Serum Selenium and Subsequent Risk of Prostate Cancer[1]

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Abstract

It is suspected that selenium is protective against prostate cancer. To test this hypothesis, we conducted a nested case-control study in a cohort of 9345 Japanese-American men examined between 1971 and 1977. At the time of examination, a blood specimen was obtained, and the serum was frozen. After a surveillance period of more than 20 years, 249 tissue-confirmed incident cases of prostate cancer were identified. Their stored sera and those of 249 matched controls were measured for selenium levels. Odds ratios for prostate cancer, based on quartiles of serum selenium levels, were determined using the General Estimating Equations approach. The multivariate odds ratio for the highest quartile was 0.5 (95% confidence interval, 0.3–0.9) with a two-sided *P* for trend of 0.02. The inverse association was more notable for cases with advanced disease and for cases diagnosed 5–15 years after phlebotomy. However, the association was mainly present in current or past cigarette smokers rather than nonsmokers, which leads to caution in the interpretation of the results.

Introduction

Selenium is a nutritionally essential trace element with anticarcinogenic properties. It is a constituent of several enzymes, including some with antioxidant functions: the glutathione peroxidases and thioredoxin reductase, which remove hydroperoxides formed during oxidative metabolism, thereby reducing the potential for oxidative damage to DNA, proteins, and polyunsaturated membrane phospholipids (1). Supranutritional doses of selenium compounds have also been shown to inhibit tumorigenesis induced by chemical or viral agents or by transplantation in a large number of studies using animal models (2). Human epidemiological investigations have been less conclusive but have generally supported the plausibility of antitumorigenic effects of selenium for at least some cancers (2).

There have been only a few controlled prevention trials to test the hypothesis that selenium can be protective against cancer in humans. Studies conducted in China suggested that selenium supplementation reduced liver cancer incidence (3) and, together with β-carotene and vitamin E, reduced stomach cancer mortality (4). In the United States, a randomized, double-blind, cancer prevention trial was done in which 1312 patients with a history of basal cell or squamous cell carcinomas of the skin were given either 200 μg of selenium or a placebo. The investigators reported the lack of a protective effect of selenium against recurrent skin cancer (5). However, the incidence of carcinomas, especially carcinomas of the lung, colorectum, and prostate, was lower in the treatment group. A subsequent report highlighted the observation that there were 35 incident cases of prostate carcinoma in the placebo group, but only 13 prostate carcinoma cases in the selenium supplementation group (6).

A recent study strengthened the case that selenium may be protective against prostate cancer (7). Toenail clippings were collected from 33,737 men in the Health Professional Follow-Up Study. Toenails are regarded as being useful in reflecting the average intake of selenium over many months (8). After a 7-year observation period, the researchers found that high selenium levels in toenails were associated with a reduced risk of advanced prostate cancer in 181 patients. In this study, the controls were matched to the cases on smoking status because past investigators have reported that cigarette smoking is a predictor of lowered selenium levels (9–11).

A single serum measurement of selenium also correlates well with selenium intake (8). Therefore, several prospective studies have investigated the relation of serum selenium levels to the subsequent incidence of cancers at different sites (12–19). Three of the studies included cases of prostate cancer that, when combined, totaled just 75 cases in all (17–19). The largest study reported no association (17), whereas the two smaller studies showed a nonsignificant inverse association of serum selenium with prostate cancer (18–19).

The purpose of the present study was to further investigate the relation of serum selenium levels to prostate cancer risk. We conducted a nested case-control study among Japanese-American men who provided a serum sample and have been followed prospectively for over 20 years to identify 249 incident cases of prostate cancer.

Materials and Methods

Study Population. Between 1965 and 1968, 8006 Japanese-American men were examined by the Honolulu Heart Program on the Hawaiian island of Oahu. They were born between 1900 and 1919 and were approximately 45–68 years of age at the time of examination. Approximately 6 years later, 6860 of these men returned for another round of examination between 1971 and 1975. At that time, a nonfasting venous blood sample was obtained. The sera were stored at −75°C, and serum samples were available on 6811 (99%) of the 6860 men recruited for the study.

