

SERUM SELENIUM AND RISK OF PROSTATE CANCER IN U.S. BLACKS AND WHITES

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Prostate cancer is the fourth most common cancer in men worldwide and the most common cancer in men in the United States, with reported incidence rates for U.S. blacks being the highest in the world. The etiology of prostate cancer and an explanation for the racial disparity in incidence in the United States remain elusive. Epidemiologic studies suggest that selenium, an essential trace element, may protect against the disease. To further explore this hypothesis, we measured serum selenium in 212 cases and 233 controls participating in a multicenter, population-based case-control study that included comparable numbers of U.S. black and white men aged 40–79 years. Serum selenium was inversely associated with risk of prostate cancer (comparing highest to lowest quartiles, OR = 0.71, 95% CI 0.39–1.28; *p* for trend = 0.11), with similar patterns seen in both blacks and whites. Cubic regression spline analysis of continuous serum selenium indicated a reduced risk of prostate cancer above concentrations of 0.135 µg/ml (median among controls) compared to a reference value set at the median of the lowest selenium quartile. Because both the selenoenzyme GPX and vitamin E can function as antioxidants, we also explored their joint effect. Consistent with other studies, the inverse association with selenium was strongest among men with low serum α-tocopherol concentrations. In conclusion, our results suggest a moderately reduced risk of prostate cancer at higher serum selenium concentrations, a finding that can now be extended to include U.S. blacks. Since selenium exposure varies widely throughout the world, further research on optimal concentrations for cancer prevention is justified.

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Key words: prostate cancer; selenium; vitamin E; biomarkers; race; diet; epidemiology

Prostate cancer is the fourth most common cancer among men worldwide,¹ with incidence rates highest in the United States, Canada, Australia, New Zealand and western and northern Europe.¹ In the United States, it is the most commonly diagnosed cancer and the second leading cause of cancer mortality among men.² U.S. black men bear a disproportionately heavy burden from this disease. With incidence rates over 50% higher than U.S. whites, they experience the highest incidence worldwide.³ The etiology of prostate cancer and an explanation for the racial disparity in incidence remain elusive. However, migrant studies and temporal shifts in incidence within countries suggest that modifiable factors, such as diet, could be involved.^{4–6}

Selenium is a trace element essential to human health. Dietary exposure to selenium comes mainly from cereals, meats and fish. Concentrations in food depend on local soil conditions and thus vary geographically, both internationally and in the United States.⁷ Populations living in some parts of the world, such as eastern Finland prior to selenium fortification, New Zealand and especially certain areas of China, ingest relatively little selenium and are at risk of deficiency. Conversely, selenium toxicity is possible in particularly seleniferous regions, such as other parts of China, Venezuela and the U.S. midwest.⁸

Selenium has been hypothesized to play a role in preventing cancer.⁷ Several ecologic studies have reported strong associations

between low regional exposure to selenium and increased cancer incidence or mortality.^{9–11} Subsequently, a limited number of analytic epidemiologic studies have provided mixed but encouraging evidence for a protective association with cancer in general and prostate cancer in particular.^{12,13} A randomized, placebo-controlled skin cancer prevention trial also reported a significant reduction in prostate cancer incidence among men given selenium supplements for 4.5 years.^{14,15}

To explore the reasons for the racial disparity in prostate cancer incidence in the United States, the NCI conducted a multicenter, population-based case-control study of prostate cancer that included comparable numbers of black and white men between the ages of 40 and 79 years. By purposely oversampling blacks, a population often underrepresented in epidemiologic studies, this design allowed risk patterns among blacks to be examined separately and in comparison to whites. Blood was collected and potential risk factors were assessed in detail by structured at-home interviews. In the present analysis, we investigated the risk of prostate cancer associated with serum concentrations of selenium.

MATERIAL AND METHODS

Study design

Subjects comprised a subset from a multicenter, population-based case-control study of 4 cancers that occur excessively in blacks, including multiple myeloma and cancers of the prostate, esophagus and pancreas.¹⁶ The study received institutional review board approval. Eligible cases were between 40 and 79 years of

Abbreviations: CI, confidence interval; GPX, glutathione peroxidase; NCI, National Cancer Institute; OR, odds ratio; QC, quality control; RR, relative risk; SEER, Surveillance, Epidemiology and End Results Program; SELECT, Selenium and Vitamin E Cancer Prevention Trial.

