ORIGINAL INVESTIGATION

Serum Selenium Levels and All-Cause, Cancer, and Cardiovascular Mortality Among US Adults

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Background: Selenium, an essential trace element involved in defense against oxidative stress, may prevent cancer and cardiovascular disease. We evaluated the association between selenium levels and all-cause and cause-specific mortality in a representative sample of US adults.

Methods: Serum selenium levels were measured in 13 887 adult participants in the Third National Health and Nutrition Examination Survey. Study participants were recruited from 1988 to 1994 and followed up for mortality for up to 12 years.

Results: The mean serum selenium level was 125.6 ng/mL. The multivariate adjusted hazard ratios comparing the highest (≥130.39 ng/mL) with the lowest (<117.31 ng/mL) serum selenium level tertile were 0.83 (95% confidence interval [CI], 0.72-0.96) for all-cause mortality, 0.69 (95% CI, 0.53-0.90) for cancer mortality, and 0.94 (95% CI, 0.77-1.16) for cardiovascular mortality. However, based on spline regression models, the association between serum selenium levels and all-cause and cancer mortality was nonlinear, with an inverse association at low selenium levels (<130 ng/mL) and a modest increase in mortality at high selenium levels (>150 ng/mL). There was no association between serum selenium levels and cardiovascular mortality.

Conclusions: In a representative sample of the US population, we found a nonlinear association between serum selenium levels and all-cause and cancer mortality. Increasing serum selenium levels were associated with decreased mortality up to 130 ng/mL. Our study, however, raises the concern that higher serum selenium levels may be associated with increased mortality.

Arch Intern Med. 2008;168(4):404-410

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SELENIUM IS AN ESSENTIAL trace element involved in defense against oxidative stress through selenium-dependent glutathione peroxidases and other selenoproteins.[1,2] In addition, selenium may have anticarcinogenic effects not related to its antioxidant properties. Therefore, selenium has been hypothesized to prevent cancer and cardiovascular disease,[2,3] and meta-analyses of observational studies have documented inverse associations between selenium levels and lung cancer,[4] prostate cancer,[5,6] and coronary heart disease.[7]

Many of the studies of selenium and chronic disease end points, however, have been conducted in countries with much lower selenium levels compared with that in the United States. Estimated selenium intake in the United States ranges from 60 to 220 µg/d,[8] higher than the recommended dietary allowance for healthy adults (55 µg/d).[9] Current recommendations on selenium intake are based on optimizing the activity of plasma glutathione peroxidases, which is maximized at serum or plasma selenium levels of 70 to 90 ng/mL (to convert to micromoles per liter, multiply by 0.0127). In the United States, the median serum selenium level among participants in the Third Nutrition and Health Examination Survey (NHANES III) was 124 ng/mL, and most participants (99%) had serum selenium levels of greater than 95 ng/mL.[9] At these levels, the health benefits of higher selenium intake are unclear.

The NHANES III measured serum selenium in a representative sample of the US population in 1988 through 1994. Mortality follow-up is available for this cohort through December 2000. Our objective was to evaluate the prospective association of serum selenium with all-cause and cause-specific mortality in the general US population using NHANES III data.

METHODS

STUDY POPULATION

The NHANES III used a stratified, multistage probability cluster design to provide data representing the noninstitutionalized US population.[10] The present study was based on the 16 469 adults aged 20 to 90 years who participated in NHANES III interviews and physical examinations. We excluded 288 participants

who were pregnant at the time of the survey, 1107 with missing information on serum selenium, 1172 with missing values on other variables of interest, and 15 participants with no follow-up information. The present cohort analysis was thus based on 13 887 NHANES III participants.

BASELINE DATA COLLECTION

Participants were interviewed in NHANES III to obtain information on age, sex, race/ethnicity, education, family income, menopausal status, smoking, alcohol consumption, physical activity, and use of vitamin and/or mineral supplements.[11] Height and weight were measured, and body mass index was calculated by dividing weight in kilograms by height in meters squared. Hypertension was defined as systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, a self-report of a physician diagnosis, or current medication use.

Laboratory procedures and quality control methods have been described in detail.[12] Serum selenium was measured using atomic absorption spectrometry under extensive quality control procedures.[12-14] The limit of detection was 8 ng/mL. The interassay coefficients of variation ranged from 4.0% to 6.4%.

