A Prospective Study of Plasma Selenium Levels and Prostate Cancer Risk

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Background: **Epidemiologic studies suggest that low selenium levels are associated with an increased incidence of prostate cancer, although results are conflicting. We examined the association between pre-diagnostic plasma selenium levels and risk of prostate cancer in men enrolled in the Physicians' Health Study.** ***Methods:*** **Using plasma samples obtained in 1982 from healthy men enrolled in the study, we conducted a nested case–control study among 586 men diagnosed with prostate cancer during 13 years of follow-up and 577 control subjects. Odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of prostate cancer in pre- (before October 1990) and post- (after October 1990) prostate-specific antigen (PSA) screening eras were calculated using multivariable logistic regression.** ***Results:*** **Pre-diagnostic plasma selenium levels were inversely associated with risk of advanced prostate cancer (5^{th} versus 1^{st} quintile OR = 0.52, 95% CI = 0.28 to 0.98; P_{trend} = .05), even among men diagnosed after 1990 (5^{th} versus 1^{st} quintile OR = 0.39, 95% CI = 0.16 to 0.97). The inverse association with prostate cancer risk was observed only for case subjects with elevated baseline PSA levels (PSA >4 ng/mL, 5^{th} versus 1^{st} quintile OR = 0.49, 95% CI = 0.28 to 0.86; P_{trend} = .002). These inverse associations were observed in both pre- and post-PSA eras.** ***Conclusions:*** **The inverse association between baseline plasma selenium levels and risk of advanced prostate cancer, even among men diagnosed during the post-PSA era, suggests that higher levels of selenium may slow prostate cancer tumor progression. Ongoing randomized trials of selenium supplements may help to further evaluate this issue. [J Natl Cancer Inst 2004;96:696–703]**

Prostate cancer is the most commonly diagnosed non-skin cancer in most western countries and the second leading cause of cancer deaths in U.S. men, yet the etiology of this disease is largely unknown *(1,2).* Although the prevalence of microscopic or latent prostate tumors is similar in most populations *(3),*

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clinical prostate cancer incidence and death rates are remarkably different in diverse geographic regions and among various racial/ethnic groups *(1)*. The variation in prostate cancer incidence and mortality across different countries and ethnic groups and the change in risk observed among migrants have motivated the search for modifiable factors that affect prostate cancer development.

A chemoprotective role of selenium against a variety of malignancies has been demonstrated in laboratory animals and cell lines *(4–6)*. The anticancer activity of selenium has been attributed to its role in inducing apoptosis, inhibiting cellular proliferation, and being a key component of glutathione peroxidase, which protects cells from peroxide damage *(7–9)*. Geographic studies have shown an inverse relationship between environmental selenium levels and cancer incidence and mortality *(10,11)*.

Several prospective epidemiologic studies *(12–17)* have examined the association between prostate cancer incidence and pre-diagnostic selenium concentrations in biologic samples, with conflicting results. In the Health Professionals Follow-up Study (HPFS), Yoshizawa et al. *(12)* prospectively examined toenail selenium levels in 181 men who later developed advanced prostate cancer (stages C and D) during 2–7 years of follow-up. They reported an odds ratio (OR) for prostate cancer of 0.4 (95% confidence interval [CI] = 0.2 to 0.8; P_{trend} = .03) comparing the highest with the lowest quintile of toenail selenium content. An inverse association between toenail selenium levels and prostate cancer risk was also recently observed in Dutch men by van den Brandt et al. *(13)* (n = 540 case subjects; 5th versus 1st quintile OR = 0.7, 95% CI = 0.5 to 1.0; P_{trend} = .01). The findings were similar for men with localized and advanced disease. An inverse association between prostate cancer risk and serum selenium levels was found by Nomura et al. *(14)* in a cohort of 249 Hawaiian Japanese men who were diagnosed with prostate cancer during more than 20 years of follow-up. This association was more notable in men with advanced disease (4th versus 1st quartile OR = 0.3, 95% CI = 0.1 to 0.8; P_{trend} = .01) and in current and former smokers. During 4 years of follow-up in the Baltimore Longitudinal Study of Aging (n = 52 case subjects), Brooks et al. *(15)* reported an inverse association between prostate cancer risk and plasma selenium levels (4th versus 1st quartile OR = 0.2, 95% CI = 0.1 to 0.8; P_{trend} = .01). Helzlsouer et al. *(16)* (n = 117 case subjects) also found an inverse association between prostate cancer risk and toenail selenium levels, albeit with no monotonic trend (5th versus 1st quintile OR = 0.6, 95% CI = 0.3 to 1.2; P_{trend} = .27). By contrast, no association between prostate cancer risk and serum selenium levels was observed in a cohort from the Carotene and Retinol Efficacy Trial (4th versus 1st quartile OR = 1.0, 95% CI = 0.7 to 1.6; P_{trend} = .69) *(17)*.

