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Research Article

Cancer Prevention Research

Colorectal Adenomas in Participants of the SELECT Randomized Trial of Selenium and Vitamin E for Prostate Cancer Prevention

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Abstract

Selenium and vitamin E micronutrients have been advocated for the prevention of colorectal cancer. Colorectal adenoma occurrence was used as a surrogate for colorectal cancer in an ancillary study to the Selenium and Vitamin E Cancer Prevention Trial (SELECT) for prostate cancer prevention. The primary objective was to measure the effect of selenium (as selenomethionine) on colorectal adenomas occurrence, with the effect of vitamin E (as α-tocopherol) supplementation on colorectal adenoma occurrence considered as a secondary objective. Participants who underwent lower endoscopy while in SELECT were identified from a subgroup of the 35,533 men randomized in the trial. Adenoma occurrence was ascertained from the endoscopy and pathology reports for these procedures. Relative Risk (RR) estimates and 95% confidence intervals (CI) of adenoma occurrence were generated comparing those randomized to selenium versus placebo and to vitamin E versus placebo based on the full factorial design. Evaluable endoscopy information was obtained for 6,546 participants, of whom 2,286 had 1+ adenomas. Apart from 21 flexible sigmoidoscopies, all the procedures yielding adenomas were colonoscopies. Adenomas occurred in 34.2% and 35.7%, respectively, of participants whose intervention included or did not include selenium. Compared with placebo, the RR for adenoma occurrence in participants randomized to selenium was 0.96 (95% CI, 0.90–1.02; $P = 0.194$). Vitamin E did not affect adenoma occurrence compared with placebo (RR = 1.03; 95% CI, 0.96–1.10; $P = 0.38$). Neither selenium nor vitamin E supplementation can be recommended for colorectal adenoma prevention. *Cancer Prev Res; 10(1); 45–54. ©2016 AACR.*

Introduction

Colorectal cancer is the second most common fatal malignancy in the United States (1), and the great majority of these tumors develop from premalignant colorectal adenomas. The benefits of screening for colorectal cancer notwithstanding (2), there remains an unmet need for improved strategies for prevention of the disease. High body levels and dietary supplements of the micronutrient selenium have been suggested to protect against several cancers, including colorectal cancer (3), and although the randomized, placebo-controlled Nutritional Prevention of Cancer Trial (NPCT) of selenium, as selenized yeast, demonstrated no effect on the primary endpoint of skin cancer, significant reductions of colorectal and prostate cancers were observed in secondary analyses (4).

Evidence from individual observational studies of dietary intake and serum levels that vitamin E reduces the risk of colorectal cancer or adenoma is at most equivocal (5–10), and there was no evidence that dietary intake of vitamin E reduced colorectal adenoma risk in a meta-analysis of observational studies (11). To date, there have been no prospective randomized trials of vitamin E with colorectal cancer or adenoma as the primary endpoint.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was a randomized, controlled trial of selenium (as selenomethionine) and vitamin E (as α-tocopherol) for the prevention of prostate cancer (12), in which a total of 35,533 men were randomized at 427 clinical sites in the United States, Canada, and Puerto Rico. SELECT was sponsored by the NCI (Bethesda, MD) and designed and managed by SWOG. Participation in SELECT was originally planned for a minimum of 7 and a maximum of 12 years. Recognizing that the SELECT population at risk for prostate cancer is also at risk for colorectal adenomas and cancer, an ancillary study was undertaken to compare the occurrence of colorectal adenomas in SELECT participants randomized to selenium or vitamin E with placebo.

Materials and Methods

Trial design and participants

The Adenomatous Colorectal Polyp (ACP) ancillary study was conducted in SELECT participants who reported undergoing lower endoscopy (colonoscopy or flexible sigmoidoscopy)

