Predictors of Serum Selenium in Cigarette Smokers and the Lack of Association with Lung and Prostate Cancer Risk[1]

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Abstract

Epidemiological studies have suggested that low levels of selenium are associated with a higher incidence of both lung and prostate cancer. We analyzed the selenium serum concentration in 356 Carotene and Retinol Efficacy Trial (CARET) participants who later developed lung cancer and 356 matched controls and in 235 prostate cancer cases and 456 matched controls. Serum samples were obtained a mean of 4.7 years before diagnosis for both tumor types. Controls were matched to cases by year of randomization, age, smoking status, treatment arm, exposure population (asbestos workers or cigarette smokers), and year of blood draw. In the control population ($n = 820$), significant predictors of low serum selenium concentration were current smoking status and East Coast locations of the study center. Overall, there was no significant difference in mean serum selenium in lung cancer cases *versus* controls (11.91 μg/dl *versus* 11.77 μg/dl) or prostate cancer cases *versus* controls (11.48 μg/dl *versus* 11.43 μg/dl). No statistically significant trend in odds ratio was seen across quartiles of serum selenium for lung cancer ($P = 0.49$) or prostate cancer ($P = 0.69$). In a subpopulation of 174 prostate cancer patients who had clinical and pathological staging material reviewed, there was no association between serum selenium and Gleason score or clinical or pathological stage. In the CARET population of current and former smokers consuming an *ad libitum* diet, the serum concentration of selenium was not a risk factor for either lung cancer or prostate cancer.

Introduction

Geographic studies have shown an inverse relationship between low selenium content in the local soil (which is hypothesized to be reflected in local foods, dietary intake, and serum concentrations) and cancer incidence rates (1, 2). These findings led to epidemiological studies of the association of cancer incidence with selenium concentrations in biological samples. In patients with lung and prostate cancer, findings have been conflicting. Even recent, well-designed, adequately powered, retrospective, nested case-control studies have been inconclusive. Yoshizawa *et al.* (3) studied toenail clippings from 181 men who later developed prostate cancer and reported an adjusted RR[3] of 0.35 (95% CI, 0.16–0.7) for the highest to lowest quintile of toenail selenium content. Hartman *et al.* (4) studied 317 prostate cancer cases who were participants in the Alpha-Tocopherol Beta-Carotene lung cancer prevention trial and found no association between dietary selenium and the later development of prostate cancer. Helzlsouer *et al.* (5) found no statistically significant association between toenail selenium and prostate cancer in 117 men in Washington County, MD. Nomura *et al.* (6) found an inverse association with serum selenium only in those with higher stage prostate cancer disease, in current or past smokers. Studies in individuals later developing lung cancer have also been divergent. Knekt *et al.* (7) reported an adjusted RR of 0.41 (95% CI, 0.17–0.94) for the highest *versus* the lowest quintile for serum selenium content in 95 Finnish smokers who developed lung cancer. But Comstock *et al.* (8) found no significant relationship between serum selenium concentrations and lung cancer in 258 never, former, and current smokers in Washington County, MD.

Although the epidemiological evidence has been inconclusive, there has been a growing body of laboratory studies that strengthen the theoretical basis for selenium as a cancer-inhibitory agent. *In vitro* studies suggest a mechanism for selenium via its role as an essential cofactor of the cellular enzyme glutathione peroxidase, as well as inhibition of cell proliferation and protein synthesis, stimulation of apoptosis, and interactions with retinoids and their receptors (9–14).

The strongest evidence for the potential efficacy of selenium as a cancer prevention agent has come from a randomized, double-blind, placebo-controlled clinical trial by Clark *et al.* (15). This trial was designed to test the effect of a dietary supplement of 200 μg of selenium as selenized yeast on skin cancer recurrence in a high-risk patient population. There was no effect on the primary skin cancer end point; however, secondary analyses noted a much lower incidence of multiple cancers on the active treatment arm, including decreases of 63% in the incidence of prostate cancer (RR, 0.37) and 46% in incidence of lung cancer (RR, 0.54). Although these findings

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[3] The abbreviations used are: RR, relative risk; CI, confidence interval; OR, odds ratio; CARET, Carotene and Retinol Efficacy Trial.

were observed on a secondary analysis and the numbers of end points were small, this study has revitalized interest in selenium supplementation as a potential cancer prevention agent. This renewed interest prompted us to study predictors of serum selenium in cigarette smokers and to assess the association with lung and prostate cancer incidence in 812 control, 356 lung cancer, and 235 prostate cancer CARET participants.

Materials and Methods

The Study Population. In the 1980s and 1990s, β-carotene was the dietary micronutrient with the most consistent evidence to suggest that it may act as a dietary cancer prevention agent (16, 17). Individuals with a high dietary intake of β-carotene-rich foods and those who had high serum concentrations of β-carotene had a 40–60% lower incidence of cancer, especially lung cancer, than those with a low dietary intake or low serum concentrations (18, 19). These findings were consistent across many epidemiological studies and were part of the evidence used to support the initiation of clinical trials testing the effect of supplemental β-carotene on the incidence of skin, colon, and lung cancer in high-risk individuals (20). One of these trials was CARET (21).