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age with histologically confirmed, incident prostate cancer diagnosed between August 1986 and April 1989. They were identified from records of hospitals covered by the population-based cancer registries for Atlanta, Georgia; Detroit, Michigan; and 10 counties in New Jersey. For each region, cases were selected based on a race- and age-stratified sampling scheme that oversampled blacks and younger men to ensure approximately equal numbers of men from each race and across a broad age range. Population-based controls were identified by either random-digit dialing¹⁷ (under age 65) or Health Care Financing Administration records (age 65 and older) and frequency-matched to the anticipated case distribution by region, race and 5-year age group.

After obtaining informed consent from participants, in-person structured interviews were conducted, usually in the subjects' homes. Questions were asked regarding demographics, family history of cancer, medical and sexual history, alcohol and tobacco use, diet and occupational history. Diet was ascertained *via* a 60-item food-frequency questionnaire containing a variety of foods consumed by U.S. blacks and whites.¹⁸ Subjects were asked to recall their usual frequency of consumption over their adult lives, excluding the past 5 years.

Study participation

Of 1,292 cases and 1,767 controls approached to participate in the study, 981 cases (479 blacks, 502 whites) and 1,315 controls (594 blacks, 721 whites) successfully completed the interview phase. The participation rate among cases was 76% overall (blacks = 78%, whites = 75%). After accounting for nonresponse in the initial phase of screening for eligibility among random-digit dialing contacts, response rates were for controls 71% for blacks and 68% for whites. A subset of these participants was selected to donate blood for further analyses. Cases were considered ineligible if they had undergone orchiectomy or had or were presently undergoing hormone treatment, chemotherapy or radiation therapy. A total of 483 (234 black, 249 white) cases were eligible and invited to participate. Of these, blood was successfully obtained from 127 black (54%) and 147 white (59%) cases. Eligible controls were selected to be frequency-matched to cases on region, race and age. A total of 467 (213 black, 254 white) controls were invited to participate. Blood was successfully collected from 137 black (64%) and 158 white (62%) controls. When considering both the interview and blood collection, overall participation rates for eligible subjects were as follows: black cases, 42%; black controls, 45%; white cases, 44%; white controls, 42%.

Because of budgetary constraints, laboratory assays were performed on a subset of cases and controls that had donated blood. The subset was balanced by age and race for each study center. After excluding 1 control with an unrealistically high serum selenium value (15 SDs from the mean among controls), 212 cases (101 blacks, 111 whites) and 233 controls (112 blacks, 121 whites) were included in the final analytic data set.

Blood collection and laboratory analysis

A phlebotomist visited each participating subject in his home and drew approximately 50 ml of blood. The median interval between prostate cancer diagnosis and blood draw was 3.7 months (ranging from 27 days to 2.3 years). For nutrient analyses, blood was collected in serum separator tubes. After allowing at least 30 min for clot formation, samples were refrigerated. Within 6 hr of blood collection, serum was separated by centrifugation and 0.5 ml aliquots were stored at -70°C .

In 1991, serum samples were analyzed for total selenium by neutron activation at the Massachusetts Institute of Technology Nuclear Reactor Laboratory. Because selenium emits γ -rays at multiple energies, the 2 most intense, those at 136 and 264 keV, were measured and averaged to improve accuracy. Samples consisting of 0.5 ml of serum were placed in polyethylene vials and heat-sealed in polyethylene bags.

QC was monitored by analyzing bovine liver selenium standards. Two samples were inserted along with 10 study samples in

each run. No evidence of temporal trends was noted upon visual inspection of the plotted data, and the variation for these standards met all requirements of the QC rules established by Westgard *et al.*¹⁹ The coefficient of variation was 6%.

Statistical analysis

Cases and controls were compared in terms of demographic and other factors using χ^2 , Student's *t*- or Fisher's exact test. Using Student's *t*-test, mean serum selenium concentrations were compared between cases and controls and, among controls only, between the races and regions.

