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Journal

Journal of the National Cancer Institute, 108(12)

ISSN

0027-8874

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Publication Date

2016-12-01

DOI

10.1093/jnci/djw152

Peer reviewed

JNCI J Natl Cancer Inst (2016) 108(12): djw152

doi: 10.1093/jnci/djw152
First published online August 16, 2016
Article

ARTICLE

Selenium Supplementation for Prevention of Colorectal Adenomas and Risk of Associated Type 2 Diabetes

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Abstract

Background: Selenium supplementation may help to prevent colorectal cancer; as precursors of colorectal cancer, colorectal adenomas are a surrogate for colorectal cancer. Selenium supplementation may increase risk of type 2 diabetes (T2D).
Methods: The Selenium and Celecoxib (Sel/Cel) Trial was a randomized, placebo controlled trial of selenium 200 μg daily as selenized yeast and celecoxib 400 mg once daily, alone or together, for colorectal adenoma prevention. Men and women between age 40 and 80 years were eligible following colonoscopic removal of colorectal adenomas. The primary outcome was adenoma development. Celecoxib was suspended because of cardiovascular toxicity in other trials, but accrual continued to selenium and placebo. A total of 1621 participants were randomly assigned to selenium or placebo, of whom 1374 (84.8%) were available for analysis. All statistical tests were two-sided.
Results: In the respective placebo and selenium arms of 689 and 685 participants, adenoma detection after medians of 33.6 (range = 0.0–85.1 months) and 33.0 months (range = 0.0–82.6 months) were 42.8% and 44.1% (relative risk [RR] = 1.03, 95% confidence interval [CI] = 0.91 to 1.16, $P = .68$). In participants with baseline advanced adenomas, adenoma recurrence was reduced by 18% with selenium (RR = 0.82, 95% CI = 0.71 to 0.96, $P = .01$). In participants receiving selenium, the hazard ratio for new-onset T2D was 1.25 (95% CI = 0.74 to 2.11, $P = .41$), with a statistically significantly increased risk of selenium-associated T2D among older participants (RR = 2.21; 95% CI = 1.04 to 4.67, $P = .03$).
Conclusions: Overall, selenium did not prevent colorectal adenomas and showed only modest benefit in patients with baseline advanced adenomas. With limited benefit and similar increases in T2D to other trials, selenium is not recommended for preventing colorectal adenomas in selenium-replete individuals.

Deficiency of selenium, a dietary micronutrient that is incorporated into selenomethionine and selenocysteine, has been associated with cancer risk (1). The Nutritional Prevention of Cancer Trial (NPCT), a randomized controlled trial of selenized yeast to prevent skin cancer, showed no effect on the primary endpoint but showed statistically significant reductions of prostate and

Received: December 29, 2015; **Revised:** April 1, 2016; **Accepted:** May 17, 2016

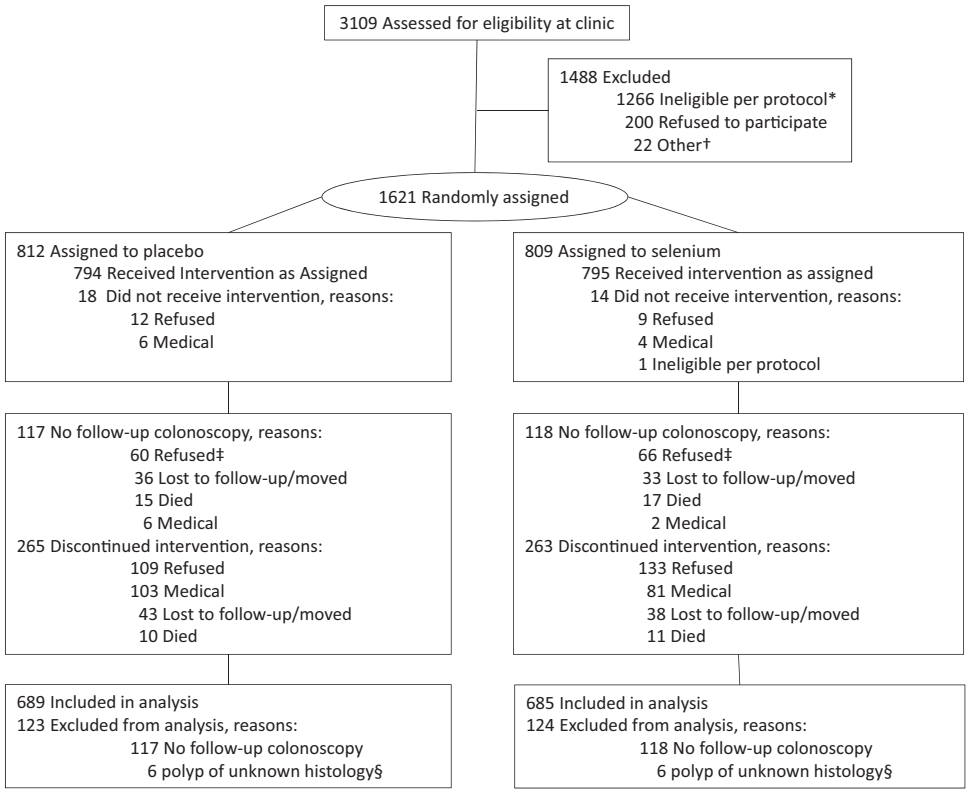

Figure 1. Patient flow diagram – original cohort. *Not eligible per protocol includes medical conditions (n = 484), medication use (n = 178), regular high-dose aspirin/NSAID use (n = 333), clinical lab results (n = 21), supplemental selenium use (n = 76), other (n = 174). †Other includes 16 lost to follow-up or moved, one deceased, five toxicity during placebo run-in. ‡Includes some participants with no follow-up colonoscopy at the close of the trial who agreed to participate in long-term follow-up and provide colonoscopy results in the future, participants lacking insurance coverage, etc. §The colonoscopy report indicated that either a polyp was destroyed in vivo or lost during the retrieval process, or a polyp was removed but there is no histological analysis on the pathology report, and no other polyp information was available. Without histological analysis, presence of adenomatous tissue cannot be determined.

colorectal cancers in secondary analyses (2). Despite enthusiasm for the chemopreventive potential of selenium, SELECT, a randomized controlled trial of *l*-selenomethionine and vitamin E for the prevention of prostate cancer, closed early for lack of any reduction in prostate cancer incidence (3). In a secondary analysis, there was also no reduction in colorectal cancer incidence. Further, the safety of selenium supplementation has been questioned (4). The incidence of type 2 diabetes (T2D) increased with selenium supplementation in NPCT participants during long-term follow-up (5), and there was a statistically nonsignificant hazard ratio (HR) of 1.07 (99% CI = 0.94 to 1.22, $P = .16$) for new diagnoses of T2D in SELECT participants receiving selenium alone.