CARET is a multicenter randomized, double-blind, placebo-controlled, lung cancer chemoprevention trial of 25,000 IU/day retinol and 30 mg/day β-carotene. Eligible participants included asbestos workers who had occupational exposure to asbestos beginning 15 years or more before randomization with either a chest radiograph positive for asbestos-related disease or a work history in specific high-risk trades for 5 years, ages 45–74, and either current smokers or those who had quit within the previous 15 years; male and female cigarette smokers recruited from health insurance rolls and managed health care organizations were 50–69 years of age, had at least 20 pack years of cigarette smoking, and were either currently smoking or had quit within the previous 6 years. In all, 4,060 asbestos workers and 14,254 heavy smokers (44% women) were randomized.

The design of CARET called for active intervention until the end of 1997. At an interim analysis in late 1995, increased risks of both lung cancer incidence and cardiovascular disease mortality were observed in the active treatment arm. Because the results were similar to and confirmed the findings of the Alpha-Tocopherol Beta-Carotene lung cancer prevention trial in Finland (22), the CARET Steering Committee decided to end the active intervention 21 months early, in January 1996 (23). Participants for this analysis were followed to April 1999.

End Point Determination. When a cancer end point is reported, the medical records and pathology reports are obtained from the diagnosing hospital/physician. Central CARET pathology review is conducted on all lung cancer cases (the CARET primary end point). For prostate cancer, pathology reports from the diagnosing institution are reviewed. This may consist of a report of a prostate needle biopsy or a radical prostatectomy and lymph node dissection. End point materials are reviewed by three physician adjudicators. A consensus is required on the site of primary, histology, and date of diagnosis to consider the end point confirmed. A single physician (G. E. G.) abstracted the case for Gleason score (histological grade) and staging of prostate cancer, based on a review of surgical, pathological, and clinical records.

Design of This Study. As part of CARET, we collected and stored serum on all participants prior to randomization and then either yearly or every other year. Blood was collected in foil-covered Vacutainers at the time of the study center visits and was centrifuged to separate serum. Serum aliquots of 2 and 0.5 ml were placed in amber glass vials and stored at −25°C for a maximum of 2 weeks before being placed in long-term storage at −70°C.

Serum samples chosen for analysis were drawn 3 or more years prior to the date of reported diagnosis of lung and prostate cancer for 385 and 236 CARET participants, respectively, diagnosed prior to January 1999. Controls were matched to cases by randomization year, age group (5-year intervals), randomization smoking status, treatment arm, exposure population (asbestos workers or cigarette smokers), and year of blood draw. Control participants had follow-up time greater than or equal to the case follow-up time at cancer diagnosis. Lung cancer cases were matched with one control. Because of the lower number of prostate cancer cases, two controls were matched to each case to increase statistical power. Only one control each was available for five prostate cases. After laboratory analysis, 9 lung cancer cases and 20 controls were missing serum selenium results. The results for the corresponding matches for these samples were removed. Remaining for statistical analysis were 356 lung cancer cases matched to 356 controls. For prostate cancer, laboratory analysis was missing serum selenium results for 1 case and 1 control. We removed the control results for the case with missing serum selenium. It was discovered at this time that there were 8 occurrences in which the same control sample had been selected for 2 cases. In each occurrence, the control result was randomly matched to 1 of the 2 cases to which it had originally been matched. Remaining were 221 prostate cancer cases with 2 matched controls and 14 cases with 1 matched control for a total of 235 prostate cancer cases and 456 matched controls. To examine the demographics of serum selenium content in healthy CARET participants, we pooled the control samples from the lung and prostate cancer case-control studies. For this analysis, we included the 11 samples excluded from the matched analysis due to missing selenium results for the corresponding case and 17 additional cancer-free samples that were sent to the laboratory. Controls who were never smokers ($n = 11$) and former smokers at randomization who relapsed and started smoking prior to blood draw ($n = 9$) were dropped from the analysis. Remaining were 820 samples for the control-only analysis.

Selenium Analysis. Serum was analyzed by flameless atomic absorption (Perkin-Elmer 5000; Perkin-Elmer Corp., Norwalk, CT) using an electrodeless discharge lamp operating at $\lambda = 196.0$ nm and a l'Vov platform graphite furnace. Background correction was performed by the Zeeman method (24).

All standards, controls, and specimens were diluted 99:300 in 0.5% Triton X-100 (Sigma Chemical Co., St. Louis, MO), using a digital auto-dilutor (Hamilton Co., Reno, NV). The autosampler was programmed to deliver 20 μl of sample to the l'Vov platform, followed by 5 μl of 0.24% nickelous nitrate hexahydrate (Mallinckrodt Baker, Inc., Phillipsburg, NJ) in deionized water as the matrix modifier. The assay was calibrated using dilutions of a selenium standard (Aldrich, Milwaukee WI; 980 μg/ml of selenium in 1% HNO_3). A selenium standard was made, and different volumes of selenium were added to 5% bovine albumin (98% fraction V; Aldrich) to generate the different concentrations of selenium. The 5% bovine albumin without any selenium added was also assayed for the presence of selenium and determined to be selenium free. The standards and known College of American Pathologists (Northfield, IL) selenium samples were run and correlated within 2–3%.