For both stratified and unstratified analyses, serum selenium concentrations were categorized into quartiles based on the total distribution of controls. Unconditional logistic regression²⁰ was used to generate adjusted ORs and 95% CIs for prostate cancer risk, with the lowest quartile serving as the referent. To test for linear trend, a variable with values equal to the median among controls for each quartile was treated as continuous and tested in the model. When cases were stratified according to disease aggressiveness, each case group was compared to all controls using polychotomous logistic regression.²¹

Adjusted ORs for prostate cancer were estimated for continuous values of serum selenium in logistic regression analyses that included terms for a 4-knot cubic regression spline.²² These estimated ORs and 95% CIs were graphically displayed by serum selenium percentile, based on the distribution among controls of both races. To increase comparability with the analyses that generated ORs by serum selenium quartile, the reference value for these curves (OR = 1.00) was set at 12.5%, the midpoint of the lowest quartile among controls.

To evaluate confounding, suspected prostate cancer risk factors as well as other potential confounders suggested in the literature were screened. Variables included family history of prostate cancer, personal history of benign prostatic hyperplasia, personal history of vasectomy, daily alcohol consumption, current smoking status, number of cigarettes smoked per day, Quetelet's index, daily energy intake, intake of foods high in animal fat, education, income, ever vs. never married, month of blood draw, serum cholesterol, serum α -tocopherol and serum lycopene. Potentially confounding variables were added one at a time to models adjusted only for study design factors. The variable was considered a confounder if, upon addition to the model, the selenium ORs shifted in a consistent direction and the proportional change for at least one OR exceeded 10%. Confounding was further evaluated using forward and backward modeling, in which potentially confounding variables were added/subtracted sequentially. Because none of these variables confounded the selenium-prostate cancer relationship, all models were adjusted only for the study design factors: age collapsed into 10-year categories, race and region. Effect modification was assessed both by examining ORs across strata and by statistical significance testing of multiplicative interaction terms.

All statistical tests were 2-tailed, with $\alpha = 0.05$. The SAS (Cary, NC) system²³ was used for all analyses except the polychotomous logistic regression modeling, for which SUDAAN (Research Triangle Park, NC)²⁴ was used.

RESULTS

Of interviewed subjects asked to donate blood, participation was nearly equal by race (59% for blacks and 61% for whites). Subjects were more likely to participate if they were younger, lived in Atlanta vs. Detroit or New Jersey, had a positive family history of prostate cancer, earned a higher income or were more educated. However, participation by cases vs. controls did not vary across levels of these factors in consistent ways (Table I).

Among subjects who gave blood, cases and controls were compared in terms of study design variables and potential prostate cancer risk factors. For both races, cases were similar to controls

TABLE I—PARTICIPATION RATES BY SELECTED CHARACTERISTICS FOR INTERVIEWED CASES AND CONTROLS ASKED TO DONATE BLOOD FROM A U.S. MULTICENTER CASE-CONTROL STUDY, 1986–1989

	Cases (%)	Controls (%)
Overall participation	57	63
Race		
Blacks	54	64
Whites	59	62
Age (years)		
<50	67	75
50–59	58	65
60–69	59	63
70–79	53	59
Region		
Atlanta	89	85
Detroit	43	59
New Jersey	46	48
Family history of prostate cancer		
Positive	72	100
Negative	56	63
Highest education		
Grades 0–8	57	59
Grades 9–11	52	58
High school or equivalent	52	60
Some college	66	71
Annual income		
<\$15,000	51	58
\$15,000–34,999	55	74
\$34,000+	63	71

by region and educational achievement (Table II). Cases were slightly older and reported a family history of prostate cancer more frequently than controls for both races, though the differences were not statistically significant.

Cases had modestly lower mean serum selenium concentrations than controls in each race and region, though none of these case-control differences was statistically significant (Table III). Mean concentrations were significantly lower in black controls than white controls ($p = 0.05$). Controls from Atlanta had lower mean concentrations than those from either Detroit ($p < 0.0001$) or New Jersey ($p = 0.08$).