Shortly after the initiation of SELECT, we launched The Selenium and Celecoxib (Sel/Cel) Trial, a randomized, placebo-controlled trial of selenized yeast and celecoxib, alone or together, for the prevention of colorectal adenomas. Selenium was selected on the basis of preclinical evidence (6–8) and the colorectal cancer–related results in NPCT. The celecoxib intervention was terminated early (9) on evidence of cardiovascular toxicity in other trials (10–13). Here, we report the effect of selenium supplementation on the development of colorectal adenomas and risk of T2D. Results from the celecoxib arm of Sel/Cel are reported in a companion article (14).

Methods

Trial Design

Sel/Cel was designed as a phase III, randomized, placebo-controlled, two-by-two factorial trial of celecoxib crossed with selenium for preventing colorectal adenomas (Clinical Trials.gov No. NCT00078897). As noted (9), on the recommendation of our External Data and Safety Monitoring Committee (EDSMC), the celecoxib arm was suspended in December 2004 because of reported coxib-associated cardiovascular toxicity (10–13). With permission from the Federal Drug Administration and the National Cancer Institute (NCI), the trial was modified to a two-arm design comparing selenium with placebo. Participants randomly assigned during the factorial phase were retained in the appropriate selenium or placebo arm but were no longer allocated celecoxib or its placebo (9).

Participants and Eligibility

Participants were recruited through clinical centers in Arizona, Colorado, Texas, and New York following ambulatory colonoscopies. Eligible participants were between age 40 and 80 years and had undergone colonoscopic removal of one or more colorectal adenomas 3 mm or larger within six months prior to random assignment. Patients with a family history of familial adenomatous polyposis or Lynch syndrome or a diagnosis of invasive cancer within five years were excluded. Individuals with unstable cardiac disease, uncontrolled hypertension, poorly controlled diabetes mellitus or renal insufficiency were excluded. Use of low-dose (≤81 mg daily) aspirin was allowed. To enhance power to assess the effect of selenium intervention among higher-risk individuals, recruitment of an additional 200 participants with one or more advanced adenomas (ie, adenomas ≥ 10 mm, villous

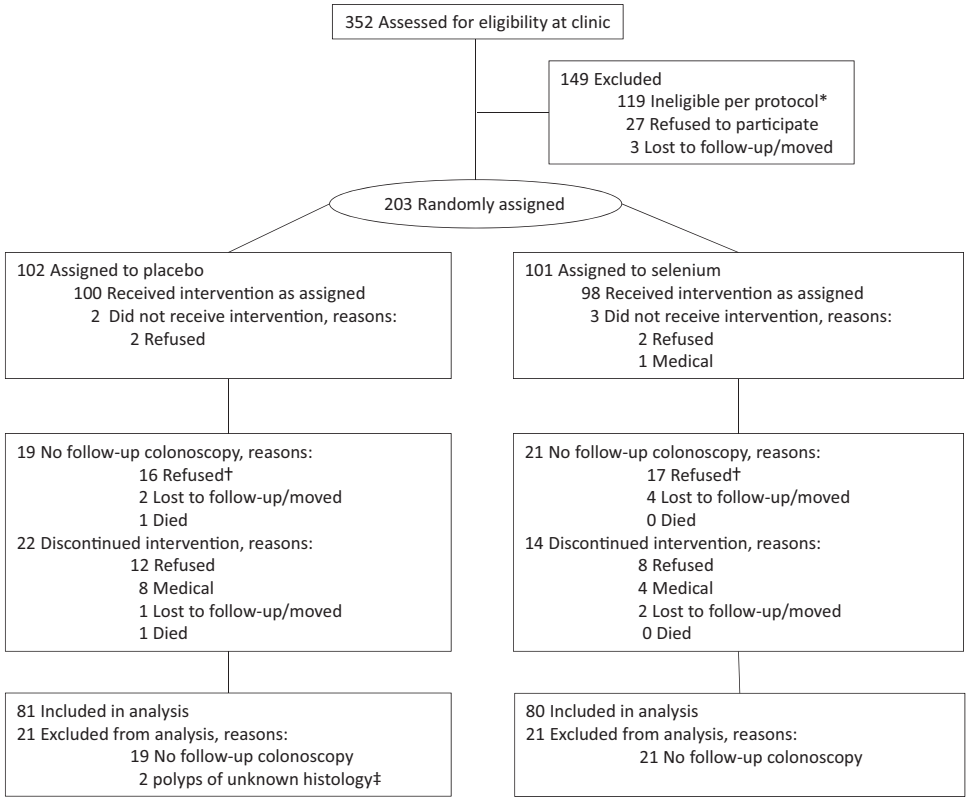

Figure 2. Patient flow diagram – Advanced Adenomas–Only cohort. *Not eligible per protocol includes medical conditions (n = 37), medication use (n = 50), regular high-dose aspirin/NSAID use (n = 1), clinical lab results (n = 2), supplemental selenium use (n = 20), other (n = 9). †Includes some participants with no follow-up colonoscopy at the close of the trial who agreed to participate in long-term follow-up and provide colonoscopy results in the future, participants lacking insurance coverage, etc. ‡The colonoscopy report indicated that either a polyp was destroyed in vivo or lost during the retrieval process, or a polyp was removed but there is no histological analysis on the pathology report, and no other polyp information was available. Without histological analysis, presence of adenomatous tissue cannot be determined.

histology, or high-grade dysplasia) was approved by the EDSMC and the NCI. Adenomatous histology was confirmed by review of pathology reports from local study sites.

All data and biospecimens were collected, managed, and archived at the University of Arizona Cancer Center (Tucson, AZ). The University of Arizona Institutional Review Board (IRB) approved and oversaw the study protocol. Conduct of the trial was in accordance with requirements of local IRBs at each study site. Written informed consent was obtained from all participants.

