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Selenium Supplementation and Prostate Cancer Mortality

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Abstract

Background: Few studies have evaluated the relation between selenium supplementation after diagnosis and prostate cancer outcomes.

Methods: We prospectively followed 4459 men initially diagnosed with nonmetastatic prostate cancer in the Health Professionals Follow-Up Study from 1988 through 2010 and examined whether selenium supplement use (from selenium-specific supplements and multivitamins) after diagnosis was associated with risk of biochemical recurrence, prostate cancer mortality, and, secondarily, cardiovascular disease mortality and overall mortality, using Cox proportional hazards models. All *P* values were from two-sided tests.

Results: We documented 965 deaths, 226 (23.4%) because of prostate cancer and 267 (27.7%) because of cardiovascular disease, during a median follow-up of 8.9 years. In the biochemical recurrence analysis, we documented 762 recurrences during a median follow-up of 7.8 years. Crude rates per 1000 person-years for prostate cancer death were 5.6 among selenium nonusers and 10.5 among men who consumed 140 or more µg/day. Crude rates per 1000 person-years were 28.2 vs 23.5 for all-cause mortality and 28.4 vs 29.3 for biochemical recurrence, for nonuse vs highest-dose categories, respectively. In multivariable analyses, men who consumed 1 to 24 µg/day, 25 to 139 µg/day, and 140 or more µg/day of supplemental selenium had a 1.18 (95% confidence interval [CI] = 0.73 to 1.91), 1.33 (95% CI = 0.77 to 2.30), and 2.60-fold (95% CI = 1.44 to 4.70) greater risk of prostate cancer mortality compared with nonusers, respectively, P_{trend} = .001. There was no statistically significant association between selenium supplement use and biochemical recurrence, cardiovascular disease mortality, or overall mortality.

Conclusion: Selenium supplementation of 140 or more µg/day after diagnosis of nonmetastatic prostate cancer may increase risk of prostate cancer mortality. Caution is warranted regarding usage of such supplements among men with prostate cancer.

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The Nutritional Prevention of Cancer (NPC) Study, a randomized trial examining the effect of 200 µg/d of selenium in 0.5-g high-selenium yeast on incidence of nonmelanoma skin cancer, reported that men randomized to selenium had a lower risk of prostate cancer compared with the placebo group (1). The effects were most pronounced among men with low baseline selenium. Among men in the lowest tertile of baseline selenium (≤106.4 ng/mL), men randomized to selenium supplementation had an 86% lower risk of prostate cancer (hazard ratio [HR] = 0.14, 95% CI = 0.03 to 0.61, 17 events). In contrast, selenium supplementation was positively, but not statistically significantly, associated with risk of prostate cancer among men in the highest tertile of baseline selenium (HR = 1.14, 95% CI = 0.51 to 2.59, 24 events) (2). The randomized, controlled Selenium and Vitamin E Cancer Prevention Trial (SELECT) (3,4) reported no effect of selenium supplementation (200 µg/d from *L*-selenomethionine) on prostate cancer incidence (HR = 1.09, 95% CI = 0.93 to 1.27, n = 575 events) (4). However, SELECT participants had adequate levels of selenium at baseline (median serum selenium levels of 135 ng/mL vs 113 ng/mL in NPC), and a large proportion of the detected cancers may have been indolent cases (99% of case patients in the selenium arm were localized T1/T2 cancers, 89% were Gleason score ≤3+4, and 71% were biopsied based on elevated PSA only, with a similar pattern observed across all groups) (3). Recently, SELECT investigators reported that selenium supplementation increased risk of high-grade prostate cancer among those with high-baseline toenail selenium (HR = 1.91, 95% CI = 1.20 to 3.05) and did not increase risk among those with lower baseline levels (5).

The lack of demonstrated benefit for supplemental selenium has dampened enthusiasm for using supplements for the primary prevention of prostate cancer, but the effect of selenium supplements taken after diagnosis on prostate cancer progression is unknown. Additionally, there may be a U-shaped dose response curve, where very high selenium levels may have adverse effects (6,7). Thus, we prospectively examined postdiagnostic selenium supplementation in relation to risk of prostate cancer mortality, biochemical recurrence, and overall mortality among men initially diagnosed with nonmetastatic disease. In a population that we expected to be selenium sufficient, we examined the possibility that high-dose selenium supplement use after diagnosis would be associated with higher prostate cancer mortality.

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Methods

Study Population

The Health Professionals Follow-Up Study is a prospective cohort study of 51 529 US male health professionals who enrolled in 1986 by completing a mailed questionnaire. Participants were age 40 to 75 years at enrollment and provided extensive data at baseline, including medical history, medication, height, weight, and lifestyle factors (smoking, physical activity, supplement use, etc.) and completed a validated semiquantitative food-frequency questionnaire (FFQ) (8). Participants complete biennial follow-up questionnaires to update information on new medical diagnoses and lifestyle (response rate 96%); diet information is updated every four years. This study was approved by the institutional review board of the Harvard School of Public Health. Participants gave informed consent to participate by returning the baseline questionnaire.