ORs by increasing serum selenium quartile as well as p values for trend are presented in Table IV for blacks and whites combined and for each race separately. With both races combined, an inverse association between prostate cancer risk and serum selenium was suggested (comparing the highest to lowest quartiles, OR = 0.71, 95% CI 0.39–1.28, p for trend = 0.11). This relationship was further analyzed by treating serum selenium as a continuous variable in a 4-knot cubic regression spline analysis. In Figure 1, predicted ORs are plotted by percentile of serum selenium. Starting at approximately the 50th percentile (corresponding to 0.135 $\mu\text{g/ml}$ of serum selenium), ORs fall below 1.00 and decrease monotonically thereafter, suggesting a protective association in the upper half of the serum selenium range.

When risk of prostate cancer by increasing serum selenium quartile was examined in each race separately, comparable inverse trends were noted (Table IV). Comparing highest to lowest quartiles, ORs were 0.68 for blacks and 0.70 for whites. Although the patterns were similar, the interaction between race and serum selenium concentration was statistically significant ($p = 0.04$), largely due to a divergence in the second quartile.

Blacks and whites were combined to evaluate effect modification by disease aggressiveness, age, region and current smoking status. Quartile cut-off points continued to be based on all controls. A stronger inverse relationship between prostate cancer and serum selenium was observed among those with nonaggressive disease than among those with aggressive disease (Table V). For all cases combined, the inverse association was particularly evident among older men (p for trend = 0.04) and current and past smokers.

Both vitamin E and selenium have been proposed to reduce the risk of cancer, possibly through a shared mechanism. Our data

suggest that the inverse association between serum selenium and risk of prostate cancer is more evident at lower ($<900 \mu\text{g/dl}$) serum α -tocopherol concentrations (comparing above to below the median of serum selenium, OR = 0.36, 95% CI 0.16–0.82) than higher ($>1,211 \mu\text{g/dl}$) serum α -tocopherol concentrations (OR = 0.86, 95% CI 0.44–1.66) (Table VI).

DISCUSSION

Prostate cancer rates vary substantially by race and geographic region, yet explanations remain elusive. Our data suggest an inverse association between serum selenium and risk of prostate cancer, with steady reductions in risk becoming apparent above serum selenium concentrations of 0.135 $\mu\text{g/ml}$. Our data also demonstrate generally similar patterns of risk for U.S. black and white men. While several other epidemiologic studies have addressed the hypothesis that selenium is protective for prostate cancer in various populations and with varying results, we examined the association among substantial numbers of U.S. blacks.

Perhaps the most persuasive evidence for a protective effect comes from a randomized, placebo-controlled clinical trial designed to test the ability of selenium supplements (200 $\mu\text{g/day}$) to reduce skin cancer incidence among 1,312 men and women living in a region of the United States with low levels of soil selenium.^{14,15} In terms of skin cancer, the trial was a disappointment. Nonetheless, after a mean of 4.5 years of treatment and approximately 6.2 years of follow-up, a 63% reduction in prostate cancer incidence ($p = 0.002$) was observed among those receiving selenium supplements.

Of 5 prospective observational studies that included relatively large numbers (>100) of prostate cancer cases, 3 reported inverse associations with selenium. Specifically, in a cohort of male health professionals, most of whom were white, investigators found that high toenail selenium levels were associated with a significantly lower risk of advanced prostate cancer (comparing the highest to lowest quintile, RR = 0.35) after several years of follow-up.²⁵ An analysis of white residents of Washington County, Maryland, indicated a similarly substantial inverse association between overall prostate cancer risk and prediagnostic toenail selenium levels (comparing highest to lowest quintiles, RR = 0.38),²⁶ as did a nested case-control study of serum selenium among Japanese-American men living in Hawaii (comparing highest to lowest quartiles, RR = 0.50).²⁷ However, an association between risk of prostate cancer and serum selenium was not noted in a prospective analysis of participants in a β -carotene–retinol lung cancer prevention trial.²⁸ A Finnish cohort of heavy smokers also reported no association between baseline selenium intake, including selenium from supplements, and risk of prostate cancer.²⁹ Exposure assessment in that study may have been complicated by selenium fortification of fertilizer in Finland, an area with low soil selenium concentrations.²⁹