Sample concentrations, reported in μg/dl, are the average

of duplicate measurements of separate serum aliquot. Concentrations were determined by calculation from a standard curve, prepared from duplicate measurements of six standard solutions of selenium-supplemented 5% BSA in saline, spanning a range of 0.00 to 48.82 μg/dl. Control samples at two concentration levels (prepared from normal and selenium-supplemented pooled human serum) were run with each batch of 12 samples. The batch was retested if either of the control values was outside ± 2 SDs of the mean of 20 consecutive interassay control measurements (26).

Statistical Methods. Univariate statistics (means and SDs) were used to describe the distributions of key factors influencing serum selenium values in this population. In the analysis of data for control subjects, tests for heterogeneity were obtained using analysis of variance. Least-squares regression models of serum selenium were fit using a single continuous predictor variable to test for trends. Statistically significant predictors at $P < 0.10$ from the univariate tests were used in an analysis of covariance model to obtain adjusted means and SEs. For the matched analysis, the lung and prostate cases and controls were stratified into quartiles based upon the respective control serum selenium distributions. Conditional logistic regression stratified on the matched set was used to obtain ORs of cancer and to test for linear trends. An ordinal score variable was created to test for a linear trend in ORs across serum selenium quartiles. Analyses were conducted using SAS Institute, Inc. software.

Results

Characteristics of the control-only population are summarized in Table 1. Ninety-three % were white, 85% were male, and 67% came from the heavy-smoker-exposure population. The sera analyzed were mostly drawn at the prerandomization visit (60%) and the year 2 visit (25%). At the time of the blood draw, 53% of the population were current smokers, and 39% reported using supplemental vitamins. Mean selenium concentrations were 5% higher in females ($P = 0.002$), 9% lower in blacks ($P = 0.006$), 3% lower in current smokers ($P = 0.005$), and 9% higher in heavy smokers compared with the asbestos-exposed population ($P < 0.0001$). Selenium levels differed among recruitment study centers, with participants at the Baltimore study center having the lowest mean level (9.60 μg/dl) and Seattle participants having the highest (12.11 μg/dl). Also detected was a modest inverse correlation between selenium concentration and year of blood draw (test for trend, $P = 0.06$). We examined the years since persons had quit smoking among the heavy-smoker population and found selenium levels were 7–10% higher in participants who had not been smoking for >4 years compared with current smokers (test for trend, $P < 0.0001$).

Adjusted means and SEs are shown in Table 2. All statistically significant variables in the univariate analysis except the years since persons quit smoking among the heavy-smoker population were included in the model. The associations between selenium levels and exposure population, study center, and smoking status found in the univariate analysis were observed in the multivariate analysis as well. Gender and race, however, were no longer statistically significant predictors of selenium concentrations after adjusting for other covariates. Controlling for treatment arm in those participants who had a postrandomization blood sample showed no or negligible changes in the adjusted means. Years since persons quit smoking was examined in a separate analysis of covariance model restricted to participants in the heavy-smoker population (data not shown). In this model, each additional year of quitting

Table 1 Characteristics of control participants and mean serum selenium (μg/dl) concentrations

	n (%)	Mean (SD)	$P^{a,b}$
Gender			0.002[a]
Male	695 (85)	11.49 (1.96)	
Female	125 (15)	12.09 (2.02)	
Race			0.006[a]
White	760 (93)	11.63 (1.92)	
Black	35 (4)	10.53 (3.06)	
Other/Unknown	25 (3)	11.62 (1.76)	
Exposure population			0.0001[a]
Asbestos	269 (33)	10.93 (2.06)	
Heavy smoker	551 (67)	11.90 (1.86)	
Treatment arm			0.73[a]
Active	415 (51)	11.61 (1.99)	
Placebo	405 (49)	11.56 (1.98)	
Blood draw age group (yr)			0.90[b]
44–49	6 (1)	12.86 (1.83)	
50–54	93 (11)	11.46 (2.12)	
55–59	182 (22)	11.66 (1.70)	
60–64	228 (28)	11.56 (1.97)	
65–69	247 (30)	11.52 (2.16)	
70–74	56 (7)	11.72 (1.75)	
75–79	8 (1)	11.82 (2.67)	
Study center			0.0001[a]
Baltimore[c]	67 (8)	9.60 (2.10)	
Irvine	83 (10)	10.76 (1.57)	
New Haven[c]	55 (7)	10.99 (1.93)	
Portland	224 (27)	11.98 (1.75)	
San Francisco[c]	47 (6)	10.80 (1.57)	
Seattle	344 (42)	12.11 (1.89)	
Blood draw year			0.06[b]
1985	6 (1)	12.50 (3.11)	
1986	23 (3)	12.43 (1.77)	
1987	28 (3)	12.06 (1.89)	
1989	89 (11)	11.64 (2.04)	
1990	116 (14)	11.26 (2.43)	
1991	136 (17)	11.45 (2.09)	
1992	191 (23)	11.82 (1.80)	
1993	156 (19)	11.61 (1.67)	
1994	69 (8)	11.00 (1.81)	
1995	6 (1)	11.99 (2.25)	
Blood draw visit			0.94[b]
Baseline	491 (60)	11.57 (2.07)	
Year 2	202 (25)	11.67 (1.74)	
Year 3	15 (2)	11.34 (2.17)	
Year 4	55 (7)	11.50 (2.40)	
Year 5	17 (2)	11.38 (1.67)	
Year 6	17 (2)	12.00 (1.35)	
Year 7	12 (1)	11.84 (1.52)	
Year 8	11 (1)	10.77 (1.34)	
Blood draw supplemental vitamin use[d]			0.81[a]
Yes	307 (39)	11.60 (2.11)	
No	487 (61)	11.56 (1.92)	
Blood draw smoking status			0.005[a]
Current	434 (53)	11.40 (1.88)	
Former	386 (47)	11.79 (2.07)	
Years quit smoking[e]			0.0001[a]
Current smokers	338 (61)	11.68 (1.82)	
<1	28 (5)	11.77 (1.67)	
1–2	27 (5)	12.04 (2.02)	
2–3	27 (5)	11.94 (2.07)	
3–4	30 (5)	11.89 (1.80)	
4–5	29 (5)	12.87 (1.79)	
5–6	27 (5)	12.49 (2.07)	
6–7	16 (3)	12.55 (1.67)	
>7	29 (5)	12.54 (1.80)	