Assessment of Selenium Supplementation

Participants completed detailed information on the use and dosage of supplements (including multivitamins and individual vitamins and minerals) every two years beginning in 1986. Current use and dosage in predefined categories were assessed for vitamins A, C, and E, calcium, selenium, iron, and zinc. The selenium supplement categories were: less than 80 µg, 80–130 µg, 140–250 µg, 260 or more µg, and "don't know". Additional supplements were assessed for current use only (yes/no). The baseline questionnaire also inquired about past use for individual supplements (yes/no) if the participant was not a current user.

Frequency of multivitamin use was assessed at baseline and every two years thereafter; the usual brand and type of multivitamin used was assessed on the FFQ every four years. Brand information was used to calculate selenium intake from multivitamins in years when the FFQ was administered; the most common multivitamin brand and dosage was used to calculate selenium supplementation from multivitamins in years when FFQ data was not available (ie, 1988, 1992, 1996, 2000, 2004, 2008). Total selenium supplement intake was calculated as the sum from multivitamins and selenium supplements. If information on the frequency of multivitamin use or selenium dosage was missing, we used the frequency/dosage from the previous questionnaire cycle, if available; otherwise the mode was used (eg, 6–9 multivitamins/week [once/day]). The results remained unchanged, excluding participants in cycles where they were missing selenium or multivitamin dosage. The following categories of total selenium supplement dosage were used: nonuser, 1–24 µg/day, 25–139 µg/day, and 140 or more µg/day, based on the distribution of selenium intake in the population. We also calculated total duration of use to assess whether the association between selenium supplement use and prostate cancer morality differed by duration.

Ascertainment of Prostate Cancer Diagnosis, Recurrence, and Death

After participants report a prostate cancer diagnosis, we obtain medical records to confirm the diagnosis and record clinical T-stage, Gleason score, treatments, prostate-specific antigen (PSA) values at diagnosis, PSA levels after treatment (to identify events of biochemical recurrence), and metastasis. Participants also complete biennial follow-up questionnaires to update data on treatments, PSA levels, and clinical progression.

Our primary outcome was prostate cancer mortality. We evaluated biochemical recurrence, overall mortality, and cardiovascular mortality as secondary outcomes. Cardiovascular mortality was evaluated after examining overall mortality, to determine if this outcome explained the non–statistically significant inverse association observed for overall mortality. Biochemical recurrence was defined from medical records and physician and patient questionnaires using standard definitions: for radical prostatectomy (9,10), PSA greater than 0.2 ng/mL after surgery for at least two consecutive measures; for radiation (11), an increase of 2 or more ng/mL over the nadir PSA; for brachytherapy (12), hormones, or other treatments, an increase of 1 or more ng/mL over the nadir PSA for at least two consecutive measures. For watchful waiting, progression was defined as a postdiagnosis PSA increase of 1 or more ng/mL for at least two consecutive measures. Patient-reported data comprised 40% of all recorded increases in PSA values. Date of biochemical recurrence was the date of first PSA increase. Men who reported metastasis or died of prostate cancer for whom we could not

ascertain a biochemical recurrence were assigned a date of biochemical recurrence as the earliest date for any of these events because a PSA rise nearly always precedes a clinical diagnosis of prostate cancer metastases. Deaths were identified from family reports and National Death Index searches; we ascertained more than 98% of deaths (13). Causes of death were centrally adjudicated by study physicians who reviewed medical records and death certificates without knowledge of participants' selenium supplement use.

Population for Analysis

The population for analyses of mortality endpoints included men who were free of cancer (except nonmelanoma skin cancer) at baseline, diagnosed with localized prostate cancer (cT3a or lower) during follow-up from 1986 to 2010 who had information on selenium supplement use before and after diagnosis (n = 4459). For the biochemical recurrence analysis, we additionally excluded 741 participants without data on recurrence or progression, leaving 3718 eligible participants.

Statistical Analysis

We used Cox proportional hazards regression to examine postdiagnostic selenium supplement use and risk of prostate cancer, cardiovascular disease, overall mortality, and biochemical recurrence. For the mortality analyses, person-time was contributed from diagnosis to death or end of follow-up (January 31, 2010), whichever occurred first. For the biochemical recurrence analysis, person-time was contributed from diagnosis until the earliest of the following events: biochemical recurrence, metastasis, death, or end of follow-up. Cross-product terms of selenium dosage by a function of time were added to the models to check the proportionality assumption; no violation was found.