Diabetes mellitus was defined as a fasting plasma glucose level of at least 126 mg/dL, a nonfasting plasma glucose level of at least 200 mg/dL (to convert to millimoles per liter, multiply by 0.0555), self-report of a physician diagnosis of diabetes, or current use of insulin. Hypercholesterolemia was defined as a serum total cholesterol level of at least 240 mg/dL (to convert to millimoles per liter, multiply by 0.0259), self-report of a physician diagnosis, or current medication use. Glomerular filtration rate was estimated by the Modification of Diet in Renal Disease Study formula after alignment of the serum creatinine concentration with the assay used to develop the formula.[15,16]

MORTALITY FOLLOW-UP

For each study participant, follow-up extended from the date of the survey until the date of death, the date when they turned 90 years of age, or December 15, 2000, whichever occurred first. Vital status was ascertained through the National Death Index, and the cause of death was determined on the basis of the underlying cause of death listed on the death certificate.[17] The *International Classification of Diseases, Ninth Revision (ICD-9)* was used for deaths occurring from 1988 through 1998, and the *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) was used for deaths occurring from 1999 through 2000. In addition to all-cause mortality, we studied the following specific causes of death: cancer (*ICD-9* codes 140-209 and *ICD-10* codes C00-C97), colorectal cancer (*ICD-9* codes 153-154.1 and *ICD-10* codes C18-C20 or C26), lung cancer (*ICD-9* codes 162.2-162.9 and *ICD-10* code C34), prostate cancer (*ICD-9* code 185 and *ICD-10* code C61), cardiovascular disease (*ICD-9* codes 390-434 and 436-459 and *ICD-10* codes I00-I99), coronary heart disease (*ICD-9* codes 410-414 and 429.2 and *ICD-10* codes I20-I25), and stroke (*ICD-9* codes 430-434 and 436-438 and *ICD-10* codes I60-I69).

STATISTICAL ANALYSIS

Study participants were divided in tertiles of serum selenium levels based on the weighted population distribution. The hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause and cause-specific mortality associated with each tertile of selenium level compared with the first tertile were calculated using Cox proportional hazards regression. To further assess the dose-response relationship of serum selenium levels with total and cause-specific mortality, we used restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles of the serum selenium distribution. Using restricted quadratic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles resulted in similar findings (data not shown). The *P* values for these relationships were obtained from likelihood ratio tests comparing models with and without serum selenium terms.

We also evaluated the association of serum selenium levels with all-cause and cause-specific mortality for subgroups defined by sex, age, race/ethnicity, smoking status, alcohol consumption, body mass index, and vitamin and/or mineral supplement use. The *P* values for the interactions between serum selenium levels and participant characteristics were obtained from likelihood ratio tests comparing models with and without the interaction terms.

We analyzed the data using SUDAAN statistical software (version 9.0; Research Triangle Institute, Research Triangle Park, North Carolina) to account for the NHANES weights and complex design.

RESULTS

The mean serum selenium level in the study sample was 125.6 ng/mL. Participants with higher selenium levels were more likely to be male, non-Hispanic white, high school educated, and hypercholesterolemic and less likely to be current smokers, to have elevated C-reactive protein levels, or to have a history of cardiovascular disease (**Table 1**).

Serum selenium levels were associated with decreased all-cause mortality (**Table 2**). The multivariate-adjusted HRs for all-cause mortality comparing tertiles 2 and 3 of serum selenium levels with the lowest tertile were 0.84 (95% CI, 0.73-0.96) and 0.83 (95% CI, 0.72-0.96), respectively. In spline regression models, all-cause mortality decreased with increasing serum selenium levels up to 130 ng/mL (**Figure 1**). At the higher levels (>150 ng/mL), however, there was a gradual increase in mortality with increasing selenium levels.

The multivariate-adjusted HRs for cancer mortality comparing tertiles 2 and 3 of serum selenium levels with the lowest tertile were 0.73 (95% CI, 0.57-0.94) and 0.69 (95% CI, 0.53-0.90), respectively (Table 2). In spline regression models, serum selenium levels were inversely associated with all-cancer and colorectal, lung, and prostate cancer mortality (**Figure 2**). For all-cancer and lung cancer mortality, there was no further decrease but a potential increase with serum selenium levels of greater than 150 ng/mL.