[a,b] *P* from test for: [a] equal means; or [b] from trend test.
[c] Asbestos-exposed participants only; no smoker population.
[d] Twenty-six participants were missing supplemental vitamin usage at blood draw.
[e] Years persons had quit smoking at blood draw for the heavy-smoker-exposure population only ($n = 551$).

Table 2 Adjusted mean serum selenium (μg/dl) concentration in control participants

	Adjusted mean (SE)[a]	P^b
Gender		0.30
Male	11.55 (0.07)	
Female	11.75 (0.17)	
Race		0.99
White	11.58 (0.07)	
Black	11.57 (0.32)	
Other/Unknown	11.64 (0.37)	
Exposure population		0.06
Asbestos	11.31 (0.16)	
Heavy smokers	11.72 (0.09)	
Study center		0.0001
Baltimore	9.89 (0.27)	
Irvine	10.76 (0.22)	
New Haven	11.20 (0.28)	
Portland	11.96 (0.13)	
San Francisco	10.99 (0.30)	
Seattle	12.01 (0.10)	
Blood draw smoking status		0.0001
Current	11.34 (0.09)	
Former	11.86 (0.09)	

[a] Adjusted means from model including all variables with $P < 0.1$ in Table 1 except years quit smoking for the heavy-smoker population. Adjusted means for blood draw year ($P = 0.28$) not given because this was a linear variable in the model.
[b] P for test of heterogeneity.

smoking was associated with a 0.15 μg/dl increase in serum selenium (test for trend, $P < 0.0001$).

Characteristics of the matched lung and prostate cancer case-control populations are shown in Table 3. In the lung cancer case-control population, participants were predominantly white (cases, 94%; controls, 95%), male (cases, 71%; controls, 66%), and in the heavy-smoker-exposure population (cases, 73%; controls, 73%); and 72% were current smokers at baseline. Fifty-five % of cases and of controls were in the active arm. Serum from both cases and controls was mainly drawn at baseline (57%) and the year 2 visit (26%). The mean time from blood draw to diagnosis of lung cancer was 4.7 years. In the prostate cancer case-control population, the case and control participants were primarily white (91%) and in the heavy-smoker-exposure population (60%), whereas 51% of cases and controls were former smokers at baseline. Forty-seven % of cases and 46% of controls were in the active arm. Serum for prostate cancer cases and controls was mainly drawn at baseline (59% and 60%, respectively) and the year 2 visit (24%). The mean time from blood draw to diagnosis of prostate cancer was 4.7 years.

Table 4 presents means of serum selenium concentrations by case-control status and ORs of lung cancer by quartile of control selenium distribution overall, by gender, baseline smoking status, exposure population, and treatment arm. No statistically significant difference in means was seen in the overall analysis or any subgroup analysis. No statistically significant association between selenium and the OR of lung cancer was observed for the fourth quartile compared with the first quartile of serum selenium overall or for any subgroup. In the point estimates, high serum selenium among males was directly associated with higher OR of lung cancer (OR, 1.53; 95% CI, 0.83–2.82; P (trend), 0.26), whereas among females, serum selenium had an inverse association with the OR of lung cancer (OR, 0.76; 95% CI, 0.29–2.01; P (trend) = 0.75). In the asbestos-exposure population, the test for trend across the quartiles in the OR had a borderline statistically significant increasing linear trend ($P = 0.05$). No other statistically significant trends were observed. To consider the effect of time between blood draw and diagnosis of lung cancer, we divided matched pairs into subgroups based upon the timing of the case blood draw [4 years ($n = 372$), 5 years ($n = 238$), 6+ years ($n = 102$)]. Conditional logistic regression models showed negligible differences in quartile point estimates among subgroups (data not shown).