The strongest evidence for the efficacy of selenium as a cancer prevention agent has come from a randomized, double-blind clinical trial *(18–20)*. The trial was designed to test the effect of a dietary supplement of 200 μg of selenium (in the form of selenized yeast) on the risk of skin cancer. Selenium supplementation had no effect on the primary skin cancer endpoint; however, secondary analyses noted a much lower incidence of other cancers. After a mean follow-up of 7.4 years, men randomly assigned to receive selenium had a 63% lower incidence of prostate cancer (relative risk [RR] = 0.37; P = .002) than men assigned to receive the placebo *(18–20)*. In the same trial, Clark et al. *(19)* also found a protective effect of selenium on prostate cancer among patients with prostate-specific antigen (PSA) levels of less than 4 ng/mL or between 4 and 10 ng/mL ($P<.05$) but not among those with PSA levels of greater than 10 ng/mL.

To assess the association between pre-diagnostic plasma selenium levels and risk of prostate cancer and whether the association differs by the case subject's baseline PSA level, we conducted a nested case–control study within the Physicians' Health Study. PSA-based cancer screening, introduced in the early 1990s, helps to detect tumors before manifestations of aggressive behavior. Since then, shifts have been observed in the incidence of prostate cancer, age of men diagnosed with prostate cancer, stage and grade of disease, and possibly age-adjusted prostate cancer mortality rate *(21)*. Hence, the etiology of prostate cancer may be different for men diagnosed with prostate cancer in the pre-PSA era than in men diagnosed in the post-PSA era. Because our study included men diagnosed with prostate cancer during a 13-year follow-up (between 1982 and 1995), i.e., in both pre- and post-PSA eras, we were able to assess the association between pre-diagnostic selenium levels and risk of prostate cancer by PSA era.

Subjects and Methods

Study Population

The Physicians' Health Study was a randomized, double-blind, placebo-controlled trial of aspirin and beta-carotene among 22 071 healthy U.S. male physicians, aged 40–84 years, that began in 1982. This current study concerns reports of prostate cancer that occurred during 13 years of follow-up. Written informed consent was obtained from each participant, and the investigation was approved by the Human Subjects Committee at Brigham and Women's Hospital. Men were excluded at baseline if they had a history of myocardial infarction, stroke, transient ischemic attack, or unstable angina; cancer (except for non-melanoma skin cancer); current renal or liver disease, peptic ulcer, or gout; or current use of platelet-active agents, vitamin A, or beta-carotene supplements. The participants were predominately Caucasian (94%). Detailed descriptions of the Physicians' Health Study have been published *(22,23)*.

Participants completed two mailed questionnaires before being randomly assigned to a study arm. Additional questionnaires were mailed at 6 and 12 months after assignment and annually thereafter. Blood samples were collected at baseline in 1982, as described previously *(24)*. We received specimens from 14 916 (68%) study participants before they were randomly assigned; more than 70% of the specimens were collected between September and November 1982. During 13 years of follow-up, more than 99% of surviving participants were still reporting morbidity events; vital status was ascertained for 100% of the participants.

Selection of Prostate Cancer Case and Control Subjects

When a participant reported a diagnosis of prostate cancer, we requested hospital records and pathology reports for review by study physicians from the End Point Committee. For each case subject, one control subject was selected from those who had provided a baseline blood sample, had not had a prostatectomy, and had not reported a diagnosis of prostate cancer at the

time the diagnosis was reported by the case subject; control subjects were individually matched to case subjects by age (within 1 year for men aged 55 years or younger and within 5 years for men older than 55 years) and smoking status (never, former, or current). Of all case subjects who were diagnosed between 1982 and 1995 and who provided blood samples at baseline, 586 of the samples were sufficient for analysis. Although 10% of the participants provided blood samples that were not sufficient for the analysis, it is unlikely to have introduced a bias because case subjects with and without adequate blood samples were not substantially different with respect to baseline lifestyle characteristics. In addition, it is unlikely that subjects who did or did not provide a sample would differ substantially in terms of the potential relationship between baseline plasma selenium levels and subsequent diagnosis of prostate cancer.