For cardiovascular mortality, the multivariate-adjusted HRs comparing tertiles 2 and 3 of serum selenium levels with the lowest tertile were 0.95 (95% CI, 0.78-1.17) and 0.94 (95% CI, 0.77-1.16), respectively (Table 2). For coronary heart disease mortality, the corresponding HRs were 1.02 (95% CI, 0.71-1.46) and 0.99 (95% CI, 0.67-1.47), respectively, and for stroke mortality they were 0.73 (95% CI, 0.41-1.30) and 1.23 (95% CI, 0.66-2.28), respectively (Table 2). In spline regression models, cardiovascular and coronary heart disease mortality decreased with increasing serum selenium levels up to 120 ng/mL and they increased at higher levels (**Figure 3**), but these associations were not statistically significant (for selenium terms in spline regression models, $P=.16$, $P=.44$, and $P=.25$ for cardiovascular, coronary, and stroke mortality end points, respectively).

Table 1. Baseline Characteristics of the 13 887 Study Participants by Tertile of Serum Selenium Levels[a]

Characteristic	Tertile of Serum Selenium Level (Selenium Level, ng/mL)			*P* Value for Trend
	1 (<117.31)	2 (117.32-130.38)	3 (≥130.39)	
Age, mean, y	44.8	44.3	45.2	.44
Male	43.8	49.8	52.8	<.001
Race/ethnicity				
Non-Hispanic white	71.8	77.6	83.4	<.001
Non-Hispanic black	15.1	8.8	6.3	<.001
Mexican American	5.1	5.1	4.6	.48
High school education	71.5	76.6	78.4	<.001
Mean body mass index[b]	26.7	26.7	26.3	.05
Current smoking	33.4	29.2	23.4	<.001
Current alcohol consumption	61.7	62.9	65.2	.15
Hypertension	29.8	31.3	32.7	.10
Diabetes mellitus	6.6	6.2	7.7	.14
Hypercholesterolemia	26.8	31.4	35.5	<.001
Vitamin and/or mineral supplement users	41.7	42.4	42.0	.89
Mean C-reactive protein level, mg/L	4.7	3.9	3.7	<.001
History of cardiovascular disease	5.9	5.1	4.0	<.001
History of cancer	3.6	3.7	4.1	.30

SI conversion factors: To convert C-reactive protein to nanomoles per liter, multiply by 9.524; to convert selenium to micromoles per liter, multiply by 0.0127.
[a] Unless otherwise indicated, data are expressed as percentage of patients. Means and percentages were adjusted for age, sex, and race/ethnicity.
[b] Calculated as weight in kilograms divided by height in meters squared.

Table 2. Hazard Ratios for All-Cause and Cause-Specific Mortality Among 13 887 Study Participants by Tertile of Serum Selenium Levels[a]

Variable	Tertile of Serum Selenium Level (Selenium Level, ng/mL)			*P* Value for Trend
	1 (<117.31)	2 (117.32-130.38)	3 (≥130.39)	
All-cause mortality, No. of events	819	579	570	
Model 1[b]	1 [Reference]	0.78 (0.67-0.91)	0.76 (0.67-0.86)	<.001
Model 2[c]	1 [Reference]	0.82 (0.72-0.95)	0.83 (0.72-0.95)	.01
Model 3[d]	1 [Reference]	0.84 (0.73-0.96)	0.83 (0.72-0.96)	.01
Model 3[d,e]	1 [Reference]	0.83 (0.70-0.99)	0.83 (0.67-1.02)	.08
Model 3[d,f]	1 [Reference]	0.86 (0.73-1.02)	0.88 (0.74-1.04)	.12
Cancer mortality, No. of events	192	137	128	
Model 1[b]	1 [Reference]	0.71 (0.55-0.90)	0.65 (0.50-0.84)	.002
Model 2[c]	1 [Reference]	0.73 (0.57-0.94)	0.69 (0.53-0.90)	.007
Model 2[c,e]	1 [Reference]	0.75 (0.54-1.04)	0.68 (0.48-0.97)	.03
Model 2[c,f]	1 [Reference]	0.77 (0.57-1.04)	0.76 (0.58-1.00)	.055
Cardiovascular mortality, No. of events	346	265	270	
Model 1[b]	1 [Reference]	0.90 (0.73-1.12)	0.90 (0.75-1.09)	.30
Model 2[c]	1 [Reference]	0.97 (0.79-1.19)	1.00 (0.81-1.23)	.98
Model 3[d]	1 [Reference]	0.95 (0.78-1.17)	0.94 (0.77-1.16)	.58
Model 3[d,e]	1 [Reference]	1.00 (0.79-1.26)	0.98 (0.74-1.30)	.89
Model 3[d,f]	1 [Reference]	0.90 (0.71-1.14)	0.98 (0.79-1.22)	.87
Coronary mortality, No. of events	149	117	124	
Model 1[b]	1 [Reference]	0.93 (0.63-1.35)	0.95 (0.65-1.38)	.78
Model 2[c]	1 [Reference]	1.01 (0.72-1.42)	1.06 (0.73-1.55)	.76
Model 3[d]	1 [Reference]	1.02 (0.71-1.46)	0.99 (0.67-1.47)	.97
Stroke mortality, No. of events	52	46	40	
Model 1[b]	1 [Reference]	0.71 (0.40-1.25)	1.17 (0.61-2.25)	.63
Model 2[c]	1 [Reference]	0.74 (0.42-1.32)	1.26 (0.68-2.34)	.48
Model 3[d]	1 [Reference]	0.73 (0.41-1.30)	1.23 (0.66-2.28)	.52