Table 5 presents means of serum selenium concentrations

Table 3 Characteristics of the lung and prostate cancer case-control study participants

	Lung cancer		Prostate cancer	
	Case (%)	Control (%)	Case (%)	Control (%)
Gender				
Male	254 (71)	236 (66)	235 (100)	456 (100)
Female	102 (29)	120 (34)		
Race				
White	333 (94)	337 (95)	215 (91)	415 (91)
Black	13 (4)	8 (2)	11 (5)	28 (6)
Other/Unknown	10 (3)	11 (3)	9 (4)	13 (3)
Exposure population[a]				
Asbestos	95 (27)	95 (27)	94 (40)	181 (40)
Heavy smoker	261 (73)	261 (73)	141 (60)	275 (60)
Intervention arm[a]				
Active	196 (55)	196 (55)	111 (47)	212 (46)
Placebo	160 (45)	160 (45)	124 (53)	244 (54)
Age group (yr)[a]				
44–49	4 (1)	4 (1)	4 (2)	7 (2)
50–54	52 (15)	52 (15)	41 (17)	81 (18)
55–59	80 (22)	80 (22)	65 (28)	129 (28)
60–64	122 (34)	122 (34)	61 (26)	119 (26)
65–69	93 (26)	93 (26)	59 (25)	111 (24)
70–74	5 (1)	5 (1)	5 (2)	9 (2)
Study center				
Baltimore	24 (7)	26 (7)	25 (11)	39 (9)
Irvine	34 (10)	32 (9)	30 (13)	49 (11)
New Haven	20 (6)	19 (5)	24 (10)	35 (8)
Portland	105 (29)	94 (26)	47 (20)	118 (26)
San Francisco	13 (4)	15 (4)	12 (5)	33 (7)
Seattle	160 (45)	170 (48)	97 (41)	182 (40)
Baseline smoking status[a]				
Current	255 (72)	255 (72)	109 (46)	213 (47)
Former	101 (28)	101 (28)	119 (51)	232 (51)
Never			7 (3)	11 (2)
Randomization year[a]				
1985	6 (2)	6 (2)	7 (3)	9 (2)
1986	33 (9)	33 (9)	24 (10)	42 (9)
1987	37 (10)	37 (10)	12 (5)	26 (6)
1988	1 (<1)	1 (<1)	1 (<1)	2 (<1)
1989	42 (12)	42 (12)	16 (7)	32 (7)
1990	80 (22)	80 (22)	66 (28)	128 (28)
1991	75 (21)	75 (21)	47 (20)	94 (21)
1992	50 (14)	50 (14)	36 (15)	72 (16)
1993	27 (8)	27 (8)	18 (8)	35 (8)
1994	5 (1)	5 (1)	8 (3)	16 (4)
Year of blood draw[a]				
Baseline	203 (57)	203 (57)	139 (59)	274 (60)
Year 2	91 (26)	91 (26)	56 (24)	111 (24)
Year 3	6 (2)	6 (2)	6 (3)	11 (2)
Year 4	28 (8)	28 (8)	14 (6)	26 (6)
Year 5	8 (2)	8 (2)	5 (2)	9 (2)
Year 6	7 (2)	7 (2)	7 (3)	12 (3)
Year 7	7 (2)	7 (2)	5 (2)	8 (2)
Year 8	6 (2)	6 (2)	3 (1)	5 (1)

[a] Matching variable.

Table 4 Mean and risks of lung cancer by quartile of control selenium (μg/dl) distributions[a]

	Overall	Gender		Baseline smoking status			Exposure population		Treatment arm	
		Male	Female	Former	Current		Asbestos	Heavy smoker	Placebo	Active
Mean (SD)										
Case	11.91 (1.96)	11.70 (1.87)	12.42 (2.09)	12.07 (1.96)	11.85 (1.96)		11.33 (1.71)	12.12 (2.00)	11.93 (2.01)	11.90 (1.92)
Control	11.77 (1.85)	11.58 (1.76)	12.14 (1.96)	11.99 (1.87)	11.68 (1.83)		10.88 (1.82)	12.09 (1.75)	11.69 (1.79)	11.84 (1.89)
ORs[b] (95% CI)										
Q1	1.00	1.00	1.00	1.00	1.00		1.00	1.00	1.00	1.00
Q2	1.02 (0.66–1.56)	1.35 (0.80–2.28)	0.57 (0.19–1.68)	0.85 (0.36–2.02)	1.08 (0.66–1.77)		1.07 (0.53–2.17)	0.92 (0.53–1.58)	0.68 (0.36–1.29)	1.37 (0.77–2.43)
Q3	0.93 (0.57–1.48)	1.18 (0.66–2.08)	0.38 (0.12–1.19)	1.04 (0.43–2.52)	0.89 (0.53–1.50)		1.72 (0.73–4.07)	0.71 (0.41–1.23)	0.71 (0.36–1.39)	1.14 (0.63–2.06)
Q4	1.20 (0.77–1.88)	1.53 (0.83–2.82)	0.76 (0.29–2.01)	1.19 (0.49–2.88)	1.21 (0.71–2.04)		2.50 (0.96–6.47)	0.93 (0.54–1.60)	1.35 (0.70–2.61)	1.09 (0.60–1.98)
P (trend)	0.49	0.26	0.75	0.57	0.64		0.05	0.71	0.32	0.40

[a] Quartiles of serum selenium (μg/dl) distribution: Q1 (6.39–10.55); Q2 (10.56–11.76); Q3 (11.77–12.93); and Q4 (12.94–17.23).
[b] OR from conditional logistic regression model stratified on year of randomization, age at randomization within 5-year intervals, smoking status at randomization, intervention arm, exposure population, and blood draw visit.