Severity of Disease

Physicians who were unaware of the selenium assay results reviewed the medical records (including pathology reports) for each case subject to determine tumor stage, tumor grade, and Gleason score *(24)*. Stage was determined according to the modified Whitmore–Jewett classification scheme *(25)*. Case subjects without pathologic staging were classified as indeterminate stage unless there was clinical evidence of distant metastases. Case subjects diagnosed with stage C or D disease were considered to have advanced cancer.

Laboratory Assessment

Plasma samples for each case and matched control subject were analyzed in the same batch, but in random order, with the case status unknown to the laboratory personnel. Selenium concentrations were determined by instrumental neutron activation analysis using the Se-77m isotope *(26)* at the University of Missouri Research Reactor Center (Columbia, MO). Each sample was tested in duplicate; the mean coefficient of variation for duplicate analyses was 6.4%. Total PSA levels from the same baseline samples for case and control subjects had been analyzed previously *(27,28)* using the Tandem-R immunoradiometric assay (Hybritech, San Diego, CA); details on the quality and reproducibility of the assay are described elsewhere *(27,28)*.

Statistical Analysis

Baseline plasma selenium levels for 586 case and 577 control subjects were available for analysis; among these, 576 case and control subjects were matched and 10 case subjects and one control subject were unmatched. The samples were measured in two batches, with 18 pairs of samples measured in 1993 and the remaining samples measured in 1999. Plasma selenium levels (from specimens collected at baseline) for 258 study participants (i.e., 168 case and 90 control subjects from our analytical sample) measured at both time points were available for comparison. Plasma selenium levels measured in 1993 were 7.7% higher than those measured in 1999 ($P>.05$) but were correlated (Pearson coefficient $r = .62$; $P<.001$). To minimize possible misclassification, we calibrated the levels of plasma selenium for the 18 pairs measured in 1993 using data from the 258 subjects who had plasma selenium levels measured twice. In addition, we conducted all the principal analyses among the 586 case and 577 control subjects and repeated them after excluding the 18 pairs who had measurements from 1993; no substantial differences were observed.

The univariate distribution of plasma selenium concentrations was approximately normal. We used Student's *t* tests to compare the baseline plasma selenium levels in 586 case subjects and 577 control subjects and paired *t* tests for the 576 matched pairs. We examined the association between plasma selenium concentration and risk of total prostate cancer and then refitted models for subgroups of case subjects classified by severity of disease or baseline PSA status of the case subjects (i.e., PSA $\leq$4 ng/mL and $>$4 ng/mL, or PSA $\leq$4 ng/mL, between 4 and 10 ng/mL, and $\geq$10 ng/mL). Case subjects were excluded from these analyses if they had unknown disease stage (n = 67) or no baseline PSA level (n = 65). Additionally, we examined the association between prostate cancer risk and plasma selenium levels within subgroups of case subjects diagnosed during the pre- (October 1982 through September 1990) and post- (October 1990 through December 1995) PSA eras.

For all of these analyses, including subgroup analyses, we included all control subjects to maximize statistical power and used quintile cut points from the control subjects to assign each study participant to a quintile. We used unconditional logistic regression models, in which all models were adjusted for age at baseline, smoking status, and duration of follow-up, with consideration of the case–control selection criteria and matching. The duration of follow-up for case subjects was calculated as years between baseline (1982) and year at diagnosis; for a control subject, the follow-up duration was considered to be the same as that of the matched case subject. We calculated the ORs and 95% CIs for each quintile, using the lowest quintile as the reference category; tests for trend were conducted by using median levels of quintiles. All statistics were calculated by using SAS, version 8.12 (SAS Institute, Cary, NC) with a significance level of .05 (two-sided).

Results

The baseline characteristics of the 586 case and 577 control subjects are presented in Table 1. The average interval from baseline to a diagnosis of prostate cancer was 8.1 years (range =

Table 1. Baseline characteristics of prostate cancer case and control subjects enrolled in the Physicians' Health Study*

	Case subjects (n = 586)	Control subjects (n = 577)
Mean age at baseline ± SD, y†	60.3 ± 7.7	60.0 ± 7.6
Mean age at diagnosis ± SD, y	68.3 ± 6.7	
Disease status, %		
Localized (stage A or B)	59.4	
Advanced (stage C or D)	29.2	
Unknown	11.4	
Smoking status, %†		
Current	9.2	8.8
Former	45.2	44.9
Height, m ± SD	1.79 ± 0.07	1.78 ± 0.08
Weight, kg ± SD	79.1 ± 9.6	77.8 ± 9.6
Body mass index, kg/m^2 ± SD	24.8 ± 2.7	24.7 ± 2.7
Plasma selenium, ppm ± SD	0.106 ± 0.018	0.108 ± 0.018

*Case and control subjects were matched 1:1. The analytical sample above included 576 matched case and control subjects, 10 unmatched case subjects, and one unmatched control subject.