SI conversion factor: To convert selenium to micromoles per liter, multiply by 0.0127.
[a] Unless otherwise indicated, data are expressed as hazard ratio (95% confidence interval).
[b] Adjusted for age (continuous), sex (male or female), and race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other).
[c] Further adjusted for education (≥12 or <12 years of school completed), annual family income (≥$20 000 or <$20 000), postmenopausal status for women (yes or no), cigarette smoking (current, former, or never), serum cotinine level (continuous), alcohol consumption (current, former, or never), physical activity (0, 1-2, or ≥3 times per week), body mass index (continuous), and vitamin and/or mineral supplement use (yes or no).
[d] Further adjusted for C-reactive protein level (≥10, 3-9, or <3 mg/L [to convert to nanomoles per liter, multiply by 9.524]), hypercholesterolemia (yes or no), hypertension (yes or no), glomerular filtration rate (continuous), and diabetes mellitus (yes or no).
[e] Indicates subjects with cardiovascular disease and/or cancer at baseline are excluded. This analysis was based on 1385 events for all-cause mortality, 328 events for cancer, and 581 events for cardiovascular mortality.
[f] Indicates adding a 2-year lag period. This analysis was based on 1626 events for all-cause mortality, 390 events for cancer, and 712 events for cardiovascular mortality.

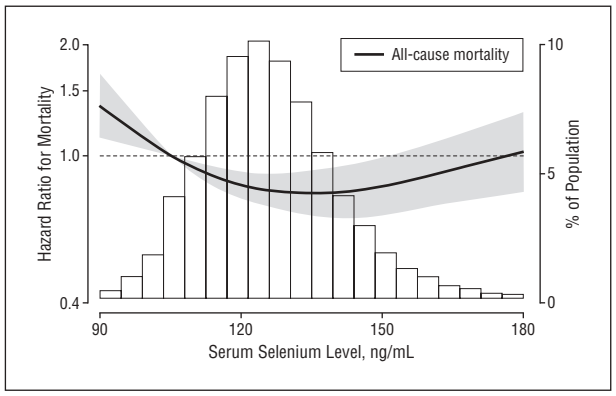

Figure 1. Hazard ratios (and 95% confidence intervals [shaded area alongside curve]) for all-cause mortality by serum selenium levels. The curve represents multivariate-adjusted hazard ratios based on restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles of the serum selenium level distribution. The reference value (hazard ratio, 1) was set at the 10th percentile of the serum selenium level distribution (105.4 ng/mL). Hazard ratios were adjusted for age, sex, race/ethnicity, education, family income, menopausal status, cigarette smoking status, serum cotinine level, alcohol consumption, physical activity, body mass index, vitamin and/or mineral supplement use, C-reactive protein level, hypercholesterolemia, hypertension, glomerular filtration rate, and diabetes mellitus. For all-cause mortality, $P<.001$. The histogram represents the frequency distribution of serum selenium level in the study sample. To convert selenium to micromoles per liter, multiply by 0.0127.