by case-control status and OR of prostate cancer by quartile of control selenium distribution overall, by baseline smoking status, exposure population, and treatment arm. No statistically significant difference in means was seen in the overall analysis or any subgroup analysis. No statistically significant association between selenium and the OR of prostate cancer was observed for the fourth quartile compared with the first quartile of serum selenium overall or for any subgroup. In the point estimates, serum selenium in current smokers at baseline was associated with increased odds of prostate cancer (OR, 1.38; 95% CI, 0.73–2.59; *P* (trend) = 0.29), whereas in former smokers at baseline it had an inverse association with increased odds of prostate cancer (OR, 0.82; 95% CI, 0.43–1.55, *P* (trend) = 0.65). No statistically significant trends across quartiles were observed. To consider the effect of time between blood draw and diagnosis of prostate cancer, we divided matched pairs into subgroups based upon the timing of the case blood draw [4 years (cases, 115; controls, 219), 5 years (cases, 83; controls, 165), 6+ years (cases, 37; controls, 72)]. Conditional logistic regression models showed negligible differences in quartile point estimates among subgroups (data not shown).

Table 6 shows the quartile of selenium distribution among the 175 participants with prostate cancer who had Gleason scores recorded in their medical records and the 114 participants for whom accurate staging (either clinical or pathological) could be determined. No statistically significant association between selenium and the odds of prostate cancer was observed for the fourth quartile compared with the first quartile of serum selenium overall or for any subgroup. No statistically significant linear trend in the OR of cancer across the four quartiles of serum selenium concentration was found.

Discussion

The best method to measure an individual's selenium status is not firmly established. Investigators have estimated dietary selenium intake and have measured serum and toenail selenium concentrations. Each of these sources has its advantages (25). However, there is no consensus among investigators, and conflicting results have been seen with each type of analysis. CARET has available both serum and a food frequency questionnaire, each collected every other year. Because it is well known that dietary selenium calculated from food frequency questionnaires poorly predicts serum selenium concentration, we chose to use serum selenium. In our analyses, we also found that estimates of dietary selenium from food frequency questionnaires had negligible correlation (−0.03) with serum selenium values (data not shown).

It is known that selenium supplementation can raise serum selenium (15, 26). The more common use of selenium supplements in recent years could lead to higher selenium serum concentration in recently accrued participants. Although this study selected cases and controls based on year of blood draw, we wanted to confirm that the potential use of selenium supplementation in more recent years would not raise the mean selenium concentration in our population. In this study, 84% of our blood samples were collected between 1989 and 1991. At the time of the blood collection, 39% of CARET participants were taking multivitamins. Individual selenium supplements were available at that time, but it was not commonly included in multivitamin and mineral preparations (27, 28). Although we did not document the specific use of selenium supplements, we found no correlation between serum selenium and multivitamin use, and, contrary to our concerns, serum selenium concentrations in our controls actually showed a decreasing trend over

Table 5 Mean and risks of prostate cancer by quartile of control selenium (μg/dl) distributions[a]

	Overall	Baseline smoking status		Exposure population		Treatment arm	
		Former/Never	Current	Asbestos	Heavy smoker	Placebo	Active
Mean (SD)							
Case	11.48 (1.96)	11.59 (1.85)	11.36 (2.09)	11.22 (1.91)	11.65 (1.99)	11.30 (1.87)	11.69 (2.05)
Control	11.43 (2.04)	11.67 (2.14)	11.15 (1.89)	11.01 (2.13)	11.70 (1.92)	11.47 (2.08)	11.38 (2.00)
ORs[b] (95% CI)							
Q1	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Q2	0.85 (0.53–1.35)	1.03 (0.53–1.99)	0.68 (0.35–1.33)	0.86 (0.42–1.73)	0.82 (0.44–1.53)	0.82 (0.45–1.48)	0.89 (0.43–1.83)
Q3	1.08 (0.69–1.71)	1.33 (0.70–2.52)	0.85 (0.43–1.66)	1.11 (0.55–2.25)	1.03 (0.56–1.88)	0.88 (0.46–1.66)	1.40 (0.74–2.68)
Q4	1.02 (0.65–1.60)	0.82 (0.43–1.55)	1.38 (0.73–2.59)	1.26 (0.65–2.46)	0.88 (0.48–1.61)	0.75 (0.41–1.36)	1.52 (0.78–2.79)
P (trend)	0.69	0.65	0.29	0.42	0.86	0.40	0.12

[a] Quartiles of serum selenium (μg/dl) distribution: Q2 (5.07–10.12); Q2 (10.13–11.25); Q3 (11.26–12.59); and Q4 (12.60–21.96).
[b] OR from conditional logistic regression model stratified on year of randomization, age at randomization within 5-year intervals, smoking status at randomization, intervention arm, exposure population, and blood draw visit.