†Matching variable.

0–13 years). Of the 586 men diagnosed with incident prostate cancer, 171 had advanced (stage C or D) and 348 had localized (stage A or B) disease; we were unable to classify 67 men because of insufficient information. Plasma selenium levels among control subjects ranged from 0.058 ppm to 0.185 ppm. Case subjects did not differ statistically significantly from control subjects for any variable presented in Table 1, including the baseline plasma selenium concentration.

The association between plasma selenium levels and subsequent prostate cancer risk according to quintiles of plasma selenium levels is shown in Table 2. Overall, men in the highest quintile of pre-diagnostic plasma selenium levels had a statistically nonsignificant 22% (OR = 0.78, 95% CI = 0.54 to 1.13; P_{trend} = .16) lower risk of prostate cancer than men in the lowest quintile. However, plasma selenium concentration was statistically significantly inversely associated with subsequent risk of advanced prostate cancer (5^{th} versus 1^{st} quintile OR = 0.52, 95% CI = 0.28 to 0.98; P_{trend} = .0498) but not of localized prostate cancer. These associations were similar for nonsmokers, former smokers, and current smokers.

We found that higher plasma selenium levels were associated with a lower risk of prostate cancer only for case subjects with increased baseline PSA levels (PSA >4 ng/mL; 5^{th} versus 1^{st} quintile OR = 0.49, 95% CI = 0.28 to 0.86; P_{trend} = .002) and that the inverse association was particularly strong for those with baseline PSA levels of 10 ng/mL or greater (4^{th} versus 1^{st} quintile OR = 0.27, 95% CI = 0.11 to 0.70; 5^{th} versus 1^{st} quintile OR = 0.38, 95% CI = 0.16 to 0.90; P_{trend} = .001) (Fig. 1). We observed an inverse correlation between baseline plasma selenium and PSA levels (Spearman coefficient $r = -.16$; $P < .001$) (Fig. 2) among case subjects, but baseline selenium levels were unrelated to PSA levels among control subjects (Spearman coefficient $r = .07$; $P = .13$).

We next assessed the association between prostate cancer risk and plasma selenium levels for case subjects diagnosed with prostate cancer in the pre- (follow-up time = 0–8 years) and post- (follow-up time = 9–13 years) PSA eras (Table 3). Inverse associations were observed in both eras, although neither was statistically significant. Furthermore, a statistically nonsignificant inverse association was seen for case subjects with localized and advanced disease in the pre-PSA era. By contrast, for case subjects diagnosed in the post-PSA era, a statistically significant inverse association was observed for case subjects with advanced disease (5^{th} versus 1^{st} quintile OR = 0.39, 95% CI =

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) for prostate cancer during 13 years of follow-up among men enrolled in the Physicians' Health Study according to quintile of plasma selenium level, by severity of disease or prostate-specific antigen (PSA) level in case subjects at baseline*

	Quintile of selenium level					
	1	2	3	4	5	P_{trend}
Median selenium level (range), ppm†	0.09 (0.06–0.09)	0.10 (0.09–0.10)	0.11 (0.10–0.11)	0.12 (0.11–0.12)	0.13 (0.12–0.19)	
All prostate cancer case (n = 586) and control subjects						
No. of case subjects/No. of control subjects	121/115	137/116	105/112	127/118	96/116	
OR (95% CI)	1.00 (referent)	1.13 (0.79 to 1.61)	0.88 (0.61 to 1.28)	1.02 (0.71 to 1.45)	0.78 (0.54 to 1.13)	.16
By severity of disease‡						
Localized case (n = 348) and all control subjects						
No. of case subjects/No. of control subjects	68/115	76/116	56/112	79/118	69/116	
OR (95% CI)	1.00 (referent)	1.11 (0.73 to 1.69)	0.84 (0.54 to 1.31)	1.11 (0.73 to 1.68)	0.97 (0.64 to 1.49)	.91
Advanced case (n = 171) and all control subjects						
No. of case subjects/No. of control subjects	36/115	45/116	37/112	35/118	18/116	
OR (95% CI)	1.00 (referent)	1.17 (0.70 to 1.97)	1.01 (0.59 to 1.73)	0.99 (0.58 to 1.70)	0.52 (0.28 to 0.98)	<.05‖
By baseline PSA level§						
Case subjects with PSA ≤4 ng/mL (n = 293) and all control subjects						
No. of case subjects/No. of control subjects	60/115	62/116	43/112	80/118	48/116	
OR (95% CI)	1.00 (referent)	1.04 (0.67 to 1.62)	0.77 (0.48 to 1.23)	1.30 (0.85 to 1.99)	0.77 (0.48 to 1.22)	.59
Case subjects with PSA >4 ng/mL (n = 228) and all control subjects						
No. of case subjects/No. of control subjects	55/115	62/116	51/112	34/118	26/116	
OR (95% CI)	1.00 (referent)	1.10 (0.69 to 1.74)	0.83 (0.51 to 1.34)	0.64 (0.38 to 1.08)	0.49 (0.28 to 0.86)	.002