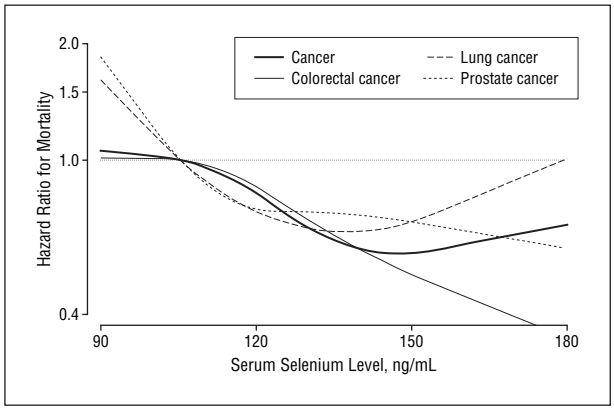

Figure 2. Hazard ratios for all-cancer and colorectal, lung, and prostate cancer mortality by serum selenium levels. The curves represent multivariate-adjusted hazard ratios based on restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles of the serum selenium level distribution. The reference value (hazard ratio, 1) was set at the 10th percentile of the serum selenium level distribution (105.4 ng/mL). Hazard ratios were adjusted for age, sex, race/ethnicity, education, family income, menopausal status, cigarette smoking status, serum cotinine level, alcohol consumption, physical activity, body mass index, and vitamin and/or mineral supplement use. The *P* values were .006 for all-cancer mortality, .72 for colorectal cancer mortality, .14 for lung cancer mortality, and .77 for prostate cancer mortality. To convert selenium to micromoles per liter, multiply by 0.0127.

Exclusion of participants with cardiovascular disease or cancer at baseline or exclusion of participants who died in the first 2 years (Table 2) or 5 years (data not shown) of follow-up did not appreciably alter the HRs of serum selenium levels with all-cause and cause-specific mortality.

When the associations of serum selenium levels with mortality end points were evaluated by study subgroups (**Figure 4**), none of the interactions was statistically significant except for the interaction of serum selenium level and smoking status on all-cause mortality ($P=.001$) and the interaction of serum selenium level and age on cancer mortality ($P=.02$).

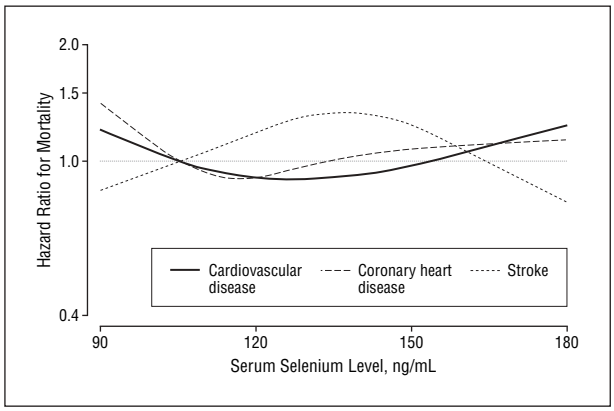

Figure 3. Hazard ratios for cardiovascular disease, coronary heart disease, and stroke mortality by serum selenium levels. The curves represent multivariate-adjusted hazard ratios based on restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles of the serum selenium level distribution. The reference value (hazard ratio, 1) was set at the 10th percentile of the serum selenium level distribution (105.4 ng/mL). Hazard ratios were adjusted for age, sex, race/ethnicity, education, family income, menopausal status, cigarette smoking status, serum cotinine level, alcohol consumption, physical activity, body mass index, vitamin and/or mineral supplement use, C-reactive protein level, hypercholesterolemia, hypertension, glomerular filtration rate, and diabetes mellitus. The *P* values were .16 for cardiovascular disease mortality, .44 for coronary heart disease mortality, and .25 for stroke mortality. To convert selenium to micromoles per liter, multiply by 0.0127.

COMMENT

In this large prospective study based on a representative sample of the US population, we identified a nonlinear association of serum selenium with all-cause and cancer mortality. At serum selenium levels of less than 130 ng/mL, increases in serum selenium level were associated with a reduced risk of all-cause and cancer mortality. The association was essentially flat at serum selenium levels from 130 to 150 ng/mL. At levels greater than 150 ng/mL, there was a small positive association between serum selenium levels and all-cause and cancer mortality. We found no association between serum selenium levels and cardiovascular mortality.

There are only limited prospective data on the association between selenium levels and all-cause mortality. The Etude du Vieillissement Artériel[18] (EVA) followed up 1389 elderly men and women during 9 years in France, a country with a lower selenium intake compared with that in the United States. In their study, the relative risk of all-cause mortality comparing the highest (≥96.3 ng/mL) with the lowest (<75.0 ng/mL) quartile of plasma selenium levels was 0.30 (95% CI, 0.15-0.58), with an inverse linear dose-response trend across the quartiles.[18] However, in an observational analysis of 1103 participants in the General Population Trial of Linxian, China, the relative risk of all-cause mortality during 15 years of follow-up comparing the highest (≥84.5 ng/mL) with the lowest (<61.6 ng/mL) quartile of serum selenium levels was 0.93 (95% CI, 0.27-1.19).[19] In addition, in a cohort of 215 elderly Spanish individuals, the relative risk of all-cause mortality during 4.3 years of follow-up comparing the highest (>99.5 ng/mL) with the lowest (≤72.6 ng/mL) quintile