Supplement use data was collected every two years and was updated in our models for every two-year period, maintaining a two- to four-year lag to reduce the potential impact of advanced disease on selenium supplement use. For example, for a man diagnosed in 1993, his 1990 supplement use was applied to person-time from diagnosis to 1994, 1992 supplement use was applied to person-time from 1994 to 1996, and so on. This approach allowed us to capture recent supplement use in relation to risk of the outcomes of interest, while minimizing the potential for reverse causation. We defined prediagnostic supplement use as the exposure reported on the questionnaire preceding the first "postdiagnosis" questionnaire (eg, 1988 for the man described above).

Our basic model included age at diagnosis (years). Multivariable models were additionally adjusted for clinical T-stage (T1, T2, T3), Gleason score (<7, 7, ≥8), primary treatment (radical prostatectomy, radiation therapy, hormonal therapy, watchful waiting, other), body mass index (<25, 25 to <30, ≥30 kg/m^2), vigorous physical activity (<1, 1 to <3, ≥3 hours/week), smoking (never, quit ≥10 years, quit <10 years, current with <40 pack-years, current with ≥40 pack-years), vitamin E, vitamin C, calcium, and zinc supplement use in dosage categories, multivitamin use (yes-<6/week, yes-≥6/week, no), and selenium supplement use before diagnosis (same categories as main analysis). We included prediagnosis selenium supplement use because we were interested in the association between supplement use after diagnosis and mortality, independent of prediagnostic use. We used months since diagnosis as the time scale and stratified by calendar time in two-year intervals.

We considered models adjusted for PSA at diagnosis, diabetes, race, height, family history of prostate cancer, energy, intake of unprocessed and processed red meat, eggs, fish, tomato sauce, coffee, whole milk, low-fat dairy, and vegetable fat, selenium bioavailability based on soil content (low, medium, or high, based on state of residence) (14), and total number of nutritional supplements used. The addition of these variables did not affect the main estimates and were excluded from the multivariable models. For overall and cardiovascular disease mortality, additional adjustment for the covariables described above (except for diabetes) did not affect the main estimates and were excluded from the multivariable models. We included the following or a subset (see Table 2 footnotes) in the models for cardiovascular and overall mortality: parental history of myocardial infarction before age 60 years, hypertension, diabetes, elevated cholesterol, and comorbid conditions (myocardial infarction, coronary artery bypass, coronary angioplasty, stroke, emphysema/chronic obstructive pulmonary disease, and Parkinson's disease). Linear trends across categories were evaluated using the median of each category as a continuous variable. All *P* values were two-sided, with a *P* value below .05 considered statistically significant. Analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

Results

Among 4459 men with nonmetastatic prostate cancer at diagnosis, we documented 965 deaths, 226 (23.4%) because of prostate cancer and 267 (27.7%) because of cardiovascular disease, during a median follow-up of 8.9 years. For analyses of biochemical recurrence, we observed 762 events among 3718 men followed for a median of 7.8 years. Age-standardized characteristics after diagnosis are presented in Table 1. At diagnosis, the highest-dosage (≥140 µg/d) selenium supplement users did more vigorous physical activity, smoked less, used other supplements, and were more likely to have clinical T1 stage cancers; usage did not vary by biopsy Gleason score.

Prostate Cancer-Specific Mortality

Crude rates of prostate cancer death were 5.6 per 1000 person-years among selenium nonusers and 10.5 per 1000 person-years among men who consumed the most selenium (≥140 µg/day). Compared with nonusers, selenium supplement users had an increased risk of prostate cancer mortality (Table 2). In multivariable analyses, men who consumed 1–24 µg/day, 25–139 µg/day, and 140 or more µg/day of supplemental selenium after diagnosis had a 1.18 (95% confidence interval [CI] = 0.73 to 1.91), 1.33 (95% CI = 0.77 to 2.30), and 2.60-fold (95% CI = 1.44 to 4.70) greater risk of prostate cancer mortality compared with nonusers, respectively, P_{trend} = .001. There was some attenuation of the main estimates after adjustment for clinical factors; the addition of lifestyle factors and prediagnosis supplement use strengthened the association. The hazard ratios for selenium did not differ statistically significantly by duration of selenium use ($P_{interaction}$ > .05 for continuous selenium dosage X duration in years).