Table 6 Risks of prostate cancer, by grade and stage, by quartile of control selenium (μg/dl) distributions

	Gleason scores[a]		Stage of cancer[b]	
	Low	High	Early	Advanced
n	97	78	77	37
OR (95% CI)[c]				
Q1	1.00	1.00	1.00	1.00
Q2	0.71 (0.32–1.61)	1.26 (0.58–2.74)	0.38 (0.15–0.94)	0.90 (0.27–2.98)
Q3	1.44 (0.70–2.95)	0.90 (0.41–1.96)	0.91 (0.43–1.90)	0.50 (0.15–1.73)
Q4	1.36 (0.69–2.67)	0.76 (0.34–1.71)	0.77 (0.37–1.59)	1.07 (0.37–3.06)
P (trend)	0.17	0.35	0.96	0.93

[a] Gleason scores 7 and greater were classified in the high group [quartiles of serum selenium (μg/dl) distribution: Q1 (7.59–10.13); Q2 (10.14–11.47); Q3 (11.48–12.46); and Q4 (12.47–21.96)] and scores 6 and lower in the low group [quartiles of serum selenium (μg/dl) distribution: Q1 (5.07–10.10); Q2 (10.11–11.24); Q3 (11.25–12.78); and Q4 (12.79–17.60)].
[b] Advanced stage of cancer includes pathological stages 3 ($n = 23$) and 4 ($n = 5$) and clinical stages 3 ($n = 4$) and 4 ($n = 5$). Early stage quartiles of serum selenium (μg/dl) distribution: Q1 (5.07–10.26); Q2 (10.27–11.44); Q3 (11.45–12.97); and Q4 (11.98–17.60). Late stage quartiles of serum selenium (μg/dl) distribution: Q1 (7.74–9.89); Q2 (9.90–11.45); Q3 (11.46–12.44); and Q4 (12.45–21.96).
[c] OR from conditional logistic regression model stratified on year of randomization, age at randomization within 5-year intervals, smoking status at randomization, intervention arm, exposure population, and blood draw visit.

time (Table 1). These findings support that the use of supplemental selenium was low among CARET participants.

The large size of the CARET control population has permitted us to describe the determinants of serum selenium in cancer-free current and ex-smoker participants. Among the 820 current or past smoker control participants, we found no association between selenium serum concentration and gender, race, or exposure (asbestos-exposed or cigarette smoker) population. Comparing control participants who had postrandomization blood sampling with those who were sampled prior to randomization, there was no effect of the intervention agents. There was, however, a significant difference in the serum concentration of selenium between current smokers (11.34 μg/dl) and former smokers (11.86 μg/dl). The serum concentration of selenium increases the longer the individual abstains from smoking. These findings were independent of diet and are similar to those we (and others) have reported for selenium and other micronutrients, including the tocopherols, carotenoids, and retinoids (29–33). As with other micronutrients, the mechanism of the association with smoking is unknown, potentially reflecting dietary intake and micronutrient absorption and clearance.

The location of CARET participants at study centers located in several different parts of the United States also allowed us to reexamine the association of serum concentrations of selenium with different geographic areas. Overall, there was a statistically significant difference in selenium concentrations across study centers ($P < 0.0001$). The populations recruited at study centers located in the Northwest (Portland, OR and Seattle, WA) had the highest serum selenium levels with adjusted means of 11.96 and 12.01 μg/dl, respectively. The California study centers had intermediate levels with Irvine, CA, at 10.76 μg/dl, and San Francisco, CA, at 10.99 μg/dl The study center in Baltimore, MD had the lowest adjusted mean serum concentrations of selenium, 9.89 μg/dl, whereas the study center in New Haven, CT had an adjusted mean of 11.20 μg/dl. These latter two study centers are fairly closely situated yet had widely divergent serum concentrations. All these findings correlate poorly with the reported soil content of selenium, because the west coast states and the New England states are reported to both be low selenium areas (1). Our findings illustrate that serum selenium poorly reflects local soil selenium content in the CARET population. Differences in the participant populations at CARET study centers and consumption of nonlocally produced foods may be part of the explanation of these findings. Because of the wide origin of consumed foods, it may be time to reexamine the role soil content and locally grown foods play in determining serum selenium. It is important to point out that our study did not include never-smokers but only current or ex-smokers. CARET was a lung cancer prevention study and recruited only persons at high risk for that disease. The association found in our control population may not reflect those seen in a never-smoker population.

In general, the serum selenium concentrations we describe are similar to those reported in both the Clark study (15) and the

Table 7 Nested case-control studies of prediagnosis serum or toenail selenium concentrations in lung or prostate cancer

Author (date)	Site	Cancer	Sample size	Serum (toenail) selenium	RR[a]	P[b]
Lung cancer						
Nomura *et al.* (34), 1987	Hawaii	Lung	71	12.54 μg/dl	1.1	0.46
		Control	293	12.49 μg/dl		
Comstock *et al.* (8), 1997	United States	Lung	258	10.8 μg/dl[c]	0.65	0.08
		Control	515	11.0 μg/dl		
Knekt *et al.* (7), 1998	Finland	Lung	95	5.32 μg/dl	0.41	.046
		Control	190	5.78 μg/dl		
Ratnasinghe *et al.* (35), 2000	China	Lung	108	4.65 μg/dl	1.2	0.52
	Tin mines	Control	216	4.50 μg/dl		
CARET (2001)	United States	Lung	356	11.91 μg/dl	1.2	0.49
		Control	356	11.77 μg/dl		
Prostate cancer						
Yoshizawa *et al.* (3), 1998	United States	Advanced prostate	181	(0.82 ppm)[d]	0.49	0.11
		Control	181	(0.96 ppm)		
Ghadirian *et al.* (36), 2000	Canada	Prostate	83	(0.91 ppm)	1.14	0.62
		Control	82	(0.91 ppm)		
Nomura *et al.* (6), 2000	Hawaii	Prostate	249	12.99 μg/dl	0.50	0.02
		Control	249	13.41 μg/dl		
Helzlsouer *et al.* (5), 2000	United States	Prostate	117	(0.77 ppm)	0.58	0.27
		Control	233	(0.79 ppm)		
CARET (2001)	UA	Prostate	235	11.48 μg/dl	1.02	0.69
		Control	456	11.43 μg/dl		

[a] RR for highest to lowest quartile or quintile.
[b] *P* is a test for trend.
[c] Reported as ppm.
[d] Reported as μg/g.