The 6860 men were asked to name their brothers at the time of their reexamination. As a result, 3843 additional broth-

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Table 1 Characteristics of prostate cancer cases and matched controls

Characteristics	Cases (n = 249)	Controls (n = 249)	Two-sided P^a
Born in United States (%)	88.4	85.5	0.42
Buddhist/Shinto religion (%)	67.5	68.7	0.79
High school education (%)	57.8	49.8	0.07
Married once (%)	88.3	86.7	0.69
Alcohol use (%)	76.3	75.1	0.83
Mean systolic blood pressure (mm/Hg)	135.7	137.9	0.23
Mean serum cholesterol (mg/dl)	218.3	217.8	0.92
Mean body mass index (kg/m^2)	23.8	24.0	0.40

[a] The exact binomial probability test for matched sample was used for comparing proportions; a paired t test was used for comparing means.

Table 2 Age-adjusted ORs[a] and 95% confidence intervals for prostate cancer by cigarette smoking

Cigarette smoking history	No. of cases/ controls	ORs	95% Confidence interval
Nonsmoker	87/98	1.0	
Past smoker	86/83	1.2	0.8–1.8
Current smoker	76/67	1.3	0.8–2.0
1–30 pack-years	20/16	1.4	0.7–2.9
>30 pack-years	56/51	1.2	0.8–2.0

[a] ORs and 95% confidence intervals were estimated by the Generalized Estimating Equations approach to correct for intracluster correlation.

Table 3 ORs[a] for prostate cancer by quartile of serum selenium levels

Selenium quartile[b] (ng/ml)	No. of cases/ controls	ORs	95% CI	Adjusted ORs[c]	95% CI
1 (<119.3)	75/62	1.0		1.0	
2 (119.3 < 130.6)	64/63	0.9	0.5–1.5	0.9	0.5–1.4
3 (130.6 < 147.2)	72/62	0.9	0.6–1.6	1.0	0.6–1.6
4 (≥147.2)	38/62	0.5	0.3–0.9	0.5	0.3–0.9
Two-sided P for trend		0.02		0.02	

[a] ORs and 95% confidence intervals (CIs) were estimated by the Generalized Estimating Equations approach to correct for intracluster correlation.
[b] Quartiles were based on the cutpoint value of the controls.
[c] ORs were adjusted for cigarette smoking history (nonsmoker, past smoker, or current smoker) in addition to age (by matching).

ers were identified who were born between 1889 and 1938. Of these, 2553 (66% of the total) were subsequently recruited and examined between 1975 and 1977. A nonfasting venous blood sample was also obtained from 2534 of the examined brothers and stored at −75°C.

The data collected on these men included birthplace, marital status, religion, education, history of alcohol use, cigarette smoking history, blood pressure, and body mass index, based on weight (kg)/height (m^2). Serum cholesterol values were determined by the AutoAnalyzer N-24A method. A total of 28 of the 9345 men had been diagnosed with prostate cancer before their examination and were thus excluded from the study.

To identify cases of prostate cancer occurring among the men during the study, discharge records of all general hospitals on Oahu were monitored. To reduce the possibility of missing diagnosed cases, a computer linkage file was established with the Hawaii Tumor Registry, a member of the Surveillance, Epidemiology and End Results Program of the National Cancer Institute. The data should be nearly complete because only 2.5% of the 6860 reexamined men could not be located on Oahu during a survey completed in 1993.

There were 360 cases of prostate carcinoma diagnosed between 1972 and 1995 and confirmed by examination of tissue obtained surgically or by biopsy. An additional 26 cases were diagnosed clinically but were not confirmed histologically and were excluded from the study. Because resources were not sufficient to measure serum selenium levels in all 360 cases and their controls, a table of random numbers was used to identify the 249 tissue-confirmed incident cases.

The severity of disease was divided into three categories: (*a*) occult, in which tumors were found incidental to TURs[3] in no more than three of all totally embedded tissue chips; (*b*) localized, defined as clinical tumors confined to the prostate or found incidentally in more than three TUR chips; and (*c*) advanced, defined as tumors extending beyond the capsule of the prostate gland. There were 62 occult, 120 localized, and 64 advanced cases identified in this study. The severity of disease could not be determined for three cases.

Each case patient was matched with one control subject from the study. The controls were selected so that the members of each case-control pair were born within 1 year of each other, except for eight pairs (median difference, 1.3 years), and were examined within 1 month of each other, except for 15 pairs (median difference, 1.5 months). They were also matched on whether they were among the 6811 original cohort men or among the 2534 brothers. Each control subject was alive and did not have any cancer diagnosis at the time of the diagnosis of their matched case. Therefore, death was not a competing risk in this study.