Biochemical Recurrence

We observed no statistically significant association between selenium supplementation after diagnosis and risk of biochemical recurrence (≥140 µg/d vs nonuse: HR = 1.14, 95% CI = 0.78

Table 1. Age-standardized characteristics at diagnosis among 4459 men with nonmetastatic prostate cancer, by selenium supplement use*

Characteristic	Dosage of selenium supplements (μg/day)			
	Nonuser (n = 2246)	1 – 24 (n = 1455)	25 – 139 (n = 529)	≥140 (n = 229)
Selenium supplement dose, mean, μg	0.0	17.0	60.8	216.5
Age at diagnosis, mean (SD), y	68.9 (7.2)	69.8 (7.1)	69.5 (7.3)	69.3 (6.6)
Clinical T-stage, %				
T1	55.5	62.9	62.9	73.8
T2	40.8	34.5	35.8	25.1
T3a	3.6	2.7	1.3	1.2
Gleason score, %				
2–6	65.0	65.1	65.5	64.1
7	25.8	26.3	27.0	27.6
8–10	9.2	8.6	7.5	8.3
PSA at diagnosis among cases diagnosed after 1994, median (25^{th} and 75^{th} percentile)	6.7 (4.8,10.0)	6.3 (4.7, 9.0)	6.2 (4.8, 8.8)	6.5 (4.6, 9.8)
Primary treatment, %				
Radical prostatectomy	50.9	48.1	44.0	46.9
EBRT or brachytherapy	34.7	38.4	40.4	37.9
Hormones	5.6	5.3	3.9	3.8
Watchful Waiting	7.0	6.2	10.0	10.0
Other	1.8	2.0	1.6	1.4
Family history of prostate cancer, %	10.9	8.9	12.0	8.5
BMI, mean, kg/m^2	25.8	25.9	25.7	25.7
Vigorous exercise, hours per week	1.3	1.3	1.5	1.7
Current smoker, %	5.4	3.2	3.7	0.9
Diabetes, %	7.1	7.9	6.4	5.7
Intake, mean (SD)				
Calories/d	1938.8 (580.2)	1999.2 (596.6)	1974.5 (600.9)	1989.5 (568.5)
Calcium, mg/d	940.7 (418.3)	1129.4 (481.9)	1249.8 (605.9)	1369.6 (619.7)
Fish, servings/d	0.3 (0.4)	0.3 (0.3)	0.4 (0.3)	0.4 (0.3)
Unprocessed red meat, servings/d	0.5 (0.5)	0.5 (0.4)	0.4 (0.4)	0.4 (0.4)
Processed red meat, servings/d	0.2 (0.4)	0.2 (0.3)	0.2 (0.3)	0.2 (0.3)
Tomato sauce, servings/wk	1.0 (1.0)	1.1 (1.1)	1.2 (1.2)	1.3 (1.2)
Alcohol, g/d	11.6 (15.1)	12.8 (16.0)	11.8 (14.4)	12.0 (14.6)
Coffee, servings/d	1.5 (1.5)	1.6 (1.6)	1.4 (1.6)	1.2 (1.4)
Current multivitamin use, %	17.5	99.9	88.5	81.2
Current vitamin E use, %	22.0	46.8	70.2	83.9
No. of supplements taken†	1.4 (2.1)	3.3 (2.3)	7.1 (4.5)	9.2 (4.8)

* Age-standardized to the age distribution of the study population at prostate cancer diagnosis. Lifestyle factors are from participant's questionnaire prior to the diagnosis. Age is not age-standardized. For interpretability, we excluded men missing Gleason score (10.6%) when calculating distribution of Gleason score, and men missing primary treatment data (4.8%) when calculating distribution of treatment. BMI = body mass index (calculated as weight in kilograms divided by the square of height in meters); EBRT = external beam radiation therapy; PSA = prostate specific antigen.

† The total number of supplements was calculated by adding the number of supplements participants reported taking regularly from a provided list of supplements.

to 1.66, P_{trend} = .47; crude rates of recurrence [per 1000 person-years] were 28.4 and 29.3 for nonuse vs highest-dose categories) (Table 2).

Overall and Cardiovascular Disease Mortality

Crude rates for all-cause mortality (per 1000 person-years), comparing nonusers and the highest dosage selenium users (≥140 μg/day), were 28.2 and 23.5, respectively. There was a modest, not statistically significant, inverse association between selenium supplementation and risk of overall mortality (≥140 μg/d vs nonuse: HR = 0.88, 95% CI = 0.63 to 1.22), although we observed no linear association (P_{trend} = .76). The suggestion of an inverse association was unexpected, considering the strong positive association between selenium supplement use and prostate cancer mortality (23% of all deaths); therefore, we evaluated the association between selenium supplement use and cardiovascular disease mortality, the largest cause of death in this cohort (28% of all deaths). Compared with nonusers, the highest dosage selenium supplement users after prostate cancer diagnosis had

Table 2. Selenium supplement use in relation to prostate cancer, cardiovascular, and overall mortality and biochemical recurrence among 4459 men with prostate cancer*