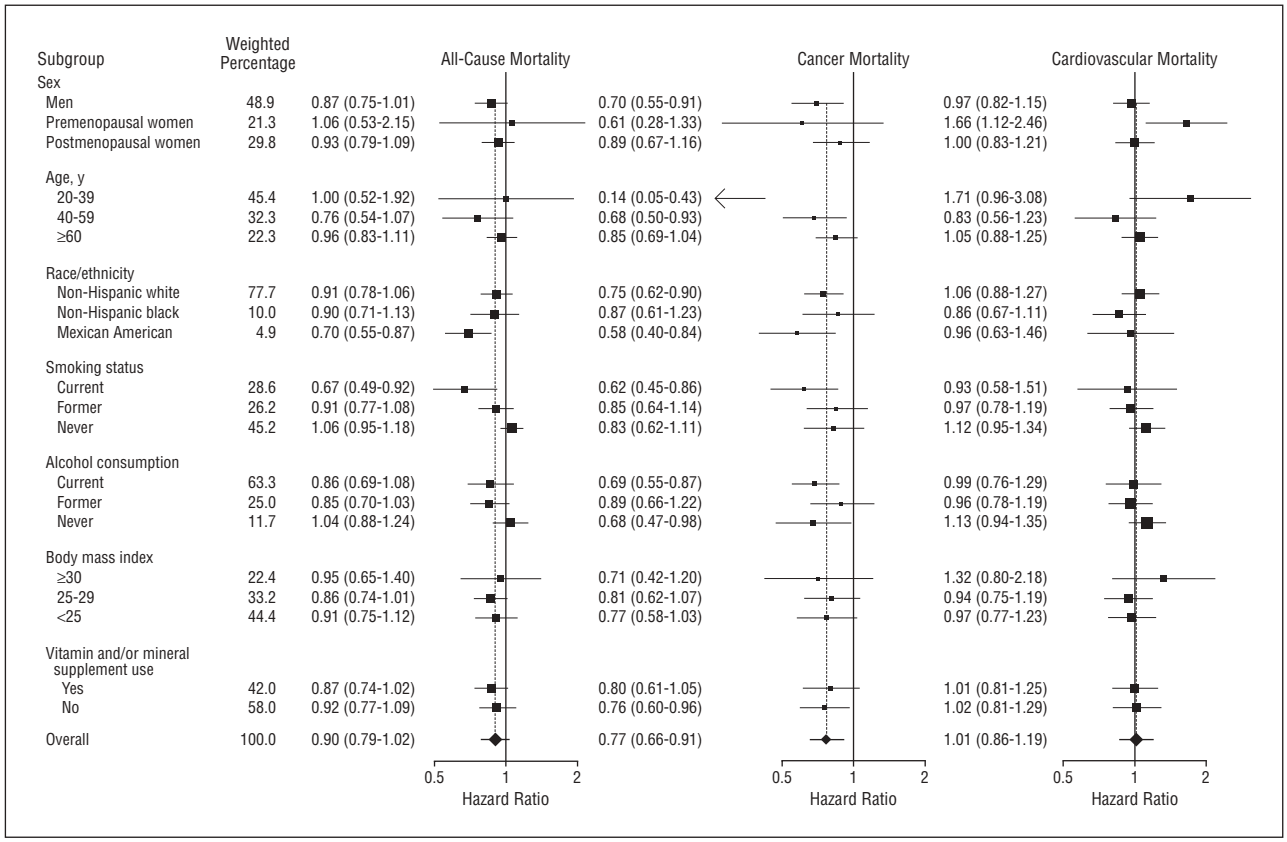

Figure 4. Hazard ratios for all-cause, cardiovascular, and cancer mortality comparing the 80th with the 20th percentile of the serum selenium level distribution (137.47 vs 111.55 ng/mL). Hazard ratios were derived from Cox proportional hazards regression models including serum selenium levels as a continuous variable. Hazard ratios were adjusted for age, sex, race/ethnicity, education, family income, menopausal status, cigarette smoking status, serum cotinine level, alcohol consumption, physical activity, body mass index, and vitamin and/or mineral supplement use. Results for all-cause and cardiovascular mortality were further adjusted for C-reactive protein level, hypercholesterolemia, hypertension, glomerular filtration rate, and diabetes mellitus. The area of each square is proportional to the inverse of the variance of the log hazard ratios. Horizontal lines represent 95% confidence intervals. None of the interactions was statistically significant except for the interaction of serum selenium levels and smoking status on all-cause mortality ($P<.001$) and the interaction of serum selenium level and age on cancer mortality ($P=.02$). Body mass index is calculated as weight in kilograms divided by height in meters squared. To convert selenium to micromoles per liter, multiply by 0.0127.