Intervention

The intervention of once-daily oral selenium 200 μg as selenized yeast was designed to replicate the NPCT intervention. SelenoExcell High Selenium Yeast tablets (200 μg) and matching placebo were provided by Cypress Systems (Madera, CA). Analysis and composition of SelenoExcell tablets were reported previously (9, 15, 16). Tablet selenium content was in the range of 191 to 201 μg throughout the study. Intervention was administered from random assignment until follow-up (surveillance) colonoscopy. The colonoscopy follow-up interval was determined by the participant's physician in conjunction with surveillance guidelines for polypectomy patients (17).

Outcomes

The primary outcome was any colorectal adenoma or cancer detected at a colonoscopy performed at least six months after random assignment until surveillance colonoscopy. Colorectal cancers diagnosed during follow-up were handled as adenoma recurrences and tabulated separately. Adenoma number, location, size, and histology were abstracted from endoscopic and pathology reports. Cumulative adenoma recurrence was ascertained over all follow-up colonoscopies.

Secondary outcomes included occurrences of multiple (≥3) or advanced adenomas (defined by one or more of the following features: 10 mm or more in size, with tubulovillous or villous villous tissue architecture, and/or with high-grade dysplasia). Toxicity outcomes included the development of T2D, brittle hair and/or nails, and squamous cell skin carcinoma (SCSC).

Sample Size

Details of sample size and statistical power adjustments following celecoxib suspension were reported (9). Sample size for the original factorial design was 800 participants per arm containing selenium, thus requiring random assignment of a total of 1600 participants. The adjusted statistical power was 94% to detect a 25% reduction in adenoma recurrence, based on recurrence rates observed in our previous adenoma prevention trials and revised guidelines for surveillance colonoscopy intervals (9, 17). The inclusion of 200 additional participants with advanced adenomas at baseline yielded 87% power to detect a 33% reduction in adenoma recurrence because of the selenium intervention in this higher-risk subgroup.

Table 1. Baseline participant and adenoma characteristics for the Modified Selenium Trial*

Characteristic	All randomized participants (n = 1824)		Modified SEL Trial (n = 1374)		Baseline advanced adenomas (n = 571)	
	Placebo No. (%) (n = 914)	Selenium No. (%) (n = 910)	Placebo No. (%) (n = 689)	Selenium No. (%) (n = 685)	Placebo No. (%) (n = 287)	Selenium No. (%) (n = 284)
Clinic						
Baylor	63 (6.9)	60 (6.6)	36 (5.2)	40 (5.8)	19 (6.6)	16 (5.6)
Phoenix	505 (55.3)	499 (54.8)	406 (58.9)	387 (56.5)	162 (56.5)	158 (55.6)
Colorado	161 (17.6)	162 (17.8)	123 (17.9)	125 (18.3)	56 (19.5)	58 (20.4)
Tucson	139 (15.2)	140 (15.4)	105 (15.2)	115 (16.8)	29 (10.1)	29 (10.2)
Mayo	31 (3.4)	33 (3.6)	19 (2.8)	18 (2.6)	8 (2.8)	7 (2.5)
Western New York	15 (1.6)	16 (1.8)	0	0	13 (2.8)	16 (5.6)
Mean age ± SD, y	62.6 ± 8.9	63.2 ± 9.0	63.1 ± 8.7	63.6 ± 8.9	62.4 ± 8.9	62.6 ± 8.8
Men	603 (66.0)	576 (63.3)	455 (66.0)	443 (64.7)	192 (66.9)	190 (66.9)
Race†						
White	851 (93.3)	857 (94.4)	650 (94.5)	652 (95.3)	277 (96.5)	268 (94.4)
Black/African	26 (2.9)	29 (3.2)	16 (2.3)	17 (2.5)	4 (1.4)	12 (4.2)
Asian	11 (1.2)	8 (0.9)	8 (1.2)	8 (1.2)	3 (1.1)	0 (0.0)
American Indian/Alaskan	5 (0.6)	4 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Other/mixed	19 (2.1)	10 (1.1)	13 (1.9)	7 (1.0)	3 (1.1)	4 (1.4)
Hispanic/Latino	54 (5.9)	36 (4.0)	39 (5.7)	25 (3.7)	10 (3.5)	7 (2.5)
Education						
<High school	14 (1.5)	21 (2.3)	9 (1.3)	13 (1.9)	1 (0.4)	7 (2.5)
High school or GED	186 (20.4)	167 (18.4)	140 (20.3)	117 (17.1)	69 (24.0)	53 (18.7)
Some college	267 (29.2)	274 (30.2)	198 (28.7)	214 (31.3)	83 (28.9)	92 (32.4)
Bachelor's degree	180 (19.7)	201 (22.1)	134 (19.5)	154 (22.5)	57 (19.9)	68 (23.9)
Graduate/professional	267 (29.2)	245 (27.0)	208 (30.2)	186 (27.2)	77 (26.8)	64 (22.5)
Mean BMI‡ ± SD	29.2 ± 5.1	29.1 ± 5.1	29.2 ± 5.2	28.8 ± 4.9	29.5 ± 5.1	29.2 ± 5.3
Cigarette smoking status§						
Current	80 (9.1)	91 (10.3)	50 (7.5)	56 (8.3)	25 (9.0)	24 (8.6)
Previous	417 (47.4)	444 (50.2)	320 (47.9)	342 (50.7)	125 (45.1)	143 (51.3)
Never	383 (43.5)	350 (39.6)	298 (44.6)	276 (41.0)	127 (45.9)	112 (40.1)
History of colorectal polyp	266 (29.7)	316 (35.4)	198 (29.2)	239 (35.5)	92 (32.2)	91 (32.5)
Family history of CRC‖	163 (18.9)	174 (20.0)	126 (19.4)	135 (20.5)	60 (21.7)	48 (17.7)
Diabetes	100 (10.9)	79 (8.7)	71 (10.3)	53 (7.7)	26 (9.1)	27 (9.5)
Personal history of cancer¶	59 (6.5)	46 (5.1)	44 (6.4)	39 (5.7)	22 (7.7)	10 (3.5)
Personal history of skin cancer#	144 (15.8)	142 (15.6)	116 (16.8)	115 (16.8)	52 (18.1)	43 (15.1)
Personal history of squamous cell skin cancer	28 (3.1)	33 (3.6)	23 (3.3)	28 (4.1)	9 (3.1)	11 (3.9)
Aspirin use in the past 20 y**						
<1 y	508 (55.6)	506 (55.7)	384 (55.7)	379 (55.3)	173 (60.3)	167 (58.8)
1–<5 y	192 (21.0)	188 (20.7)	143 (20.8)	146 (21.3)	55 (19.2)	55 (19.4)
5–<10 y	92 (10.1)	85 (9.4)	76 (11.0)	63 (9.2)	22 (7.7)	25 (8.8)
≥10 y	121 (13.3)	129 (14.2)	86 (12.5)	97 (14.2)	37 (12.9)	37 (13.0)
Aspirin use (1–81mg/d) at random assignment	423 (46.3)	426 (46.8)	330 (47.9)	336 (49.1)	117 (40.8)	129 (45.4)