Outcome	Variables added	Se supplement Use				P_{trend}
		Nonuser	1 - 24 µg/d	25 - 139 µg/d	≥140 µg/d	
Prostate cancer mortality						
No. of events: 226		92	79	29	26	
Age-Adj HR (95% CI)†		1.00	1.08 (0.79 to 1.48)	1.18 (0.77 to 1.81)	2.32 (1.47 to 3.65)	<.001
MV-Adj HR (95% CI)‡	clinical - prostate	1.00	1.12 (0.82 to 1.54)	1.15 (0.75 to 1.76)	2.19 (1.38 to 3.47)	.001
MV-Adj HR (95% CI)§	lifestyle	1.00	1.15 (0.83 to 1.58)	1.18 (0.77 to 1.82)	2.29 (1.44 to 3.64)	<.001
MV-Adj HR (95% CI)‖	pre-dx Se use	1.00	1.13 (0.81 to 1.57)	1.28 (0.82 to 1.99)	2.62 (1.61 to 4.24)	<.001
MV-Adj HR (95% CI)¶	other supplements	1.00	1.18 (0.73 to 1.91)	1.33 (0.77 to 2.30)	2.60 (1.44 to 4.70)	.001
Biochemical recurrence						
No. of events: 762		343	272	97	50	
Age-Adj HR (95% CI)†		1.00	1.08 (0.91 to 1.27)	1.07 (0.85 to 1.34)	1.31 (0.96 to 1.78)	.11
MV-Adj HR (95% CI)‡	clinical - prostate	1.00	1.09 (0.92 to 1.29)	1.01 (0.80 to 1.28)	1.27 (0.93 to 1.73)	.19
MV-Adj HR (95% CI)§	lifestyle	1.00	1.10 (0.93 to 1.30)	1.02 (0.81 to 1.28)	1.29 (0.95 to 1.75)	.17
MV-Adj HR (95% CI)‖	pre-dx Se use	1.00	1.08 (0.91 to 1.29)	1.01 (0.79 to 1.29)	1.20 (0.86 to 1.67)	.37
MV-Adj HR (95% CI)¶	other supplements	1.00	0.98 (0.75 to 1.27)	0.95 (0.70 to 1.30)	1.14 (0.78 to 1.66)	.47
Total mortality						
No. of events: 965		460	338	109	58	
Age-Adj HR (95% CI)†		1.00	0.83 (0.72 to 0.96)	0.82 (0.66 to 1.02)	0.90 (0.68 to 1.18)	.37
MV-Adj HR (95% CI)‡	clinical - prostate	1.00	0.86 (0.74 to 0.99)	0.81 (0.65 to 1.00)	0.89 (0.67 to 1.18)	.30
MV-Adj HR (95% CI)§	lifestyle	1.00	0.89 (0.76 to 1.03)	0.84 (0.68 to 1.04)	0.94 (0.71 to 1.25)	.55
MV-Adj HR (95% CI)‖	pre-dx Se use	1.00	0.87 (0.75 to 1.01)	0.87 (0.69 to 1.08)	1.00 (0.75 to 1.34)	.95
MV-Adj HR (95% CI)¶	other supplements	1.00	0.78 (0.63 to 0.97)	0.78 (0.60 to 1.02)	0.85 (0.61 to 1.18)	.65
MV-Adj HR (95% CI)#	clinical - other	1.00	0.79 (0.64 to 0.99)	0.80 (0.61 to 1.04)	0.88 (0.63 to 1.22)	.76
Cardiovascular disease mortality						
No. of events: 267		144	80	31	12	
Age-Adj HR (95% CI)†		1.00	0.66 (0.49 to 0.87)	0.77 (0.52 to 1.15)	0.63 (0.35 to 1.15)	.13
MV-Adj HR (95% CI)‡	clinical - prostate	1.00	0.68 (0.51 to 0.90)	0.76 (0.51 to 1.13)	0.63 (0.34 to 1.15)	.12
MV-Adj HR (95% CI)§	lifestyle	1.00	0.69 (0.52 to 0.92)	0.80 (0.53 to 1.19)	0.65 (0.35 to 1.18)	.16
MV-Adj HR (95% CI)‖	pre-dx Se use	1.00	0.67 (0.50 to 0.90)	0.79 (0.53 to 1.20)	0.67 (0.36 to 1.24)	.23
MV-Adj HR (95% CI)¶	other supplements	1.00	0.61 (0.40 to 0.92)	0.71 (0.43 to 1.16)	0.56 (0.28 to 1.12)	.24
MV-Adj HR (95% CI)#	clinical - other	1.00	0.65 (0.43 to 0.99)	0.78 (0.47 to 1.29)	0.64 (0.32 to 1.28)	.38

* This study included patients diagnosed with clinical stage T1-T3a. CI = confidence interval; HR = hazard ratio.

† Age-adjusted models adjusted for age at diagnosis, time period (two-year intervals), and time since diagnosis to FFQ (years, continuous). All *P* values are from Wald tests and are two-sided tests.