Several other prospective studies examining this association have included results for fewer than 100 prostate cancer cases. Some investigators have reported lower prediagnostic concentrations of blood selenium among cases compared to noncases, though all but 1³⁰ failed to reach statistical significance, mostly due to the small numbers of cases.^{31–33} Others have found no evidence of an inverse association with prostate cancer risk.^{34,35} Among case-control studies, 1 comparing plasma selenium concentrations between cases of prostate cancer and benign prostate hyperplasia reported a statistically significant inverse association,³⁶ while 5 others reported null or slightly positive associations with selenium measured in either the diet or toenails.^{37–41}

Nomura *et al.*²⁷ discussed the possibility of a threshold level of selenium exposure above which protection is more apparent, noting that, using the lowest quartile as the referent, their data showed a lack of association in all quartiles except the highest. We also postulate that if such a threshold exists, it could help explain

TABLE II—DESCRIPTION BY SELECTED CHARACTERISTICS OF BLACK AND WHITE CASES AND CONTROLS FROM A U.S. MULTICENTER CASE-CONTROL STUDY, 1986–1989

	Blacks			Whites		
	Cases (n = 101)	Controls (n = 112)	p	Cases (n = 111)	Controls (n = 121)	p
Age (mean, years)	65	63	0.10 ¹	63	61	0.22 ¹
Region (%)						
Atlanta	38	39		30	34	
Detroit	25	31		35	38	
New Jersey	38	29	0.39 ²	35	28	0.51 ²
First-degree relative with prostate cancer (%)	6	2	0.15 ³	6	4	0.56 ³
At least a high school education (%)	34	38	0.57 ²	77	73	0.45 ²

¹Student's *t*-test was used to compare means between cases and controls.—²The χ^2 test was used to compare proportions between cases and controls.—³Fisher's exact test was used to compare proportions between cases and controls.

TABLE III—MEAN (SE) SERUM SELENIUM CONCENTRATIONS ($\mu\text{g/ml}$) BY RACE AND REGION FOR CASES AND CONTROLS FROM A U.S. MULTICENTER CASE-CONTROL STUDY, 1986–1989

	Number of cases/controls	Cases		Controls		p ¹
		Mean	SE	Mean	SE	
Race						
Black	101/112	0.132	0.025	0.134	0.021	0.61
White	111/121	0.135	0.021	0.140	0.028	0.13
Region						
Atlanta	71/85	0.125	0.017	0.128	0.021	0.28
New Jersey	77/67	0.135	0.025	0.138	0.026	0.49
Detroit	64/81	0.142	0.022	0.145	0.026	0.38

¹Student's *t*-test was used to compare means between cases and controls.

TABLE IV—PROSTATE CANCER ODDS RATIOS BY SERUM SELENIUM QUARTILES FOR BLACKS AND WHITES FROM A U.S. MULTICENTER CASE-CONTROL STUDY, 1986–1989

Quartile cut-off points ($\mu\text{g/ml}$)	Both races combined ¹			Blacks ²			Whites ²		
	Number of cases/ controls	OR	95% CI	Number of cases/ controls	OR	95% CI	Number of cases/ controls	OR	95% CI
≤ 0.119 (reference)	55/60	1.00		32/31	1.00		23/29	1.00	
0.120–0.135	73/58	1.35	0.81–2.56	30/37	0.77	0.38–1.56	43/21	2.52	1.16–5.46
0.136–0.150	47/58	0.88	0.51–1.51	24/23	1.02	0.47–2.23	23/35	0.78	0.35–1.72
0.151+	37/57	0.71	0.39–1.28	15/21	0.68	0.28–1.61	22/36	0.70	0.30–1.64
<i>p</i> for trend		0.11			0.14			0.51	

¹Adjusted for age, region and race.—²Adjusted for age and region.

inconsistencies in the literature since selenium exposure varies widely geographically. To investigate this possibility, we identified, to the best of our knowledge, all studies that assessed the relationship between prostate cancer risk and circulating (serum or plasma) selenium concentration. We excluded the study by Hardell *et al.*³⁶ since the control group consisted of cases of benign prostatic hyperplasia. Among 9 studies, including the present one,^{27,28,30–35} only 3 reported no evidence of an inverse association (Fig. 2). These were, in fact, the 3 with the lowest blood selenium concentrations among controls: from the southeastern United States, mean = 0.117 $\mu\text{g/ml}$;³⁵ from multiple centers across the United States, mean = 0.114 $\mu\text{g/ml}$;²⁸ and from Finland, mean = 0.058 $\mu\text{g/ml}$.³⁴ Additionally, in the skin cancer prevention trial, a protective effect for prostate cancer was observed among subjects whose mean serum selenium concentrations increased from a relatively low level of 0.114 to 0.190 $\mu\text{g/ml}$ as a result of supplementation.¹⁴ It may follow, therefore, that circulating selenium must reach certain concentrations to influence prostate carcinogenesis.