(continued)

Table 1. Continued

Characteristic	All randomized participants (n = 1824)		Modified SEL Trial (n = 1374)		Baseline advanced adenomas (n = 571)	
	Placebo No. (%) (n = 914)	Selenium No. (%) (n = 910)	Placebo No. (%) (n = 689)	Selenium No. (%) (n = 685)	Placebo No. (%) (n = 287)	Selenium No. (%) (n = 284)
NSAID use in the past 20 y††						
<1 y	817 (89.5)	801 (88.2)	620 (90.0)	609 (88.9)	265 (92.3)	245 (86.3)
1–<5 y	51 (5.6)	73 (8.0)	42 (6.1)	51 (7.5)	10 (3.5)	29 (10.2)
5–<10 y	23 (2.5)	13 (1.4)	16 (2.3)	7 (1.0)	5 (1.7)	2 (0.7)
≥10 y	22 (2.4)	21 (2.3)	11 (1.6)	18 (2.6)	7 (2.4)	8 (2.8)
Supplement user	598 (69.4)	583 (67.4)	458 (69.3)	462 (69.6)	191 (68.2)	181 (65.3)
Selenium supplement use at recruitment, μg						
0	420 (46.0)	432 (47.5)	308 (44.7)	322 (47.0)	136 (47.4)	138 (48.6)
1–50	374 (40.9)	354 (38.9)	297 (43.1)	280 (40.9)	108 (37.6)	103 (36.3)
51–199	81 (8.9)	99 (10.9)	50 (7.3)	64 (9.3)	31 (10.8)	33 (11.6)
≥200	39 (4.3)	25 (2.8)	34 (4.9)	19 (2.8)	12 (4.2)	10 (3.5)
Selenium supplement use (≤50 μg) at random assignment	433 (51.8)	427 (51.2)	337 (54.1)	330 (53.1)	126 (48.3)	137 (51.7)
Selenium in plasma, median (Q1, Q3), ng/mL	135.2 (120.8, 153.3)	135.5 (121.5,151.8)	135.3 (120.8, 155.2)	136.6 (122.2,152.9)	134.0 (121.0,151.7)	134.9 (121.3,151.1)
No. of adenomas						
1	546 (59.7)	507 (55.7)	422 (61.3)	386 (56.4)	131 (45.6)	110 (38.7)
2	189 (20.7)	216 (23.7)	139 (20.2)	164 (23.9)	74 (25.8)	88 (31.0)
3+	179 (19.6)	187 (20.6)	128 (18.6)	135 (19.7)	82 (28.6)	86 (30.3)
Proximal adenoma	560 (64.4)	577 (66.1)	417 (63.5)	435 (66.7)	187 (67.0)	182 (65.5)
Distal/rectal adenoma	481 (55.4)	498 (57.0)	364 (55.4)	368 (56.4)	172 (61.7)	187 (67.3)
Largest adenoma (≥10 mm)	303 (34.1)	312 (35.2)	176 (26.4)	183 (27.6)	257 (90.2)	263 (93.9)
Histology (most severe)						
Tubular or adenoma, NOS	793 (86.8)	789 (86.7)	599 (86.9)	603 (88.0)	180 (62.7)	180 (63.4)
Tubulovillous or villous	121 (13.2)	120 (13.2)	90 (13.1)	82 (12.0)	107 (37.3)	104 (36.6)
Invasive cancer‡‡	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
High-grade dysplasia	18 (2.0)	17 (1.9)	13 (1.9)	11 (1.6)	13 (4.5)	15 (5.3)
Advanced adenoma§§	337 (37.8)	338 (37.9)	206 (30.8)	204 (30.6)	287 (100.0)	284 (100.0)

*SD = standard deviation; Q1 = 25th percentile; Q3 = 75th percentile; NOS = not otherwise stated; BMI = body mass index; CRC = colorectal cancer.
†Twenty-five participants marked more than one race, including 22 who selected a race they identified with primarily (and classified accordingly) and three who were unable to identify with one group (classified as mixed).
‡BMI calculated as 703 x (weight in pounds)/(height in inches)^2.
§Ever smoker defined as 100 or more cigarettes.
||Family history of CRC in a first-degree relative.
¶Excluding nonmelanoma skin cancer.
#Including basal cell, squamous cell, and skin cancer of unknown type.
**Number of years in total within the past twenty years taking aspirin or aspirin-containing products at least twice a week for at least six consecutive months.
††Number of years in total within the past twenty years taking a nonsteroidal anti-inflammatory drug (NSAID), excluding aspirin, either over-the-counter or prescription at least twice a week for at least six consecutive months.
‡‡One participant was diagnosed with CRC less than six months after random assignment. This is classified as a baseline event (ie, not an outcome).
§§Advanced adenoma defined as having one or more of the following features: adenoma 10 mm or larger, with tubulovillous or villous architecture and/or with high-grade dysplasia.

