	0.72 (0.45, 1.14)	0.78 (0.49, 1.25)	0.98 (0.61, 1.56)	0.98 (0.59, 1.62)	0.54	
Cases/controls (<i>n</i>)	92/84	75/95	87/99	94/96	93/107		
≥ 60 y	1.00	0.89 (0.61, 1.31)	0.87 (0.58, 1.30)	0.77 (0.51, 1.17)	0.87 (0.56, 1.34)	0.31	0.81
Cases/controls (<i>n</i>)	134/124	102/109	99/101	75/93	88/91		

¹ Cases and controls were matched on recruitment center, age at recruitment, time of day of blood collection, and time between blood collection and last consumption of foods or drinks. Further adjustment was made for BMI, smoking status, alcohol intake, physical activity, marital status, and education level, where appropriate.

² Test for linear trend based on the continuous log-transformed variable.

³ Test for heterogeneity between linear trends based on the continuous log-transformed variable.

⁴ Reference category.

TABLE 5Multivariable-adjusted relative risks (95% CIs) of prostate cancer by thirds of plasma selenium and plasma α -tocopherol and γ -tocopherol¹

	Plasma selenium concentration (μg/L)						<i>P</i> for interaction
	<66.3		66.3–77.0		≥77.1		
	Cases/controls	RR (95% CI)	Cases/controls	RR (95% CI)	Cases/controls	RR (95% CI)	
<i>α</i> -Tocopherol (μg/dL)							
<1248	166/151	1.00 ²	132/117	1.00 (0.70, 1.42)	70/84	0.87 (0.58, 1.30)	0.30
1248–1496	104/110	0.90 (0.63, 1.29)	96/137	0.64 (0.45, 0.92)	103/105	1.00 (0.68, 1.46)	
≥1497	75/91	0.77 (0.52, 1.14)	74/98	0.75 (0.50, 1.12)	137/162	0.95 (0.66, 1.36)	
<i>γ</i> -Tocopherol (μg/dL)							
<83	118/124	1.00 ²	133/129	1.05 (0.72, 1.52)	109/99	1.17 (0.78, 1.74)	0.42
83–131	106/111	1.06 (0.72, 1.57)	86/115	0.82(0.55, 1.24)	87/126	0.83 (0.54, 1.28)	
≥132	121/117	1.18 (0.78, 1.76)	83/108	0.95 (0.62, 1.45)	114/126	1.38 (0.89, 2.14)	

¹ Complete data for plasma selenium, α -tocopherol, and γ -tocopherol concentrations were available for 2012 participants. Cases and controls were matched on recruitment center, age at recruitment, time of day of blood collection, and time between blood collection and last consumption of foods or drinks. Further adjustment was made for BMI, smoking status, alcohol intake, physical activity, marital status, and education level.

² Reference category.

was 69 and 73 $\mu\text{g/L}$, respectively, for localized cases and 69 and 70 $\mu\text{g/L}$ for advanced-stage cases. There was no association of selenium concentration with prostate cancer risk in younger (<60 y) or older men (≥ 60 y), and there was no evidence of heterogeneity in the association of selenium with risk between countries (data not shown).

We next examined the association of plasma selenium concentration and prostate cancer risk by smoking status using unconditional regression methods to maximize power. After adjustment for center, age at blood collection, BMI, alcohol intake, physical activity, marital status and education, the RRs for the highest fifth compared with the lowest fifth of selenium concentration were 0.82 (95% CI: 0.44, 1.65; *P* for trend = 0.17) for current smokers, 0.86 (95% CI: 0.53, 1.39; *P* for trend = 0.33) for former smokers, and 1.06 (95% CI: 0.58, 1.94; *P* for trend = 0.84) for never smokers. There was no evidence of statistical heterogeneity between the groups (chi-square test on 2 df = 0.25; *P* = 0.88).

Plasma selenium, α -tocopherol, and γ -tocopherol concentration data were complete for 2012 participants. Individually, plasma α - and γ -tocopherol were not associated with prostate cancer risk, as reported elsewhere (29). There was no evidence that the risk associated with selenium concentration was modified by the plasma concentration of either α -tocopherol or γ -tocopherol (Table 5).

DISCUSSION

This is the largest prospective study to examine plasma selenium concentration and subsequent prostate cancer risk. Overall, our findings suggest that plasma selenium concentration is not associated with risk. Furthermore, this association does not differ significantly according to stage or grade of disease. The selenium content of European soils is low, and dietary intake has been declining because of a reduction in imported selenium-rich wheat from North America, together with a general decline in cereal consumption (31). Indeed, plasma selenium concentrations in EPIC (mean: 70 $\mu\text{g/L}$) are substantially lower than those found in populations from the United States (typically > 100 $\mu\text{g/L}$). The Nutritional Prevention of Cancer trial showed that selenium supplementation significantly reduced prostate cancer risk among men with a low baseline selenium concentration (ie,

<106 $\mu\text{g/L}$ at entry to the trial) (10, 11). Because the enzyme activity of glutathione peroxidases becomes saturated at high circulating selenium concentrations (32), one might expect selenium to have a greater protective effect on prostate cancer risk in populations with low average circulating concentrations. The results from the present study suggest that selenium is not associated with prostate cancer risk in this population of men with relatively low selenium concentrations, although it is possible that the range of selenium concentrations may have been too narrow to detect a significant association. Two other studies have been conducted in European populations with a relatively low selenium intake, one of which reported an inverse association (15) and the other reported no association (20). Results from prospective studies conducted in US populations, where selenium intake is relatively high, are also inconsistent; some studies have reported a significant negative association of selenium (as measured in blood or nails) with prostate cancer risk (13, 14, 16, 17), although others have found no association (18, 19, 21).