Our data suggest that the inverse association between risk of prostate cancer and serum selenium becomes stronger and reaches statistical significance at low serum concentrations of α -tocopherol. Likewise, in a cohort of U.S. health professionals, the inverse trend with toenail selenium was strengthened among subjects with lower intakes of vitamin E.²⁵ Other investigators have reported similar effect enhancement when examining the relationship between selenium and total cancer.^{33,34,42} SELECT, a large, random-

ized, placebo-controlled clinical trial that recently began enrolling 32,000 U.S. and Canadian men, will examine the independent and joint effects of these 2 nutrients and is designed to elucidate the potential synergy.⁴³

In evaluating effect modification, we also observed stronger inverse associations between prostate cancer risk and serum selenium among current and past smokers than never smokers. Similar findings were reported in an analysis conducted in a cohort of Japanese-American men living in Hawaii,²⁷ though not in a U.S. multicenter cohort of men at high risk for lung cancer.²⁸

Traditionally, it has been thought that the capacity of the selenoenzyme GPX to reduce peroxides that can cause cellular damage explained the importance of selenium in human carcinogenesis.⁷ Other proteins containing selenium might also protect against oxidative damage.⁴⁴ The overall inverse association we observed as well as the stronger associations seen at lower levels of α -tocopherol and among current and past smokers could be explained by this mechanism. Both selenium and α -tocopherol can protect cells from oxidative damage and, potentially, carcinogenesis.^{45,46} Selenium may, therefore, be more critical when vitamin E status is low. Furthermore, since cigarette smoke is known to cause oxidative damage, current and past smokers may receive greater benefit from high selenium levels. However, Neve⁴⁷ questioned whether selenium functions solely through GPX activity, demonstrating that human GPX activity did not increase above relatively low plasma

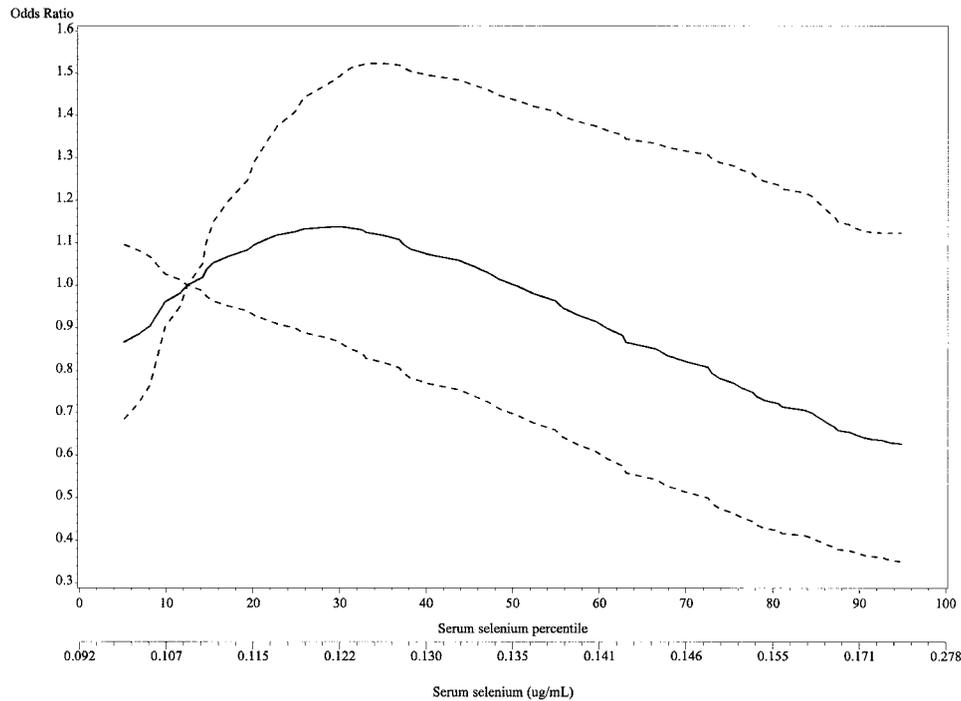


FIGURE 1 – ORs and 95% CIs by percentile of serum selenium from a U.S. multicenter case-control study, 1986–1989. Solid line, predicted OR for prostate cancer; dashed lines, upper and lower 95% confidence limits.