‡ Multivariable models adjusted for those in the previous model plus clinical variables: stage (T1, T2, T3a), Gleason score (<7, 7, ≥8), treatment (radical prostatectomy, radiation, hormones, watchful waiting, other).

§ Multivariable models adjusted for those in the previous model plus lifestyle factors: body mass index (<25, 25 to <30, ≥30), vigorous physical activity (<1, 1 to <3, and ≥3 hours/wk), and smoking (never, quit ≥10 years, quit <10 years, current with <40 pack-years, current with ≥40 pack-years).

‖ Multivariable models adjusted for those in the previous model plus selenium supplement use prior to diagnosis (nonuser, 1 to 24 µg/d, 25 to 139 µg/d, and ≥140 µg/d).

¶ Multivariable models adjusted for those in the previous model plus other supplements: vitamin C, vitamin E, zinc, and calcium supplement use (dosage categories, no), and multivitamin use (yes-<6 per week, yes- ≥6 per week, no).

Multivariable models adjusted for those in the previous model plus parental history of myocardial infarction before age 60 years, high blood pressure, diabetes (Type I or II), elevated cholesterol, and presence of comorbid conditions (myocardial infarction, coronary artery bypass, coronary angioplasty, stroke, emphysema/chronic obstructive pulmonary disease, and Parkinson's disease); all defined as yes or no. The cardiovascular analysis was not adjusted for comorbid conditions.

a statistically nonsignificant 36% decreased risk of cardiovascular disease mortality (HR = 0.64, 95% CI = 0.32–1.28, P_{trend} = .38).

Discussion

We observed an elevated risk of prostate cancer mortality among men who consumed high doses of selenium from supplements after diagnosis. While we cannot rule out that residual confounding may account for a portion of the association observed, the magnitude of effect was large, and we were able to consider confounding by many dietary and lifestyle factors. Few studies have evaluated the relation between selenium supplementation after diagnosis and prostate cancer outcomes. In the Watchful Waiting Study, a randomized trial of selenized yeast (200 or 800 µg) and prostate cancer progression in men who received no curative treatment (15), men in the highest quartile of baseline plasma selenium and randomized to high-dose selenium had a statistically significantly increased PSA velocity compared with men on placebo (suggesting that their disease was progressing) (16). The current study is the first study to examine the relation of selenium supplements taken after diagnosis with risk of prostate cancer mortality.

Several observational studies and randomized controlled trials have examined the relation between selenium supplement use in healthy men and risk of prostate cancer. We previously reported an inverse relation between toenail selenium levels measured in 1987 among healthy men and incident-advanced prostate cancer (17), and this finding is supported by other studies (18) and a recent meta-analysis (19). As noted, the SELECT trial observed no association for incident prostate cancer (3), but an increased risk for high-grade prostate cancer among those with high baseline levels. The National Institutes of Health-AARP Diet and Health Study reported that selenium supplementation prior to diagnosis may increase risk of prostate cancer mortality, although dosage was not examined (20). These data underscore the potentially complex and variable role that lifestyle factors may play in the long etiologic time course of some cancers, in particular that risk factors for incidence may be very different than those for mortality. For example, smoking is not associated with risk of incident prostate cancer, but is positively associated with disease progression and prostate-specific mortality (21–23). Associations between a given exposure and incident prostate cancer presumably reflect biologic effects of the exposure in the prostate gland, whereas associations with metastatic/fatal disease may reflect effects of the exposure in the prostate (if the tumor is still present) and/or effects on other organs or systems that influence the likelihood of metastatic disease developing and spreading. Additional studies with long-term follow-up of lifestyle factors before and after cancer diagnosis are warranted.

Although many in vitro and animal experiments support the anticarcinogenic role of selenium through apoptosis (24–27), inhibiting cellular proliferation (28–32), antiangiogenesis (33,34) and antioxidant pathways (35), other research in dogs (one of the only other species that naturally develops prostate cancer) suggests that more selenium may not be better. Waters et al. proposed a U-shaped dose response between selenium status (toenail selenium concentration) and prostatic DNA damage (6) and apoptosis (7). Foci of intense apoptosis were seen four times more often in dogs fed moderate levels of selenium compared with dogs in the low selenium group (P = .04), but apoptosis intensity did not differ statistically significantly between dogs with high vs low selenium status (P = .75) (7). A U-shaped relation between selenium supplementation and cancer may exist whereby persons with low selenium status benefit from supplementation because of increased expression of selenoenzymes, thereby increasing antioxidant protection; persons with somewhat higher levels have maximum antioxidant protection but may benefit from supplementation because of upregulation of apoptosis; and persons with high excess levels are not expected to benefit from supplementation and may be vulnerable to adverse effects. Of note, differential growth and apoptotic effects of selenium were reported on androgen-sensitive LNCaP vs androgen-independent PC-3 prostate cancer cells (36), therefore future studies should consider whether the dose-response curve differs by stage of disease (ie, carcinoma in situ, localized cancer, cancer recurrence, metastasis).