Comstock study (8). Nomura *et al.* (6) reported serum selenium concentrations of 12.8 μg/dl in prostate cases and 13.1 μg/dl in healthy controls; although they did not report their results by smoking status, approximately one-third of their cases and controls were never smokers. Their serum selenium concentrations are 10–15% higher than those seen in our study. Their inclusion of never smokers and dietary differences in Japanese-Americans living in Hawaii compared with a primary Anglo-European-American population living in the Continental United States may explain some of these differences.

The major finding of this report is the lack of an association between prediagnostic serum concentrations of selenium and the later diagnosis of either lung cancer or prostate cancer. The results in lung cancer were independent of gender, smoking status (either former or current), or the population of CARET participant (asbestos worker or heavy smoker). These findings agree with the 4 lung cancer studies reported previously (Table 7).

With regard to prostate cancer risk, both Helzlsouer *et al.* (5) and Hartman (4) found no statistically significant association between prostate cancer and toenail and dietary selenium, respectively. However, the studies of Nomura *et al.* (6) and Yoshizawa *et al.* (3) were conflicting. Nomura *et al.* (6) measured serum selenium in never, current, and ex-smokers and found a significant inverse association between serum selenium and prostate cancer incidence only in the current and past smokers. We did not find similar associations in our study, which included only current and ex-smokers. They had a total of 162 prostate cancer cases, whereas our study had 235. A significant difference between these studies was the interval between blood draw and cancer diagnosis. The Nomura study had a mean of 12.4 years from the time of serum sampling to cancer diagnosis, whereas our trial had a mean of 4.7 years between blood sample and prostate cancer diagnosis (Table 7).

Yoshizawa *et al.* (3) studied toenail selenium content in 181 cases of advanced prostate cancer (stages C and D) in the Health Professionals Follow-Up study and found an OR of 0.49 (*P* for trend, 0.11; Ref. 3). In that population when the authors controlled for family history of prostate cancer, body mass index, calcium intake, diet, prior vasectomy, and geographic region, the OR fell to 0.35 (*P* for trend, 0.03). They did not report their results in early stage (A and B) prostate cancer. In a similar study, Ghidirian *et al.* (36) reported toenail selenium in a case control study in 83 prostate cancer cases and 82 matched controls and found no association ($P = 0.62$). They did not report stage or histological grade of disease (36). To determine whether our finding would be modified by stage or histological grade, we completed a similar analysis. Although the required documentation for complete clinical or pathological staging was not available on all CARET participants, we were able to obtain a Gleason score on 174 cases and to complete pathological or clinical staging on 114 cases. We found no association between serum selenium and prostate cancer incidence by either Gleason score or stage.

Our findings suggest that, in a population of current and former cigarette smokers, serum selenium is not a risk factor for lung or prostate cancer. Studies of the association between disease incidence and nutrients can only address an association between disease and the range of serum concentrations that occur in the population studied. However, these studies are frequently used as rationale to select micronutrients to test in clinical trials for cancer prevention activity. Our results suggest that in current and former smokers, a selenium supplementation trial that modifies the serum concentration of selenium to the upper quartile of that seen in an unsupplemented population is unlikely to affect or reduce lung cancer or prostate cancer incidence. Observational studies such as ours are not useful in hypothesizing whether supraphysiological supplementation of nutrients may have cancer prevention activity. Oral supplementation can easily raise serum and tissue concentration of micronutrients such as selenium to high levels and can cause pharmacological and toxic effects (37). It is important to emphasize that the "dose/response" relationship of most nutrients

and their interaction with other nutrients are not known. Supplementation in amounts above those usually occurring in the diet can lead to results not predicted by observational studies. A striking example of the failure of these studies to predict the outcomes of a clinical intervention are the β-carotene trials. The epidemiological studies were consistent in showing that higher serum concentrations of β-carotene (in an unsupplemented population) were associated with a lower incidence of lung cancer. However, the intervention trials that administered β-carotene in doses 5–10 times the median intake in the diet led to results opposite those predicted, a higher incidence of lung cancer in high-risk populations. Epidemiology studies showing an inverse relationship between a nutrient and cancer incidence should not be used as predictors of efficacy, let alone safety, of supraphysiological supplementation but only as a potential predictor for supplementation with doses within those obtainable by dietary modification alone. Intervention trials of high-dose supplementation require careful monitoring for side effects and broad categories of disease incidence, not just the end point of interest.

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Predictors of Serum Selenium in Cigarette Smokers and the Lack of Association with Lung and Prostate Cancer Risk

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