Table 2. Adherence, duration of intervention, bioadherence, and follow-up*

Adherence and follow-up	Originally planned cohort,available for analysis (n = 1374)		Participants with advanced adenomas at baseline,available for analysis (n = 571)	
	Placebo Median (Q1, Q3) (n = 689)	Selenium Median (Q1, Q3) (n = 685)	Placebo Median (Q1, Q3) (n = 287)	Selenium Median (Q1, Q3) (n = 284)
Adherence while on study, %	96.4 (89.5, 99.0)	96.6 (91.0, 99.1)	96.4 (90.5, 98.8)	96.6 (91.0, 99.1)
Adherence until follow-up colonoscopy, %	95.9 (82.5, 99.0)	96.3 (85.1, 99.0)	96.2 (89.0, 98.8)	96.7 (90.0, 99.0)
Duration of intervention, mo	33.6 (28.9, 49.2)	33.0 (28.6, 43.5)	32.4 (28.1, 38.6)	32.4 (28.9, 37.3)
Bioadherence after 1 y on study, ng/mL†	140.0 (124.7, 157.0)	205.4 (177.6, 232.1)	138.8 (122.9, 159.5)	205.7 (180.3, 232.3)
Follow-up time, mo‡	35.6 (31.6, 53.3)	35.5 (31.2, 53.5)	33.4 (30.9, 41.8)	33.0 (30.3, 40.6)
No. of follow-up endoscopies§				
0	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
1	625 (90.7)	636 (92.9)	241 (84.0)	253 (89.1)
2	58 (8.4)	45 (6.6)	42 (14.6)	29 (10.2)
3	6 (0.9)	3 (0.4)	4 (1.4)	2 (0.7)

*Q1 = 25th percentile; Q3 = 75th percentile.
†Bioadherence available for 515 and 519 participants in the placebo and selenium arms of the original planned cohort, respectively, and for 150 and 155 participants in the placebo and selenium arms among participants with advanced adenoma at baseline, respectively.
‡Months from random assignment date to last follow-up procedure.
§Includes 1373 colonoscopies and three sigmoidoscopies among the originally planned cohort. One participant had no follow-up endoscopy, though colorectal adenomas were found during a surgery. Among the participants with advanced adenomas at baseline, there were 571 follow-up colonoscopies and two sigmoidoscopies.

Table 3. Detection of metachronous colorectal adenomas during follow-up, by treatment, in the original cohort*

Adenoma outcome	Placebo		Selenium	
Any adenoma/total (%)	295/689	(42.8)	302/685	(44.1)
RR (95% CI), P			1.03 (0.91 to 1.16), .68	
Advanced /total (%)†	63/676	(9.3)	64/673	(9.5)
RR (95% CI), P			1.02 (0.74 to 1.43), .89	
Multiple (3+) neoplasms /total (%)‡	58/678	(8.6)	85/667	(12.7)
RR (95% CI), P			1.47 (1.08 to 2.02), .02	

*Two-sided log-binomial regression analysis adjusted for celecoxib random assignment, regular aspirin use, and clinic. CI = confidence interval; RR = relative risk.
†Advanced status uncertain for 25 participants because of missing size.
‡Number of adenomas uncertain for 29 participants.

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Random Assignment

Random assignment was conducted using a Structured Query Language function that checked for previous random assignment and a valid clinic identification number. Random assignment was stratified by clinic site and use of low-dose aspirin. A block size of four was used for the factorial design.

Intervention Adherence

Adherence during active participation and until follow-up colonoscopy was derived from pill counts recorded at each clinic visit for all patients. Selenium plasma concentrations were measured at baseline and one year after random assignment (9).

Statistical Methods

All participants who had a follow-up colonoscopy were included in intent-to-treat analyses, including those randomly assigned prior to the suspension of celecoxib. A planned likelihood ratio test (LRT) for interaction between selenium and celecoxib was not statistically significant (P = .78). Hence, the celecoxib results are reported separately.

Log-binomial regression was used to estimate the relative risk (RR) and 95% confidence interval (CI) for the primary and secondary adenoma outcomes. Poisson regression with robust variance was planned as an alternative method for calculating the relative risk and 95% CI in the event of convergence failure of the log-binomial model (18,19). All models were adjusted for the design variables of random assignment to celecoxib, regular use of low-dose aspirin, and clinic site. Sensitivity analysis including only participants with an endpoint colonoscopy performed at least 2.5 years after the qualifying baseline colonoscopy did not change the overall findings, nor did adjustment for the total number of colonoscopies during follow-up.

The 200 participants randomly assigned in the Advanced Adenomas–Only cohort were excluded from the primary analysis to preserve generalizability to the adenoma severity profile of the original trial cohort. Outcome data were available for a subgroup of 571 participants with baseline, prerandomization advanced adenomas. Included in analyses of potential effect modifiers of selenium were baseline use of low-dose aspirin, sex, and baseline plasma selenium level. An LRT test was used to compare a model containing an interaction term between the intervention arm and the potential modifier with a reduced model without an interaction term. All statistical tests were two-sided, and a P value of less than .05 was considered statistically significant.

Toxicity Analysis

Time-to-event toxicity analyses included all serious adverse events and known potential selenium-associate toxicities: T2D, brittle hair and nails, and squamous cell skin cancer (SCSC). HRs and 95% CIs were generated using Cox regression adjusted for design variables.

Results

Random assignment of 1621 participants began on November 27, 2001, and was completed on November 26, 2008; at the time the celecoxib arm was terminated on December 20, 2004, 414 participants had been randomly assigned to celecoxib and 410

Table 4. Metachronous colorectal neoplasia in subgroups, by treatment, in the original cohort*