Our study is not without limitations. These results may not be generalizable to all populations. Selenium status differs widely across the world because of soil content and selenium supplementation behavior; on average, men in the United States consume 134 µg/day (37), which exceeds the 55 µg/day recommended dietary allowance. In Europe and other regions where daily selenium intake is lower (40 µg/day in Europe) (37), individuals may benefit from supplemental selenium. However, because selenium supplementation has increased over time in the United States (7.4% of men in our study population were using selenium supplements at diagnosis between 1986 and 1993, compared with 23.6% of men at diagnosis between 2000 and 2006), additional studies evaluating high-dose selenium intake are needed to confirm our results and inform clinical and public health guidelines for prostate cancer survivors.

This study focused on selenium supplementation because of the inability to accurately assess selenium intake from dietary sources via questionnaire because of the large variation in soil selenium content (38). We attempted to control for dietary selenium intake by adjusting for geographic location updated every two years as a proxy for soil selenium content. This did not affect the results; however, we could not account for food grown and transported to different parts of the country. Dietary selenium could be a modifying factor (ie, the effect of supplements may vary by high or low dietary intakes), which we could not evaluate. In addition, we had too few events in the highest-dosage category to thoroughly evaluate whether the effect of high-dose supplements varied by subgroups or whether the effect of high-dose supplements taken after diagnosis varied by level of prediagnosis supplement use (eg, there were no prostate cancer deaths in the 4% of men who consumed ≥140 µg/d of selenium before and after diagnosis). We also relied on self-reported supplement use, which will have some nondifferential measurement error; in addition, there will be some nondifferential measurement error from dietary selenium intake. Study strengths include the prospective and repeated assessment of selenium, multivitamin, and other supplement use every two years, long follow-up, and large number of events.

In conclusion, high-dose selenium supplement use may increase risk of prostate cancer mortality. Caution is warranted regarding usage of such supplements among men with prostate cancer.