*Unconditional logistic regression, adjusted for age at baseline, smoking status, and duration of follow-up (duration of follow-up for case subjects was number of years between baseline and diagnosis; duration of follow-up for control subjects was the same as that for corresponding case subjects).

†Selenium level in control subjects.

‡Case subjects (n = 67) who had unknown disease stage were excluded. Disease stage was determined according to the modified Whitmore–Jewett classification scheme *(25)*.

§Case subjects who had no data on baseline PSA level (n = 65) were excluded.

‖P = .0498.

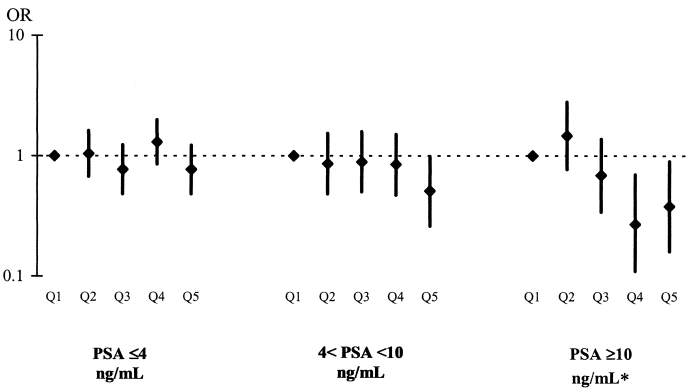

Fig. 1. Odds ratios (ORs) and 95% confidence intervals (CIs) for prostate cancer according to quintile of baseline plasma selenium levels (Q1 as referent) and prostate-specific antigen (PSA) status of case subjects at baseline among men enrolled in the Physicians' Health Study. Odds ratios and 95% confidence intervals were determined by using unconditional logistic regression, adjusted for age at baseline, smoking status, and years of follow-up (duration of follow-up was the number of years between baseline and diagnosis for case subjects; duration of follow-up for control subjects was the same as that for the corresponding case subjects). Control subjects, n = 577. Number of case subjects in each baseline PSA category is as follows: PSA ≤4 ng/mL, n = 293; PSA >4 ng/mL to <10 ng/mL, n = 129; PSA ≥10 ng/mL, n = 99. Case subjects without data for baseline PSA levels (n = 65) were excluded from this analysis. **Diamonds** = mean odds ratio; **bars** = 95% confidence intervals. *P_{trend} = .001.

0.16 to 0.97; P_{trend} = .048) but not for those with localized disease. In both eras, plasma selenium levels were inversely associated with risk of prostate cancer for case subjects who had increased PSA levels at baseline (5th versus 1st quintile: pre-PSA era OR = 0.42, 95% CI = 0.21 to 0.86; P_{trend} = .004 and post-PSA era OR = 0.44, 95% CI = 0.19 to 1.02; P_{trend} = .03). By contrast, no such association was found among case subjects with normal PSA levels at baseline.

We then examined the association between pre-diagnostic plasma selenium levels and risk of prostate cancer classified by both severity of disease (localized or advanced) and case subject PSA level at baseline (PSA ≤4 or >4 ng/mL) (Table 4). An inverse association between pre-diagnostic plasma selenium levels and prostate cancer risk was present only for case subjects with increased baseline PSA level, regardless of disease status. Among case subjects with baseline PSA levels of greater than 4 ng/mL, case subjects in the highest quintile of selenium had an odds ratio for advanced prostate cancer 0.49 (95% CI = 0.22 to 1.08) times that of case subjects in the lowest quintile (P_{trend} = .01); a similar trend of decreasing risk across selenium quintiles was observed among case subjects with localized disease, although the trend was not statistically significant. Again, these patterns were similar regardless of PSA era.