TABLE V – PROSTATE CANCER ODDS RATIOS BY SERUM SELENIUM QUARTILES, STRATIFIED BY DISEASE AGGRESSIVENESS, AGE, REGION AND SMOKING STATUS, IN A U.S. MULTICENTER CASE-CONTROL STUDY, 1986–1989

	Number of cases/controls	Quartile 1 (low) ¹ OR (reference)	Quartile 2 OR (95% CI)	Quartile 3 OR (95% CI)	Quartile 4 (high) OR (95% CI)	<i>p</i> for trend	<i>p</i> for interaction
Disease aggressiveness^{2,3}							
Nonaggressive	111/233	1.00	1.36 (0.72–2.54)	0.81 (0.41–1.62)	0.52 (0.24–1.13)	0.06	
Aggressive	65/233	1.00	0.94 (0.43–2.03)	0.84 (0.37–1.88)	0.75 (0.32–1.80)	0.49	NA
Age (years)⁴							
<70	144/166	1.00	1.34 (0.72–2.50)	0.82 (0.43–1.58)	0.92 (0.45–1.86)	0.52	
70+	68/67	1.00	1.53 (0.62–3.78)	1.02 (0.37–2.80)	0.32 (0.11–0.96)	0.04	0.56
Region⁵							
Atlanta	71/85	1.00	1.26 (0.58–2.77)	0.81 (0.33–1.96)	0.62 (0.16–2.39)	0.49	
New Jersey	77/67	1.00	1.19 (0.47–3.02)	0.99 (0.37–2.60)	0.48 (0.18–1.27)	0.12	
Detroit	64/81	1.00	1.58 (0.51–4.87)	0.81 (0.25–2.65)	0.84 (0.26–2.67)	0.38	0.86
Smoking status²							
Never smoker	66/68	1.00	1.45 (0.56–3.74)	0.92 (0.33–2.54)	0.94 (0.31–2.84)	0.85	
Past smoker	81/90	1.00	1.33 (0.56–3.15)	0.60 (0.22–1.60)	0.67 (0.25–1.78)	0.21	
Current smoker	65/75	1.00	1.23 (0.47–3.18)	1.21 (0.48–3.00)	0.60 (0.20–1.85)	0.46	0.92

¹Cut-off points, based on controls, were as follows: ≤ 0.119 , $0.120-0.135$, $0.136-0.150$, ≥ 0.151 $\mu\text{g}/\text{mL}$.²Adjusted for age, region and race.³Among cases, distributions by stage and grade, respectively, were 146 localized, 23 regional, 21 distant; 74 well-differentiated, 72 moderately differentiated, 39 poorly differentiated or undifferentiated. Stage and grade were combined to form categories of disease aggressiveness. After excluding 36 subjects due to missing information on grade and/or stage, “nonaggressive” disease included 111 cases with well or moderately differentiated grade and localized stage, and “aggressive” disease included 65 cases with poorly to undifferentiated grade and/or regional to distant stage. This system of categorization distinguishes between disease that is more vs. less likely to progress and become fatal.⁴Adjusted for region and race.⁵Adjusted for age and race.

selenium concentrations. Our data support this notion since inverse associations with prostate cancer were observed at serum selenium concentrations greater than those that apparently modulate GPX activity. Alternatively, cancer protection by selenium could be mediated by other mechanisms, including impairment of cellular proliferation through programmed cell death (apoptosis)^{48,49} and enhancement of immune function.⁵⁰

Our study had several strengths. In addition to the inclusion of a large number of U.S. blacks, laboratory reproducibility of sele-

mium measurement was excellent, with a coefficient of variation of 6% for QC material. Measuring circulating selenium as opposed to dietary intake likely characterized selenium status more accurately since the selenium content of food depends on the region where the food was grown.⁵¹