Characteristic	Any metachronous colorectal adenoma		Advanced adenomas or CRC†		Multiple (3+) neoplasms‡	
	Placebo No. (%)	Selenium No. (%)	Placebo No. (%)	Selenium No. (%)	Placebo No. (%)	Selenium No. (%)
Regular aspirin use						
Users	140/330 (42.4)	146/336 (43.5)	30/321 (9.3)	27/333 (8.1)	27/325 (8.3)	43/327 (13.1)
RR (95% CI), *P*		1.03 (0.86 to 1.22), .77		0.86 (0.53 to 1.41), .55		1.58 (1.00 to 2.49), .049
Nonusers	155/359 (43.2)	156/349 (44.7)	33/355 (9.3)	37/340 (10.9)	31/353 (8.8)	42/340 (12.4)
RR (95% CI), *P*		1.03 (0.87 to 1.21), .76		1.16 (0.75 to 1.81), .50		1.39 (0.90 to 2.15), .14
LRT $P_{interaction}$		.95		.38		.75
Sex						
Men	212/455 (46.6)	209/443 (47.2)	45/447 (10.1)	49/436 (11.2)	46/447 (10.3)	73/431 (16.9)
RR (95% CI), *P*		1.02 (0.89 to 1.17), .77		1.12 (0.76 to 1.64), .56		1.64 (1.17 to 2.31), .004
Women	83/234 (35.5)	93/242 (38.4)	18/229 (7.9)	15/237 (6.3)	12/231 (5.2)	12/236 (5.1)
RR (95% CI), *P*		1.08 (0.86 to 1.37), .51		0.82 (0.42 to 1.60), .57		0.88 (0.41 to 1.92), .76
LRT $P_{interaction}$		.75		.43		.21
Baseline plasma selenium, ng/mL§						
Tertile 1	103/234 (44.0)	91/221 (41.2)	21/230 (9.1)	20/216 (9.3)	19/232 (8.2)	28/216 (13.0)
RR (95% CI), *P*		0.94 (0.76 to 1.17), .59		1.00 (0.56 to 1.79), .99		1.47 (0.85 to 2.55), .16
Tertile 2	85/217 (39.2)	100/239 (41.8)	15/212 (7.1)	19/235 (8.1)	17/213 (8.0)	24/236 (10.2)
RR (95% CI), *P*		1.03 (0.83 to 1.29), .77		1.18 (0.62 to 2.27), .61		1.26 (0.70 to 2.27), .44
Tertile 3	105/233 (45.1)	109/221 (49.3)	26/229 (11.4)	25/218 (11.5)	21/228 (9.2)	33/212 (15.6)
RR (95% CI), *P*		1.07 (0.88 to 1.29), .52		1.01 (0.60 to 1.69), .98		1.68 (1.01 to 2.81), .047
LRT $P_{interaction}$		.57		.93		.81
≤121.6 ng/mL‖	80/177 (45.2)	69/166 (41.6)	13/174 (7.5)	10/162 (6.2)	12/175 (6.9)	17/162 (10.5)
RR (95% CI), *P*		0.93 (0.73 to 1.19), .56		0.85 (0.39 to 1.89), .70		1.43 (0.71 to 2.87), .31
>121.6 ng/mL	213/507 (42.0)	231/515 (44.9)	49/497 (9.9)	54/507 (10.7)	45/498 (9.0)	68/502 (13.6)
RR (95% CI), *P*		1.06 (0.92 to 1.21), .44		1.09 (0.75 to 1.57), .65		1.51 (1.06 to 2.15), .02
LRT $P_{interaction}$		.29		.53		.96

*Two-sided log-binomial regression analysis adjusted for random assignment to celecoxib, regular aspirin use, and clinic. CI = confidence interval; LRT = two-sided likelihood ratio test; RR = relative risk.

†Advanced status uncertain for 25 participants for whom adenoma size missing.

‡Number of adenomas uncertain for 29 participants.

§Baseline plasma sample not obtained for nine participants because of blood draw difficulties. Tertile 1: 74.100–126.287; tertile 2: 126.315–147.476; tertile 3: 147.478–435.317.

‖Cutpoint from the Nutritional Prevention of Cancer Trial (2,20).

Table 5. Metachronous colorectal adenomas among participants, by treatment, stratified by baseline advanced adenoma status, in the original cohort and the Advanced Adenomas-Only cohort*

Baseline advanced adenoma status	Any metachronous colorectal adenoma		Advanced adenomas†		Multiple (3+) adenomas‡	
	Placebo No./ Total (%)	Selenium No./ Total (%)	Placebo No./ Total (%)	Selenium No./ Total (%)	Placebo No./ Total (%)	Selenium No./ Total (%)
Nonadvanced	174/462 (37.7)	200/463 (43.2)	28/455 (6.2)	36/455 (7.9)	32/455 (7.0)	52/453 (11.5)
RR (95% CI), *P*		1.15 (0.98 to 1.34), .09		1.31 (0.82 to 2.11), .26		1.63 (1.07 to 2.48), .02
Advanced§	168/287 (58.5)	138/284 (48.6)	47/282 (16.7)	37/284 (13.0)	40/283 (14.1)	50/273 (18.3)
RR (95% CI), *P*		0.82 (0.71 to 0.96), .01		0.77 (0.51 to 1.14), .19		1.27 (0.87 to 1.84), .22
LRT $P_{interaction}$‖		.003		.10		.38

*Two-sided log-binomial regression adjusted for random assignment to celecoxib, regular aspirin use, and clinic. CI = confidence interval; LRT = two-sided likelihood ratio test; RR = relative risk.

†Advanced status colorectal adenoma defined by one or more of the following features: adenomas 10 mm or more in size; or tubulovillous or villous tissue architecture, high-grade dysplasia, regardless of size; advanced status is uncertain for 25 participants because of missing size.

‡Multiple adenomas defined as three or more adenomas; number of adenomas is uncertain for 29 participants.

§Subgroup of participants with advanced adenomas at baseline includes participants from the originally planned cohort with an advanced adenoma(s), as well as the participants in the advanced adenomas cohort.

‖LRT comparing the main effects model with a model including main effects and an interaction term between baseline advanced adenoma status and random assignment to selenium.