Our finding that current smokers have slightly lower selenium concentrations than do never smokers is consistent with previous studies (33–36). It is not known whether smoking itself lowers selenium concentrations or whether dietary intake of selenium is lower among current smokers. Nonetheless, smoking was not associated with risk in this study population, and the association between selenium concentration and cancer risk did not differ significantly by smoking status.

The inverse association observed between selenium and prostate cancer risk among men with a diagnosis <4 y after blood collection raises the possibility that the presence of undiagnosed cancer may have lowered selenium concentrations. However, the differences in risk by follow-up time were not statistically significant from each other, and this could not account for the inverse association found in other studies with more prolonged follow-up (ie, >10 y) (14, 16). When analyzed by stage and grade of disease, there was some suggestion that men with a low selenium concentration (ie, <62 $\mu\text{g/L}$) may have an increased risk of advanced-stage disease and high-grade disease. However, the number of participants in these subgroups was low and none of these associations were statistically significant and should therefore be interpreted with caution. Nonetheless, other prospective studies have also suggested that a low selenium concentration

may be associated with an increased risk of aggressive disease (15, 17), although others have reported an inverse association with increasing selenium exposure (14, 16) or no association with aggressive disease (18). In our study, although there was a higher proportion of advanced-stage cases among men with a diagnosis in the first 4 y of follow-up compared with those with a diagnosis ≥ 4 y, selenium concentration did not vary by time since blood collection to diagnosis (for either localized or advanced-stage disease), which suggests that the presence of preclinical disease did not unduly influence circulating concentrations.

This is the largest study to examine potential interactions of plasma selenium with vitamin E, and our results show no evidence of effect modification by plasma α - or γ -tocopherol concentrations. Consistent with our findings, 2 previous cohort studies reported no difference in the association of toenail selenium concentration with prostate cancer risk in relation to vitamin E intake (15, 17). However, other studies have reported a reduced prostate cancer risk among men with a high plasma or nail selenium concentration and a high plasma γ -tocopherol concentration (19) or a high vitamin E intake (21), although the interaction term was only significant in the latter study. However, both of these studies also found plasma concentrations of γ -tocopherol (19) or supplemental vitamin E intake among smokers (37) to be independently associated with a reduced risk, whereas the EPIC study reported no association of either baseline α - or γ -tocopherol concentrations with prostate cancer risk (29) and no evidence of an interaction of plasma tocopherols and selenium concentration.

The main strengths of this study are the large number of cases and controls, the ability to categorize cancers into nonaggressive and aggressive disease, and detailed information on other potential risk factors, including plasma concentrations of α - and γ -tocopherol. Measurement of plasma selenium concentration has been shown to rank individuals reliably according to dietary selenium intake, at least in areas with a high selenium intake, with a correlation coefficient of 0.7 (38), although little is known about the correlation between dietary intake and plasma concentrations in areas of lower intake, perhaps reflecting the difficulty in estimating selenium intake from food-composition tables. Moreover, although plasma concentrations are often thought to reflect short-term selenium status compared with red blood cells or nail clippings, a single plasma measure has been shown to have moderate reliability over a 5–6 y period, with correlation coefficients reported between 0.48 and 0.55, which suggests that a single measure is representative of usual levels for at least the medium term (16, 39). Finally, a randomized trial has shown selenium supplementation to increase plasma and intraprostatic selenium concentrations by a similar magnitude (40), which suggests that circulating concentrations may accurately reflect intraprostatic concentrations.

A limitation of this study is that information on stage and grade was only available for 70–80% of the patients. Although the TNM stage and Gleason score are designed to determine the aggressiveness of the disease in a systematic manner, there inevitably will be some interobserver variability in the assessment of stage and grade across recruitment centers. In particular, there is known to be considerable measurement error in the determination of the Gleason score, with a high proportion of cases likely to be undergraded (41). In addition, we did not have information

as to whether the TNM score was derived from clinical or pathological review, and it is well known that cases with pathological staging are more likely to be diagnosed with advanced-stage disease because it provides a more sensitive assessment than does palpation of extraprostatic growth (42). Another limitation, as mentioned above, is that the low selenium status of this population and the narrow range of selenium values reduces the possibility of detecting an association of selenium exposure with prostate cancer risk, if one exists. Finally, although adjustments were made for several potentially confounding factors, we did not adjust for other factors that could affect prostate cancer risk, such as family history or dietary intake of other nutrients. However, given the overall lack of association of selenium concentration with risk, it is unlikely that other unmeasured factors are strong confounders. In conclusion, the findings from this study suggest that plasma selenium concentration has little or no association with overall prostate cancer risk in European men.

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