The frozen sera were sent in dry ice to Cornell University (Ithaca, NY) for analysis. The laboratory technician could not distinguish sera of cases from those of controls and analyzed them in a random fashion.

Laboratory Analysis. Selenium was determined in serum by automated electrothermal atomic absorption spectrophotometry using pyrolytically coated graphite tubes on an instrument (VARIAN Spectra AA-600; Walnut Creek, CA) equipped with an electrodeless discharge lamp and automatic Zeeman-effect background correction. Samples were mixed with 3 volumes of a matrix modifier solution (1.25% Ni[NO_3]2.6$H_2$0, 0.09% PdCI, and 0.1% Triton X-100). For each analysis, 20 μl of the serum-matrix modifier solution, followed by 5 μl of a solution of reducing agent (3% hydroxylamine), were delivered to the graphite tube by the autosampler. Absorption was measured at 196.3 nm with a 2.0 nm slit during step 8; signal peak area was calibrated automatically using aqueous solutions of Na_2Se0_3 as standards. The limit of detection of this method is about 25 pg of selenium; using the volumes described above, this yielded a detection limit of about 20 ng selenium/ml serum. Quality control was effected using multiple aliquots of exhaustively analyzed human serum as external control samples, with a coefficient of variation of 7% (for duplicate analyses) being used as the criterion for acceptance of all sample results. That criterion was derived experimentally using the variance components analysis as described previously (20).

Data Analysis. We used the binomial probability test, which is the exact test counterpart of the McNemar test (21), and the paired t test to compare, respectively, the proportion and mean value between cases and their matched controls (Table 1).

[3] The abbreviations used are: TUR, transurethral resection; OR, odds ratio.

Table 4 ORs[a] for prostate cancer by serum selenium levels[b], stratified by age at diagnosis, time interval between examination and diagnosis, severity of disease, and cigarette smoking history

Characteristic	No. of cases	Quartile 2	Quartile 3	Quartile 4	Two-sided *P* for trend
		OR (95% CI)	OR (95% CI)	OR (95% CI)	
Age at diagnosis[c]					
≤75 years	151	0.8 (0.4–1.8)	1.1 (0.5–2.6)	0.7 (0.3–1.6)	0.19
>75 years	98	1.0 (0.5–2.2)	0.8 (0.4–1.7)	0.8 (0.3–1.8)	0.48
Interval since exam[c]					
5–15 years	142	0.9 (0.5–1.8)	1.0 (0.5–1.8)	0.4 (0.2–0.9)	0.03
>15 years	88	0.8 (0.4–1.9)	1.1 (0.5–2.7)	0.7 (0.3–1.6)	0.52
Severity of disease[c]					
Occult	62	0.4 (0.1–1.1)	0.5 (0.2–1.4)	0.4 (0.1–1.2)	0.19
Localized	120	1.1 (0.5–2.2)	1.2 (0.6–2.4)	0.8 (0.4–1.8)	0.76
Advanced	64	1.0 (0.4–2.8)	0.9 (0.4–2.5)	0.3 (0.1–0.8)	0.01
Smoking history[d]					
Nonsmoker	87	0.6 (0.3–1.5)	1.3 (0.6–3.0)	0.8 (0.4–1.9)	0.93
Past smoker	86	1.3 (0.5–3.2)	0.7 (0.3–1.6)	0.5 (0.2–1.1)	0.03
Current smoker	76	0.9 (0.4–2.1)	0.9 (0.4–2.1)	0.2 (0.1–0.8)	0.02

[a] ORs and 95% confidence intervals (CIs) were estimated by the Generalized Estimating Equations approach to correct for intracluster correlation.
[b] Quartiles were based on the cutpoint value of the controls. Quartile 1 (lowest) was used as the reference group.
[c] Adjusted for cigarette smoking history (nonsmoker, past smoker, or current smoker) in addition to age (by matching).
[d] Adjusted for age because the age-matched case-control pairs were not retained in the subgroups.

Because serum selenium showed a discernibly skewed distribution, we compared the median serum selenium level between cases and matched controls by the Wilcoxon's signed rank test.

The risk of prostate cancer associated with cigarette smoking (Table 2) and serum selenium (Tables 3 and 4) was assessed by the OR estimated by the generalized linear model, of which the response variable is binomial, and the link function is logit (22). Because some of the men in our study sample are brothers who are likely to be correlated in the risk for prostate cancer, we used the Generalized Estimating Equations approach, specifying an exchangeable "working" correlation matrix to correct for possible intracluster correlation (23, 24).