Discussion

We found a statistically significant inverse association between pre-diagnostic plasma selenium levels and subsequent risk of advanced prostate cancer among men enrolled in the Physicians' Health Study. The association was statistically significant during the post-PSA era, even after 8 years of follow-up. We found also that pre-diagnostic selenium levels were inversely associated with risk of prostate cancer only for case subjects with increased PSA levels at baseline (i.e., PSA >4 ng/mL). Because our study is larger than previous prospective studies *(12–17)* and had longer follow-up (13 years versus 4–6 years) covering both the pre- and post-PSA eras than most prospective studies *(12,13,15–17),* we had sufficient statistical power to examine the association of pre-diagnostic plasma selenium levels with risk of prostate cancer for men diagnosed in the pre- and post-PSA eras, respectively.

The statistically significant findings in our study are consistent with five *(12–16)* of the six published prospective studies *(12–17).* In agreement with other reports *(12–14),* we found a statistically significant inverse association between plasma selenium levels and risk of advanced prostate cancer. Two studies *(15,16)* reported an inverse trend, but neither examined the association with advanced disease. Goodman et al. *(17)* observed no association between serum selenium levels and total or advanced prostate cancer; however, of 235 case subjects with prostate cancer, only 114 had complete staging information and only 37 had advanced tumors.

Our findings are consistent with results from the HPFS cohort *(12),* in which men in the highest quintile of toenail selenium levels had a 60% (95% CI = 20% to 80%; P_{trend} = .03) lower risk of advanced prostate cancer than men in the lowest quintile. Both toenail and plasma selenium levels reflect body selenium status *(29).* These HPFS cohort case subjects were diagnosed between 1989 and 1994 and therefore were comparable to our case subjects with advanced disease diagnosed in the post-PSA era. In our study, we observed a trend toward an inverse association between plasma selenium levels and risk of both localized and advanced prostate cancer for subjects diagnosed in the pre-PSA era, but we observed a strong inverse association only for subjects with advanced disease diagnosed during the post-PSA era (Table 3). An explanation for this difference might be that localized tumors detected during the post-PSA era were less likely to be clinically important.

Clark et al. *(18,19)* and Duffield-Lillico et al. *(20)* reported that, after a mean follow-up of 7.4 years, men randomly assigned to receive selenium had a 63% lower incidence of prostate cancer than men who received placebo. Although the baseline plasma level of selenium for men in our study (mean, approximately 104 μg/L) was similar to the baseline level for men in the studies by Clark et al. and Duffield-Lillico et al. (115 μg/L) *(18–20),* plasma selenium concentration for men in their studies increased to a mean of 190 μg/L after intervention. Hence, the benefits of selenium supplement in the trial by Clark et al. and Duffield-Lillico et al. *(18–20)* might be related to the high dose provided in the trial (200 μg/day). This possibility is supported by data from a recent study in dogs, which found that high nontoxic doses of selenium supplements sensitize prostate epithelial cells so that cells with extensive DNA damage undergo apoptosis *in vivo (9).*

The inverse associations between pre-diagnostic plasma selenium levels and prostate cancer risk were statistically significant only for case subjects with increased baseline PSA levels (i.e., PSA >4 ng/mL) (Tables 2 and 3). One interpretation of this observation is that increased selenium levels may slow prostate cancer tumor progression and reduce the increased PSA levels. We observed an inverse correlation between levels of baseline plasma selenium and PSA among case subjects (5th versus 1st selenium quintile, median PSA = 2.6 versus 3.8 ng/mL, respectively) (Fig. 2) but not among control subjects. Although we cannot exclude the possibility that circulating PSA decreased selenium levels in blood, a potential effect of selenium on tumor

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for prostate cancer for men enrolled in the Physicians' Health Study according to quintile of plasma selenium level in pre- and post-PSA eras, and by severity of disease or baseline prostate-specific antigen (PSA) level*