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Notes

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References

1. Clark LC, Combs GF Jr, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA*. 1996;276(24):1957–1963.
2. Duffield-Lillico AJ, Dalkin BL, Reid ME, et al. Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. *BJU Int*. 2003;91(7):608–612.
3. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2009;301(1):39–51.
4. Klein EA, Thompson IM Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2011;306(14):1549–1556.
5. Kristal AR, Darke AK, Morris JS, et al. Baseline Selenium Status and Effects of Selenium and Vitamin E Supplementation on Prostate Cancer Risk. *J Natl Cancer Inst*. 2014;106(3):djt456 doi:10.1093/jnci/djt456.
6. Waters DJ, Shen S, Glickman LT, et al. Prostate cancer risk and DNA damage: translational significance of selenium supplementation in a canine model. *Carcinogenesis*. 2005;26(7):1256–1262.
7. Chiang EC, Shen S, Kengeri SS, et al. Defining the Optimal Selenium Dose for Prostate Cancer Risk Reduction: Insights from the U-Shaped Relationship between Selenium Status, DNA Damage, and Apoptosis. *Dose Response*. 2009;8(3):285–300.
8. Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. *J Am Diet Assoc*. 1993;93(7):790–796.
9. Kupelian PA, Elshaikh M, Reddy CA, Zippe C, Klein EA. Comparison of the efficacy of local therapies for localized prostate cancer in the prostate-specific antigen era: a large single-institution experience with radical prostatectomy and external-beam radiotherapy. *J Clin Oncol*. 2002;20(16):3376–3385.
10. Freedland SJ, Sutter ME, Dorey F, Aronson WJ. Defining the ideal cutpoint for determining PSA recurrence after radical prostatectomy. Prostate-specific antigen. *Urology*. 2003;61(2):365–369.
11. Roach M, 3rd, Hanks G, Thames H Jr, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys*. 2006;65(4):965–974.
12. Kuban DA, Levy LB, Potters L, et al. Comparison of biochemical failure definitions for permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys*. Aug 1 2006;65(5):1487–1493.
13. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. *Am J Epidemiol*. 1994;140(11):1016–1019.
14. Shamberger RJ, Tytko SA, Willis CE. Antioxidants and cancer. Part VI. Selenium and age-adjusted human cancer mortality. *Archives of environmental health*. 1976;31(5):231–235.
15. Stratton MS, Reid ME, Schwartzberg G, et al. Selenium and inhibition of disease progression in men diagnosed with prostate carcinoma: study design and baseline characteristics of the 'Watchful Waiting' Study. *Anticancer Drugs*. 2003;14(8):595–600.
16. Stratton MS, Algotar AM, Ranger-Moore J, et al. Oral selenium supplementation has no effect on prostate-specific antigen velocity in men undergoing active surveillance for localized prostate cancer. *Cancer Prev Res (Phila)*. 2010;3(8):1035–1043.
17. Yoshizawa K, Willett WC, Morris SJ, et al. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst*. 1998;90(16):1219–1224.
18. Geybels MS, Verhage BA, van Schooten FJ, Goldbohm RA, van den Brandt PA. Advanced prostate cancer risk in relation to toenail selenium levels. *J Natl Cancer Inst*. 2013;105(18):1394–1401.
19. Hurst R, Hooper L, Norat T, et al. Selenium and prostate cancer: systematic review and meta-analysis. *Am J Clin Nutr*. 2012;96(1):111–122.
20. Lawson KA, Wright ME, Subar A, et al. Multivitamin use and risk of prostate cancer in the National Institutes of Health-AARP Diet and Health Study. *J Natl Cancer Inst*. 2007;99(10):754–764.
21. Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the Health Professionals Follow-up Study. *Int J Cancer*. 2007;121(7):1571–1578.
22. Zu K, Giovannucci E. Smoking and aggressive prostate cancer: a review of the epidemiologic evidence. *Cancer Causes Control*. 2009;20(10):1799–1810.
23. Kenfield SA, Stampfer MJ, Chan JM, Giovannucci E. Smoking and prostate cancer survival and recurrence. *JAMA*. 2011;305(24):2548–2555.
24. Rikiishi H. Apoptotic cellular events for selenium compounds involved in cancer prevention. *J Bioenerg Biomembr*. 2007;39(1):91–98.
25. Menter DG, Sabichi AL, Lippman SM. Selenium effects on prostate cell growth. *Cancer Epidemiol Biomarkers Prev*. 2000;9(11):1171–1182.
26. Xiang N, Zhao R, Zhong W. Sodium selenite induces apoptosis by generation of superoxide via the mitochondrial-dependent pathway in human prostate cancer cells. *Cancer Chemother Pharmacol*. 2009;63(2):351–362.
27. Sarveswaran S, Liroff J, Zhou Z, Nikitin AY, Ghosh J. Selenite triggers rapid transcriptional activation of p53, and p53-mediated apoptosis in prostate cancer cells: Implication for the treatment of early-stage prostate cancer. *Int J Oncology*. 2010;36(6):1419–1428.
28. Zeng H, Combs GF Jr. Selenium as an anticancer nutrient: roles in cell proliferation and tumor cell invasion. *J Nutr Biochem*. 2008;19(1):1–7.
29. Webber MM, Perez-Ripoll EA, James GT. Inhibitory effects of selenium on the growth of DU-145 human prostate carcinoma cells in vitro. *Biochem Biophys Res Commun*. 1985;130(2):603–609.
30. Redman C, Scott JA, Baines AT, et al. Inhibitory effect of selenomethionine on the growth of three selected human tumor cell lines. *Cancer Lett*. 1998;125(1–2):103–110.
31. Sinha R, Pinto JT, Facompre N, Kilheffer J, Baatz JE, El-Bayoumy K. Effects of naturally occurring and synthetic orga-

noselenium compounds on protein profiling in androgen responsive and androgen independent human prostate cancer cells. *Nutr Cancer*. 2008;60(2):267–275.
32. Lindshield BL, Ford NA, Canene-Adams K, Diamond AM, Wallig MA, Erdman JW Jr. Selenium, but not lycopene or vitamin E, decreases growth of transplantable dunning R3327-H rat prostate tumors. *PLoS One*. 2010;5(4):e10423.
33. Corcoran NM, Najdovska M, Costello AJ. Inorganic selenium retards progression of experimental hormone refractory prostate cancer. *J Urol*. 2004;171(2 Pt 1):907–910.
34. Wang Z, Hu H, Li G, et al. Methylseleninic acid inhibits microvascular endothelial G1 cell cycle progression and decreases tumor microvessel density. *Int J Cancer*. 2008;122(1):15–24.
35. de Rosa V, Erkekoglu P, Forestier A, et al. Low doses of selenium specifically stimulate the repair of oxidative DNA damage in LNCaP prostate cancer cells. *Free Radical Res*. 2012;46(2):105–116.
36. Kandas NO, Randolph C, Bosland MC. Differential effects of selenium on benign and malignant prostate epithelial cells: stimulation of LNCaP cell growth by noncytotoxic, low selenite concentrations. *Nutr Cancer*. 2009;61(2):251–264.
37. Rayman MP. Selenium and human health. *Lancet*. 2012;379(9822):1256–1268.
38. Willett WC, Buzzard IM. Foods and Nutrients. In: Willett WC, ed. *Nutritional Epidemiology*. 2nd ed. New York, NY: Oxford University Press; 1998:18–32.