The serum selenium values were categorized into quartiles according to the frequency distribution of the matched controls to create a set of binary indicator variables with the lowest category as the reference group. These indicator variables were used as explanatory variables in the generalized linear model. The test for trend was performed using the quartile frequency class midpoints as an explanatory variable, and the score statistic was used to assess the two-sided statistical significance.

Results

The mean age of the 249 prostate cancer cases and their matched controls at time of their examination was 61.2 years, and their ages ranged from 44.0–85.1 years. The average interval from exam to diagnosis was 12.4 years for the cancer patients. The average age at time of diagnosis was 73.6 years for the cases.

A comparison of cases and controls by their demographic characteristics and laboratory values is presented in Table 1. The two groups were similar in birthplace, religion, marital status, alcohol use, blood pressure, serum cholesterol, and body mass index. More cases than controls had a high school education, but the difference was not statistically significant.

Table 2 shows the relation of cigarette smoking to prostate cancer risk in this study population. Both past and current smokers had a higher risk compared with nonsmokers, but the association was not statistically significant. There was also no dose-response relationship for current smokers.

The serum selenium values ranged from 72.8–205.0 ng/ml in the prostate cancer cases and from 77.1–227.7 ng/ml in their controls. The median serum selenium value was 128.0 ng/ml in cases and 131.6 ng/ml in the controls, which was not statistically significant (two-sided $P = 0.07$ by Wilcoxon's signed rank test). There was a greater difference in the two groups in their mean values, which was 129.9 ng/ml in cases and 134.1 ng/ml in controls (two-sided $P = 0.02$ by paired *t* test, based on the log-transformed serum selenium data).

Table 3 gives the ORs for prostate cancer by quartile of serum selenium values. The risk was lowest in the highest quartile level, which had an OR of 0.5 (95% confidence interval, 0.3–0.9). The two-sided *P* for trend using the Generalized Estimating Equations approach was 0.02. Because current cigarette smokers have been found to have somewhat low serum selenium levels (9), we adjusted for current cigarette smoking status, as shown in Table 3. The results were very similar.

In Table 4, the cases were separated according to age at diagnosis, time interval since examination, severity of disease, and cigarette smoking history. The 19 cases who were diagnosed within 5 years of their examination were not included in the time interval analysis to lessen the effect of undiagnosed prostate cancer at time of phlebotomy. The median serum selenium value was 125.1 ng/ml in the 19 cases and 132.9 ng/ml in their controls (two-sided $P = 0.34$).

With adjustment for cigarette smoking history, the ORs for prostate cancer in the highest quartile were statistically significant for cases diagnosed 5–15 years after examination (OR = 0.4) and for the advanced cases (OR = 0.3). In the subgroup analysis by cigarette smoking history, the inverse association was mainly present among current smokers and past smokers (two-sided *P* for trend = 0.02 and 0.03, respectively).

Discussion

Japanese men living in Hawaii have an average prostate cancer incidence rate of 64.2 per 100,000 per year, which is clearly lower than the rate of 108.2 among Caucasian men in Hawaii (25). However, Japanese men living in Hawaii have a prostate cancer risk that is significantly higher than that of Japanese men living in Hiroshima, Japan, who have an average incidence rate of 10.9 per 100,000 per year. These data provide support that

environmental factors have influenced the difference in rates between Japanese men in Hawaii and Hiroshima.

Serum selenium was inversely related to the risk of prostate cancer in our study population. The association was strongest for the 64 patients whose tumor extended beyond the prostate gland, supporting the clinical relevance of the association. Among the 62 occult cancer cases, there was also an inverse association, but it was not statistically significant. These cases were usually diagnosed incidentally after a TUR for benign prostatic hypertrophy.

To minimize the possible effects of undiagnosed prostate cancer lowering the selenium levels, patients diagnosed within the first 5 years of follow-up were excluded. The inverse association persisted, especially in patients who were diagnosed 5–15 years after recruitment into the study. Because the cases and controls came from the same identified population, this provided confidence in the comparability of the controls to the cases. This was supported by the similarities in characteristics not expected to differ between the two groups, such as birthplace, religion, education, marital status, blood pressure, and serum cholesterol.