	No. of case subjects/No. of control subjects	OR for quintile of selenium level (95% CI)					
		1	2	3	4	5	P_{trend}
Pre-PSA era (October 1982 through September 1990; follow-up, year 0 through year 8)							
All subjects	281/577	1.00 (referent)	1.21 (0.75 to 1.96)	0.89 (0.54 to 1.48)	0.99 (0.60 to 1.65)	0.59 (0.33 to 1.04)	.06
According to disease stage†							
A and B	134/577	1.00 (referent)	1.10 (0.61 to 1.98)	0.62 (0.32 to 1.18)	0.86 (0.46 to 1.61)	0.64 (0.32 to 1.27)	.14
C and D	106/577	1.00 (referent)	1.33 (0.68 to 2.60)	1.28 (0.65 to 2.52)	1.07 (0.52 to 2.19)	0.52 (0.22 to 1.21)	.14
According to PSA level‡							
≤4 ng/mL	101/557	1.00 (referent)	1.33 (0.67 to 2.64)	0.86 (0.40 to 1.82)	1.61 (0.82 to 3.15)	0.92 (0.43 to 1.98)	.89
>4 ng/mL	158/577	1.00 (referent)	1.14 (0.65 to 1.98)	0.83 (0.47 to 1.49)	0.61 (0.32 to 1.17)	0.42 (0.21 to 0.86)	.004
Post-PSA era (October 1990 through December 1995; follow-up, year 9 through year 13)							
All subjects	325/577	1.00 (referent)	1.00 (0.62 to 1.60)	0.84 (0.51 to 1.39)	1.02 (0.65 to 1.61)	0.66 (0.41 to 1.07)	.13
According to disease stage†							
A and B	214/577	1.00 (referent)	1.08 (0.62 to 1.87)	0.98 (0.55 to 1.76)	1.19 (0.70 to 2.02)	0.90 (0.52 to 1.54)	.80
C and D	65/577	1.00 (referent)	1.04 (0.49 to 2.22)	0.66 (0.28 to 1.59)	0.89 (0.42 to 1.89)	0.39 (0.16 to 0.97)	.048
According to PSA level‡							
≤4 ng/mL	192/577	1.00 (referent)	0.96 (0.56 to 1.64)	0.77 (0.43 to 1.37)	1.15 (0.69 to 1.91)	0.61 (0.35 to 1.07)	.21
>4 ng/mL	70/577	1.00 (referent)	0.92 (0.44 to 1.92)	0.74 (0.34 to 1.64)	0.62 (0.29 to 1.35)	0.44 (0.19 to 1.02)	.03

*Unconditional logistic regression, adjusted for age at baseline, smoking status, and duration of follow-up (duration of follow-up for case subjects was years between baseline and diagnosis; duration of follow-up for control subjects was the same as that for corresponding case subjects).

†Case subjects who had unknown disease stage (n = 67) were excluded. Disease stage was determined according to the modified Whitmore–Jewett classification scheme *(25)*. Stages A and B are considered localized disease and stages C and D are considered advanced disease.

‡Case subjects' baseline PSA level; case subjects who had no data (n = 65) were excluded.

development seems more plausible. In a recent clinical pilot study of the effects of selenium-enriched yeast supplementation that involved 36 healthy men, a small (10%) but statistically significant decrease ($P<.001$) in PSA levels was seen in men after 3 months of supplementation *(30)*. The study suggested a possible effect of selenium on decreasing PSA levels. However, the mean baseline level of PSA in men assigned to the placebo group (0.53 ng/mL) was 26% lower than that of men assigned to the selenium group (0.72 ng/mL). Thus, it is difficult to judge whether the statistically significant finding was the result of the treatment or regression to the mean. In our study, plasma selenium and PSA levels were both measured from the same baseline blood sample, and no PSA data were available during the follow-up. Thus, we could not determine whether selenium status subsequently affected PSA level in our study.

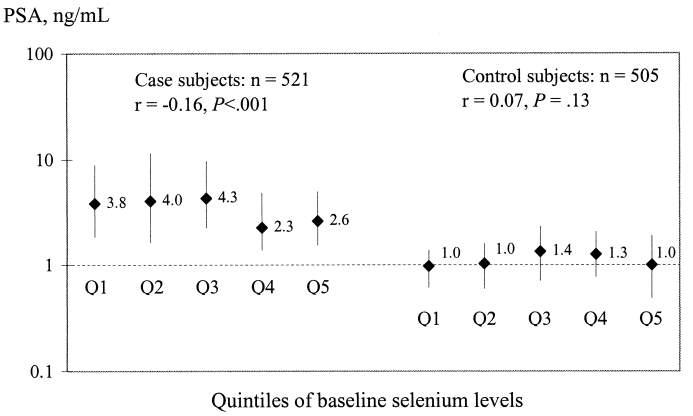

Fig. 2. Spearman correlations between baseline selenium and prostate-specific antigen (PSA) levels in prostate cancer case and control subjects from the Physicians' Health Study. **Dots** represent the medians and **lines** represent the 25th and 75th percentiles of baseline PSA levels according to quintiles of baseline plasma selenium levels (quintiles were categorized on the basis of plasma selenium levels in control subjects). Case subjects, N = 521 (quintiles, n = 115, 124, 94, 114, and 74). Control subjects, N = 505 (quintiles, n = 103, 106, 104, 101, and 91). Case (n = 65) and control (n = 72) subjects who had no baseline PSA levels were excluded.