Table 6. Selenium and serious adverse events*

Adverse event	Events/participants		Event rate/1000 person-years			
	Placebo	Selenium	Placebo	Selenium	HR (95% CI), P	LRT $P_{interaction}$
Serious adverse events	226/912	222/908	100.9	101.3	1.00 (0.83 to 1.21), .98	$P_{Sel*Sex} = .39$
Women	69/310	68/333	98.3	86.4	0.89(0.64 to 1.25), .50	
Men	157/602	154/575	102.1	109.7	1.06 (0.85 to 1.33), .60	
Brittle hair and/or nails	35/912	30/908	13.8	12.2	0.86(0.53 to 1.39), .53	$P_{Sel*Sex} = .78$
Women	17/310	15/333	21.6	17.3	0.78(0.39 to 1.57), .49	
Men	18/602	15/575	10.3	9.4	0.89(0.45 to 1.76), .73	
Squamous cell carcinoma, new primary	21/912	27/908	8.2	10.9	1.34 (0.76 to 2.37), .32	$P_{Sel*Sex} = .17$
Women	5/310	3/333	6.2	3.4	0.52 (0.13 to 2.20), .37	
Men	16/602	24/575	9.2	15.2	1.64 (0.87 to 3.09), .12	
Participants with history of SCC at baseline	5/28	6/33	68.8	78.3	1.09 (0.30 to 4.04), .89	
Type 2 diabetes†	25/812	31/828	11.0	13.7	1.25 (0.74 to 2.11), .41	$P_{Sel*Sex} = .38$
Women	6/286	12/306	8.0	15.0	1.85 (0.69 to 4.97), .21	
Men	19/526	19/522	12.5	13.0	1.05 (0.56 to 1.99), .87	
Age at random assignment < 63 y	15/395	9/393	13.5	8.1	0.59 (0.25 to 1.35), .20	$P_{Sel*Age}‡ = .02$
Age at random assignment ≥ 63 y	10/417	22/435	8.6	19.2	2.21 (1.04 to 4.67), .03	

*Two-sided Cox regression model adjusted for random assignment to celecoxib, aspirin, and clinic. CI = confidence interval; LRT = two-sided likelihood ratio test.
†Excluding participants with diabetes prior to random assignment.
‡Interaction between selenium and age as a continuous variable.

to selenium. In the 1621-participant cohort, among the 812 randomly assigned to placebo and 809 to selenium, 689 (84.7%) and 685 (84.7%), respectively, were available for the primary analysis (Figure 1). Random assignment of the additional 203 participants (102 placebo and 101 selenium) with advanced adenomas was completed on January 19, 2011. Of these, 81 (79.4%) and 80 (79.2%) randomly assigned to placebo and selenium, respectively, were available for analysis (Figure 2). The last individual to finish taking study medication did so on December 17, 2013.

Baseline participant characteristics of the placebo and selenium arms were well balanced and are shown in Table 1 for three groups: 1) the entire 1824 participant cohort (1621 in the original cohort and an additional 203 in the Advanced Adenomas-Only cohort); 2) the 1374 participants (84.8%) with outcome data from the original 1621, on whom the primary analysis was based; and 3) the combined total of 571 participants with baseline advanced adenomas with outcome data.

Adherence to intervention during active participation was assessed (Table 2). Median adherence was 95.9% (range = 0.0%–110.3%) vs 96.3% (range = 0.0%–105.9%) for the placebo vs selenium groups for the time from random assignment until follow-up colonoscopy for the periods of active participation and until follow-up and was similar in placebo and selenium groups for the original and Advanced Adenomas-Only cohorts. The median period of taking study medication was 33.6 months (range = 0.0-85.1 months and 33.0 months (range = 0.0–82.6 months), respectively, for the placebo and selenium arms. After one year on study, the median blood selenium levels among placebo and selenium participants, respectively, were 140.0 ng/mL (range = 84.9–270.2 ng/mL) and 205.4 ng/mL (range = 100.7–367.6 ng/mL, P < .001), reflecting high adherence.

In the complete cohort (n = 1824), nine colorectal cancers were detected after random assignment. Eight occurred before celecoxib was suspended; of these, two occurred in the double placebo arm, two in the celecoxib-only arm, three in the selenium-only arm, and one in the celecoxib + selenium arm. One cancer occurred in the selenium arm after celecoxib was suspended.

After medians of 35.6 months (range = 6.7–115.6 months) and 35.5 months (range = 6.5–115.6 months), respectively, recurrent adenomas were detected in 42.8% and 44.1% of participants randomly assigned to placebo and selenium (RR = 1.03, 95% CI = 0.91 to 1.16, P = .68) (Table 3). Further, there was no evidence that selenium prevented advanced adenoma recurrence (RR = 1.02, 95% CI = 0.74 to 1.43, P = .89). Recurrence with multiple adenomas was statistically significantly higher in the selenium arm, with multiple adenomas found in 12.7% of participants randomly assigned to selenium compared with 8.6% those on placebo (RR = 1.47, 95% CI = 1.08 to 2.02, P = .02); this finding was observed in men (RR = 1.64, 95% CI = 1.17 to 2.31, P = .004) but not women (Table 4). There was no evidence that baseline use of low-dose aspirin modified the effect of selenium. In a preplanned analysis of participants with advanced adenomas at baseline from the original and Advanced Adenomas–Only cohorts, adenoma recurrences in the selenium and placebo arms, respectively, were 48.6% and 58.5% (RR = 0.82, 95% CI = 0.71 to 0.96, P = .01) (Table 5). Further, there was a statistically significant interaction between random assignment to selenium and advanced adenoma status at baseline (P = .003), suggesting a selenium benefit confined to participants presenting with advanced adenomas.

To assess the impact of plasma selenium status prior to intervention, the analysis was stratified by tertile of baseline plasma selenium level and also above or below a cutpoint of 121.6 ng/mL; this was the baseline selenium level in the NPCT above which there was no evidence for a reduction of cancer risk with selenium supplementation (2,20). We found no evidence that pretreatment plasma selenium modified the effect of the selenium intervention on adenoma recurrence (Table 4). However, only 33.6% of participants had baseline selenium levels of 121.6 ng/mL or lower.

Of 1824 participants randomly assigned, 1820, for whom the duration of exposure to intervention was known, were included in toxicity analyses. The median duration of exposure was 33.0 months (range = 0.1–87.4 months). The overall HR for SCSC in participants randomly assigned to selenium was 1.34 (95% CI = 0.76 to 2.37, P = .32); in men, the HR was 1.64 (95% CI = 0.87 to 3.09, P = .12), with a $P_{interaction}$ of .17 (Table 6). For the analysis of risk for developing T2D, participants diagnosed with diabetes prior to random assignment were excluded. Among the

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remaining 1640 participants, 31 and 25 randomly assigned to selenium and placebo, respectively, were diagnosed with T2D during follow-up. This modestly higher event rate in the selenium arm was not statistically significant (HR = 1.25, 95% CI = 0.74 to 2.11, $P = .41$). However, there was a statistically significant interaction between increasing age as a continuous variable with random assignment to selenium and T2D risk (LRT $P = .02$), suggesting that with advancing age selenium supplementation may increase risk for T2D. Thus, when stratified at the mean participant age at baseline of 63 years, in participants age 63 years or older the incidence of T2D was 19.2 per 1000 person-years compared with 8.6 per 1000 person-years in those randomly assigned to selenium versus placebo, respectively (HR = 2.21, 95% CI = 1.04 to 4.67, $P = .03$). Conversely, for those younger than age 63 years, the incidence of T2D was 8.1 per 1000 compared with 13.5 per 1000 among those randomly assigned to selenium vs placebo, respectively (HR = 0.59, 95% CI = 0.25 to 1.35, $P = .20$).