It is possible, but unlikely, that the inverse associations observed in our study resulted from bias and are, therefore, spurious. Although participation in the blood component of our study was around 45%, it was comparable for cases and controls overall and

TABLE VI—PROSTATE CANCER ODDS RATIOS FOR SERUM SELENIUM CONCENTRATIONS AT 3 DIFFERENT SERUM A-TOCOPHEROL LEVELS FROM A U.S. MULTICENTER CASE-CONTROL STUDY, 1986–1989

Serum α -tocopherol tertiles ($\mu\text{g/dl}$) ⁴	Number of cases/controls ¹	Low selenium ² OR (reference)	High selenium OR (95% CI) ³
Low	57/76	1.00	0.36 (0.16–0.82) ⁵
Medium	68/75	1.00	0.62 (0.30–1.27)
High	83/76	1.00	0.86 (0.44–1.66)

¹Ten subjects were excluded due to missing values for serum α -tocopherol. ²Median cut-off point, based on controls, was 0.135 $\mu\text{g/ml}$. ³Adjusted for age, region and race. ⁴Cut-off points, based on controls, were as follows: <900, 900–1,211, >1,211 $\mu\text{g/dl}$. ⁵ $p = 0.02$.

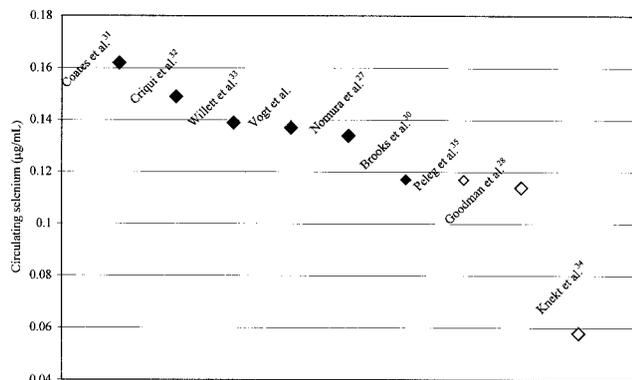


FIGURE 2—Mean circulating selenium concentrations among controls in studies examining the association between prostate cancer risk and serum or plasma selenium. Serum selenium was measured in all studies except Peleg *et al.*³⁵ and Brooks *et al.*³⁰ which measured plasma selenium. Vogt *et al.* is the present study. Solid squares, inverse association between prostate cancer risk and selenium suggested; open squares, inverse association between prostate cancer risk and selenium not suggested.

when stratified by race, age, region, family history of prostate cancer, income and education. Thus, differential participation is not likely to explain our results. Because blood was drawn from cases after diagnosis, it is also possible that the disease itself affected serum selenium levels. However, no decrease in serum selenium concentrations among cases was noted with increasingly aggressive grade or stage (0.131, 0.134 and 0.135 $\mu\text{g/ml}$ for well-differentiated, moderately differentiated and poorly/undiffer-

entiated disease, respectively, test for trend $p = 0.27$; 0.133, 0.132 and 0.137 $\mu\text{g/ml}$ for localized, regional and distant disease, respectively, test for trend $p = 0.57$). In addition, a protective effect from selenium has been suggested by several prospective studies and is corroborated by our findings.

To determine whether the cases included in our analysis were representative of incident prostate cancer across the United States, we compared the distribution of disease characteristics to national cancer statistics collected by SEER. For each race, the case distribution by stage was similar to the national data. However, a slightly higher proportion of both black and white cases had disease that was well-differentiated compared to SEER data (data not shown).^{52,53}

In summary, our results suggest that serum selenium is inversely associated with risk of prostate cancer, with risk reduction apparent at serum selenium concentrations above 0.135 $\mu\text{g/ml}$. This protective effect was suggested not only in U.S. whites but also in U.S. blacks. If evidence that selenium is protective continues to accumulate, there will be a need to determine the optimal concentration of selenium that avoids deficiency and toxicity while maximizing protection against cancer. Since selenium exposure varies widely around the world, public health recommendations would have to be carefully developed. Our findings are encouraging since the etiology of prostate cancer, a disease of worldwide impact, remains elusive, with few modifiable strategies.

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