We cannot exclude entirely an alternative interpretation for the inverse association between selenium levels and prostate cancer risk among case subjects with increased baseline PSA levels only—that preclinical disease at baseline or latent tumor decreases selenium levels among case subjects with increased PSA levels. In previous studies, case subjects diagnosed during the first 2 *(12,19)* or the first 5 years *(14)* of follow-up were excluded because of this concern. However, because prostate cancers grow slowly and the disease has a long latency (e.g., more than a decade), excluding the first 5 years of follow-up may not be sufficient.

Our study has several limitations. One is the single assessment of selenium levels. However, a single measure of selenium in blood reasonably reflects long-term selenium intake and is relatively accurate in ranking selenium intake in population studies *(29)*. We also examined the long-term reproducibility of plasma selenium levels by assessing selenium concentrations at baseline and after 5 years in a subgroup of 48 randomly chosen healthy control subjects. The mean plasma selenium levels at these two time points were similar and correlated ($r = .55$;

Table 4. Odds ratios (ORs) and 95% confidence intervals (CIs) for prostate cancer for men enrolled in the Physicians' Health Study according to quintile of plasma selenium level by severity of disease and case subjects' baseline prostate-specific antigen (PSA) level*

	Severity of disease†			
	Stages A and B		Stages C and D	
	PSA ≤4 ng/mL	PSA >4 ng/mL	PSA ≤4 ng/mL	PSA >4 ng/mL
No. of case subjects/No. of control subjects	198/577	109/577	66/577	100/577
Quintile				
1	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
2	1.18 (0.72 to 1.95)	0.88 (0.48 to 1.65)	1.14 (0.50 to 2.58)	1.30 (0.70 to 2.40)
3	0.72 (0.41 to 1.27)	0.77 (0.41 to 1.45)	1.12 (0.48 to 2.62)	0.91 (0.47 to 1.75)
4	1.21 (0.74 to 1.98)	0.74 (0.39 to 1.43)	1.78 (0.84 to 3.78)	0.51 (0.24 to 1.12)
5	0.93 (0.55 to 1.56)	0.50 (0.24 to 1.04)	0.50 (0.18 to 1.39)	0.49 (0.22 to 1.08)
P_{trend}	.85	.06	.62	.01

*Unconditional logistic regression, adjusted for age at baseline, smoking status, and duration of follow-up (duration of follow-up for case subjects was years between baseline and diagnosis; duration of follow-up for control subjects was the same as that for corresponding case subjects); case subjects who had unknown disease stage or no baseline PSA levels (n = 113) were excluded.

†Disease stage was determined according to the modified Whitmore–Jewett classification scheme *(25)*. Stages A and B are considered localized disease and stages C and D are considered advanced disease.

$P<.001$), indicating that a single measurement of selenium in plasma is valid for reflecting the long-term selenium status for healthy individuals. Another limitation is that the cut point (October 1990) that we selected to define pre- and post-PSA eras was arbitrary. Case subjects diagnosed around 1990 may or may not have been screened for PSA levels and thus may be misclassified; however, this should not affect our conclusions because our results were fairly consistent by PSA era. We used unmatched analyses (unconditional logistic regression), adjusted for age, smoking status, and duration of follow-up in consideration of the case–control selection criteria and matching. This strategy can be considered as a strength of our study because, by including all the control subjects in all models, we gained greater statistical power and stability.

In summary, we found a statistically significant inverse association between pre-diagnostic plasma selenium levels and the risk of advanced prostate cancer. Among men with increased PSA levels at baseline, higher levels of plasma selenium were associated with a reduced risk of all prostate cancer. Although it is possible that undiagnosed prostate cancer reduces plasma selenium levels, our results—especially the inverse association between plasma selenium levels and the risk of advanced prostate cancer diagnosed in the post-PSA era—suggest that selenium may influence tumor progression. Randomized trials such as the Selenium and Vitamin E Cancer Prevention Trial (SELECT) will assess directly the efficacy of selenium in the prevention of prostate cancer *(31)*.

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