of serum selenium levels was 0.98 (95% CI, 0.31-3.08) in men and 0.17 (95% CI, 0.03-0.87) in women.[20]

In a meta-analysis of randomized controlled trials, use of supplements containing selenium was associated with reduced all-cause mortality (pooled relative risk, 0.91; 95% CI, 0.84-0.99).[21] Most of these trials used selenium in combination with other antioxidants. When the analysis was restricted to the 3 trials that evaluated supplements containing only selenium,[22-24] the relative risk was 0.85 (95% CI, 0.68-1.07).[21] The Nutritional Prevention of Cancer (NPC) study[22] is the largest and longest randomized controlled trial available on selenium supplements given singly. In that trial, 1312 subjects with a history of nonmelanoma skin cancer were randomized to receive supplements containing 200 µg/d of selenium or placebo, and were followed up for 8 years for recurrence of skin cancer. Although there was no benefit on the primary trial end point, selenium supplementation was associated with a statistically insignificant reduction in all-cause mortality (relative risk, 0.83; 95% CI, 0.63-1.08).[22] Additional data from observational studies and randomized controlled trials are needed to establish the effect of selenium exposure on all-cause mortality across a wide range of selenium intake levels. Furthermore, our study indicates that ongoing randomized controlled trials of selenium supplement intake and disease end points may need to present their findings stratified by baseline selenium levels because the potential benefits of selenium may be limited to participants with low baseline selenium levels.

SELENIUM AND CANCER

Based on observational studies, several meta-analyses have summarized inverse associations between levels of selenium biomarkers and lung[4] and prostate[6] cancers. For lung cancer, the pooled relative risk comparing the highest with the lowest category of selenium levels or intake across 13 studies was 0.74 (95% CI, 0.62-0.88).[4] This inverse association was stronger at lower selenium levels: the pooled relative risk was 0.72 in studies with mean serum selenium levels of less than 100 ng/mL or mean selenium intake of less than 55 µg/d, or 0.86 µg/d in studies with higher selenium levels. For prostate cancer, the pooled relative risk comparing moderate or high categories with low categories of selenium levels or intake across 11 prospective studies was 0.72 (95% CI, 0.61-0.84).[6] Epidemiological studies have also shown an inverse association between selenium levels and colorectal cancer.[25]

The strongest support for the hypothesis that selenium may prevent cancer comes from the NPC trial. In

that trial, selenium supplementation reduced the incidence of several secondary cancer end points, including total cancer (HR, 0.75; 95% CI, 0.58-0.97), prostate cancer (HR, 0.48; 95% CI, 0.28-0.80), lung cancer (HR, 0.74; 95% CI, 0.44-1.24), and colorectal cancer (HR, 0.46; 95% CI, 0.21-1.02).[26] Consistent with a nonlinear effect of selenium on cancer end points, the NPC trial found that the protective effect of selenium supplements on cancer incidence was restricted to participants with baseline plasma selenium levels of less than 121.6 ng/mL, whereas selenium supplements induced a small, statistically insignificant increase in cancer incidence among participants with higher baseline selenium levels.[26]

An inverse association between serum selenium level and cancer risk is biologically possible. Selenium could reduce oxidative stress through antioxidant selenoproteins such as glutathione peroxidase, selenoprotein P, and thioredoxin reductase.[2,9] Selenoprotein-mediated effects, however, are dose dependent. With the possible exception of selenoprotein P, the levels and activity of selenoproteins are maximized at plasma selenium levels of 70 to 90 ng/mL,[27] and additional selenium intake above these levels does not result in additional glutathione peroxidase activity. Instead, higher serum selenium levels mainly reflect the nonspecific incorporation of selenomethionine replacing methionine in albumin and other serum proteins.[1,9,28] Because most Americans have serum selenium levels of greater than 95 ng/mL,[9] it is possible that the inverse association between serum selenium levels and cancer that we observed at low levels (<130 ng/mL) is related to other mechanisms, including the production of methylselenol, a selenium metabolite that may induce apoptosis of cancer cells and may alter gene expression,[3] and the inactivation of carcinogenic metals such as cadmium or arsenic.[29,30]