Statistically, the Generalized Estimating Equations approach was used to correct for intracluster correlation because 2534 men in the investigation were brothers of the original group of 6860 cohort men recruited into the study. In point of fact, there were just five pairs of brothers who were both cases, four pairs of brothers who were both controls, and seven pairs of brothers who were either a case or a control. There were no instances of three brothers in the study. As a result, ORs and confidence intervals estimated by conditional logistic regression (which does not correct for intracluster correlation) produced virtually identical results to those found in Tables 2–4 (data not shown).

Although previous studies have suggested that the concentration of selenium in the blood reflects the levels of dietary selenium intake (26, 27), none of them measured selenium intake directly. This was done in an investigation in which 77 free-living adults saved duplicate portions of all foods and beverages consumed on at least four separate days and provided at least two blood samples. The correlation coefficient between selenium intake and a single serum selenium measure was 0.74, after deattenuation to adjust for the effect of within-person variation in intake (8). This suggests that a single serum test to rank subjects according to long-term selenium intake yields reasonably accurate results.

There have been just three prospective serum studies that have separated out cases of prostate cancer and studied them in association with selenium levels. There were only 51, 13, and 11 prostate cancer patients included in these reports. The largest investigation found no association among residents in Finland, which is noted for its low availability of selenium (17). The two smaller studies, conducted in the United States, reported lower serum selenium levels in prostate cancer cases compared with controls, but they were not statistically significant (18, 19). A strength in the current investigation is that it included 249 cases who were identified after 20 or more years of follow-up.

The recommended daily allowance of selenium is 70 μg in men (7). It enters the food supply primarily through plants at geographically variable rates dependent on the selenium concentrations in the soil and through animal products (28). It is found mainly in grains, fish, poultry, and meats (29). Although the average intake of selenium in our study population is not known, the mean serum selenium level in controls (134 ng/ml) was comparable to the mean of 126–136 ng/ml reported among controls in studies conducted in Norway (16), the United States (19), and the Netherlands (12). In contrast, average serum selenium levels ranged from 54–62 ng/ml among male controls in studies done in Finland (14, 15, 17). Our data further suggest that the possible protective effect of serum selenium levels occurs mainly in persons who have values greater than 147 ng/ml because the ORs varied little among those with lower selenium measurements.

The inverse association between serum selenium and prostate cancer in our study was present mainly in current and past smokers. This was an unexpected finding because most large cohort studies of cigarette smoking do not report an association with prostate cancer (30). However, two relatively recent prospective surveys found a mildly positive increase in prostate cancer risk among cigarette smokers (31, 32), and a third prospective study reported that recent cigarette smokers had an increased risk for metastatic or fatal prostate cancer (33).

Lung cancer, a disease strongly related to cigarette smoking, had a weakly inverse association with serum selenium in several studies (15–18), but other reports have not supported this finding (34, 35). Most of these studies adjusted for the effects of cigarette smoking and did not investigate the association of serum selenium and lung cancer separately by smoking categories. When researchers did this in measuring toenail selenium concentration, they found that the inverse association of selenium levels with lung cancer was present for heavy smokers, light smokers, past smokers, and nonsmokers, but it was not statistically significant in any of the four subgroups (36).

Two studies have shown that persons with an elevated selenium level have a low risk of prostate cancer. These subjects participated in the selenium supplementation prevention trial against recurrent carcinoma of the skin (6) or the Health Professional Follow-up Study (7). However, the inverse association was not analyzed separately by smoking history in these reports.

The function of selenium in antioxidant enzymes (glutathione peroxidases and thioredoxin reductase) makes it inviting to consider this function as the basis of a linkage between selenium status and cigarette smoking because the latter is known as a source of oxidative stress (37, 38). However, few, if any, of the subjects in the present study had serum selenium levels that would suggest suboptimal expression of glutathione peroxidase activity; only two cases had serum selenium concentrations less than 85 ng/ml, which Neve (39) has shown is the threshold above which there is maximal expression of selenoenzyme. Because greater selenium levels are not expected to increase the expression of selenoenzymes, it must be considered unlikely that the suggested protective effect associated with the relatively high selenium levels in this population relates to differences in antioxidant enzymes. Furthermore, the lack of a strongly positive association between smoking and prostate cancer risk in our data dictates that caution be exercised in interpreting the results. Additional studies are needed to determine whether there is an inverse association between serum selenium and prostate cancer, and whether this association is present mainly in cigarette smokers.

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