Discussion

Selenium 200 μg daily as selenized yeast had no statistically significant effect on the primary outcome of adenoma recurrence. However, in a planned subgroup analysis of participants with advanced adenomas at baseline, there was a modest but statistically significant reduction in adenoma recurrence among those randomly assigned to selenium compared with placebo. Recurrence with multiple adenomas was statistically significantly increased in men but not women randomly assigned to selenium compared with placebo. We observed no overall increase in risk of T2D with selenium, but, when taking age into consideration, older age was associated with selenium-associated risk for T2D.

A study limitation is under-representation of individuals with low circulating selenium levels at baseline; after initiating our trial, NPCT investigators reported that the observed reductions in cancer risk attributed to selenium were only present in the two-thirds of participants whose baseline selenium levels were 121.6 ng/mL or lower (20). The median plasma selenium level at entry for the responsive NPCT population was 114 ng/mL (1.45 μmol/L); this contrasts with the median baseline plasma selenium level in the current trial of 135 ng/mL (1.72 μmol/L), which is well above the ceiling for response to selenium supplementation in NPCT (21,22). Differences in circulating selenium levels between study populations likely reflect geographic variability in dietary selenium content and other factors, including secular changes in the selenium content of food and use of selenium-containing supplements. Our findings are only generalizable to selenium-replete individuals.

Given the negative primary trial outcome, the finding of a beneficial effect of selenium in participants with advanced adenomas at baseline was unexpected. While chance alone may account for this finding, earlier studies suggest alternative explanations. The risk of developing advanced adenomas was reported to be related to allelic variations in selenoprotein P (*SEPP1*) and thioredoxin reductase 1 (*TXNRD1*) (23). SEPP1 contains 10 selenocysteine residues and is important for transporting selenium to the gastrointestinal tract (24). *SEPP1* expression was found to be lower in colorectal adenomas than normal tissue (25) and reduced or absent in colorectal cancers (26). While speculative, selenium supplementation might protect against redox-mediated damage in individuals with low SEPP1 levels, who might be at increased risk for advanced adenomas.

Why the excess of recurrence with multiple adenomas in participants randomly assigned to selenium is unclear. Reporting the number of small polyps at colonoscopy is prone to inaccuracy (27,29), but characteristics of selenium and placebo arm participants were well balanced by clinic site and there is no reason to suspect a random assignment artifact. A biological consideration could be unexpected protumorigenic effects of selenium at high doses as has been observed with other micronutrients (30). Although anticarcinogenic effects of selenium are often ascribed to its anti-oxidant properties, pro-oxidant activity or perturbation of redox-based cell signaling mechanisms at chronic high levels of exposure may promote neoplastic changes (31,32). This could explain the increased number of high-grade prostate cancers in the SELECT trial among men with high baseline toenail selenium levels who were randomly assigned to selenium (33). We observed no differences in circulating selenium levels between men and women at baseline or after one year on study (data not shown). However, toenail levels may reflect accumulated exposure to selenium more accurately than more transient blood levels (34), and daily selenium intake has been reported to be higher in men (151 μg) than women (108 μg). Pre-existing sufficiency and increased exposure to selenium in male compared with female participants, which was not reflected in blood levels, might explain increased recurrence with multiple adenomas in men but not women randomly assigned to selenium.

The risk for T2D associated with selenium supplementation is vigorously debated (4). Our observation of an increase in T2D risk with selenium, which was hinted at in SELECT (3), and evidence for age as a compounding factor are noteworthy. Following the NPCT report of selenium-associated T2D (5), increased risk of T2D with higher selenium levels has been reported in observational studies (35,36). Mechanistic studies, in which glutathione peroxidase (GPX) 1/2 feature prominently, have shown that selenium can both preserve pancreatic β-cell insulin secretion (antidiabetic) and enhance insulin resistance (diabetogenic) (36–39). A meta-analysis of the NPCT and three additional randomized controlled trials reported a RR of selenium-associated T2D of 1.09 (95% CI = 0.99 to 1.20) (40). However, age, duration of exposure, and interaction with other T2D risk factors were not considered. T2D is a multifactorial disease that takes many years to develop. Accordingly, even if selenium supplementation increases T2D risk and absent other new risk factors, it would be expected that new cases arising through a limited, roughly three-year exposure to selenium, as here, would be relatively infrequent. In NPCT participants, the effect of selenium-related T2D was apparent only after an average of 7.7 years of exposure (5). The interaction between selenium supplementation and increasing age as a susceptibility factor for T2D as reported here, combined with the consistency of the positive association between selenium and T2D in other studies, warrants attention.

Selenium supplementation did not prevent overall colorectal adenoma recurrence but did reduce recurrence by 18% in participants who initially had an advanced adenoma. In support of a diabetogenic effect of selenium supplementation, a positive association between selenium supplementation and T2D risk was observed as in earlier studies. In the absence of any proven overall benefit, selenium supplementation in the largely replete US population is not supported by our findings. In the context of recent estimates indicating that about 20% of the US population self-administers selenium-containing supplements (34), our study also raises further questions about the safety of this practice.

Funding

This trial is supported by grants P01 CA041108 (to PL), R01 CA151708 (to PL and PAT), and P30 CA23074 (to ASK).

Notes

The study funders had no role in the design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

The authors thank the research nurses and clinic staff: Mildred Arnold, Patricia Blair, Darlene Bunpian, Amy Carrier, Marita Clifford, Ann Dejong-Ruhnau, Theresa Dunn, Pat Graham, Dianne Parish, Eugenia M. Schleski, and Christina Yang-Hellewell; and staff of the study laboratory and data management team at the University of Arizona Cancer Center: Carole Kepler, Christina Preece, Jerilyn San Jose, and Manuel Snyder.

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