SELENIUM AND CARDIOVASCULAR DISEASE

A recent meta-analysis[7] of 14 prospective cohort studies found a modest but statistically significant inverse association between selenium levels and coronary heart disease. In this meta-analysis, the pooled relative risk of coronary heart disease comparing the highest with the lowest category of selenium levels was 0.85 (95% CI, 0.74-0.99).[7] In a dose-response analysis, a 50% increase in selenium levels was associated with a 24% (95% CI, 7%-38%) reduction in coronary heart disease risk. In contrast, our analysis of NHANES III data found no association between serum selenium levels and cardiovascular mortality, including coronary and stroke mortality. Several reasons could explain the discrepancy between past research and our findings. Most studies of the association between selenium levels and coronary heart disease risk have been conducted in European countries with substantially lower selenium intake compared with that in the United States. It is possible that selenium may prevent cardiovascular disease but only at intake levels below those in the United States. Indeed, the 2 other prospective studies of selenium levels and coronary heart disease conducted in the United States are consistent with our findings.[31,32] In addition to differences in background selenium levels, other reasons for differences in the study results include residual confounding by socioeconomic status or other determinants of selenium levels and selective publication of studies showing an inverse association between selenium and cardiovascular end points.

Few randomized trials have evaluated the effects of selenium on cardiovascular outcomes.[7,33] In a meta-analysis of 6 randomized trials, the pooled relative risk of coronary heart disease end points comparing supplements containing selenium vs placebo was 0.89 (95% CI, 0.68-1.17).[7] Only 2 of these 6 trials used supplements containing only selenium. In the NPC trial, the HR for coronary heart disease comparing selenium supplements to placebo was 1.07 (95% CI, 0.77-1.48).[34]

NARROW SAFETY MARGIN OF SELENIUM

Although selenium is an essential element, it is also toxic at relatively low doses.[9] The tolerable upper intake level (UL) of selenium has been established at 400 µg/d to avoid visible symptoms of selenium toxicity in sensitive persons.[9] Recently, high serum selenium levels were associated with the prevalence of diabetes mellitus in the NHANES III,[35] and selenium supplementation increased the risk of incident diabetes in the NPC trial.[36,37] Furthermore, our analysis of NHANES III data indicates that selenium levels now considered in the high-normal range may be associated with increased mortality. Additional epidemiological studies are needed to establish the levels of selenium associated with the lowest incidence of adverse health outcomes.

STRENGTHS AND LIMITATIONS

Our study had several strengths, including the rigorous study protocol and the extensive quality control procedures of the NHANES III, the representative nature of the sample, and the large sample size. Several limitations, however, need to be considered in the interpretation of our findings. Our study relied on a single measurement of serum selenium levels as a biomarker of exposure. Serum selenium levels reflect short-term selenium intake and may be subject to higher within-person variability compared with toenail selenium levels.[38] The type of measurement error induced by using baseline serum selenium levels to estimate long-term exposure, however, cannot explain the nonlinear association between selenium levels and mortality end points observed in the NHANES III findings. Furthermore, our study measured only total serum selenium levels but did not distinguish between selenium in selenoproteins and selenium nonspecifically incorporated in other proteins, 2 forms with a potentially different relation to the development of chronic diseases. Another limitation was the use of passive follow-up to determine mortality end points based on the National Death Index. Our findings can thus be generalized only to fatal events. Although follow-up is relatively complete, the adjudication of the causes of death from death certificates can be inaccurate. Also, although the sample size was large, relatively few deaths were due to certain specific end points such as stroke, colorectal cancer, or prostate cancer, reducing the precision of the estimates for these end points. Finally, although spline regression models can be sensi-

tive to the selected knots, the reported nonlinear dose-response relationship of serum selenium levels to total and cause-specific mortality using restricted quadratic splines remained similar with different sets of knots.

In summary, in a representative sample of the US population, we found a nonlinear association between serum selenium levels and all-cause and cancer mortality. We observed an inverse association at low selenium levels (<130 ng/mL) and a modest but positive association at high selenium levels (>150 ng/mL). Our findings are consistent with previous observational studies that identified an inverse association between selenium levels and prostate, lung, and colorectal cancer, but our study raises the concern that high-normal selenium levels may be associated with an increased risk of mortality.

Accepted for Publication: September 13, 2007.
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Financial Disclosure: None reported.
Funding/Support: This study was supported by grants R01 ES012673 from the National Institute of Environmental Health Sciences and 0230232N from the American Heart Association.

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