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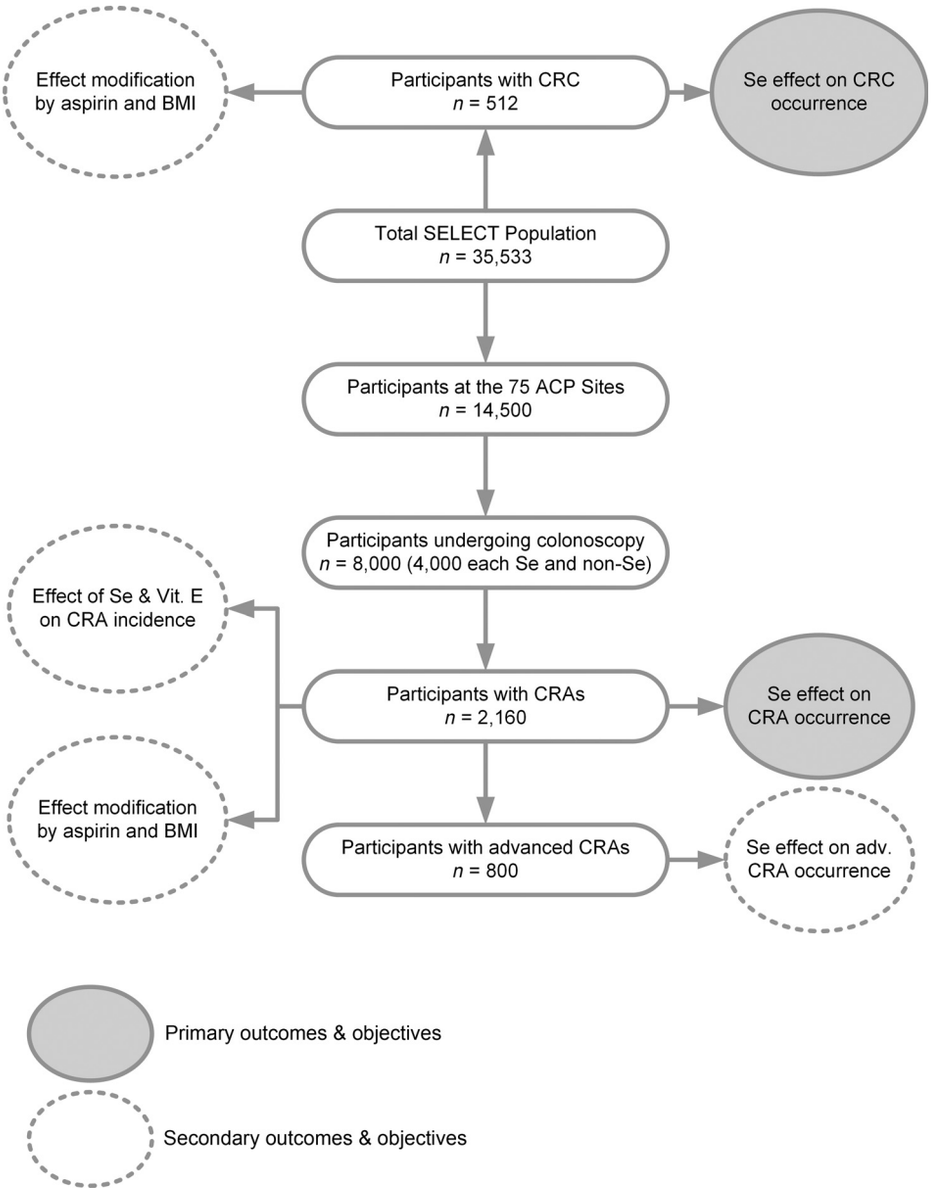

Figure 1.
Study design. Se, selenium; Vit. E, vitamin E; CRA, colorectal adenoma.

while actively participating in the trial (12). As noted, SELECT comprised a total of 35,533 men randomized at 427 clinical sites to 1 of 4 interventions in a factorial design (13): oral selenium (200 μg/day from L-selenomethionine) and matched vitamin E placebo, vitamin E [400 IU/day of *all rac*-α-tocopheryl acetate (α-tocopherol)] and matched selenium placebo, selenium + vitamin E, or double placebo taken for a planned follow-up of a minimum of 7 years and a maximum of 12 years. Eligibility for SELECT included age ≥50 years (African American men) or ≥55 years (all other men), serum PSA ≤4 ng/mL, and a normal digital rectal examination. SELECT exclusion criteria included a prior history of malignancies other than basal or squamous cell carcinoma of the skin within the previous 5 years and use of selenium and/or vitamin E supplements. Concomitant use of aspirin up to a daily dose of 175 mg was allowed.

The major hypothesis of the ACP SELECT ancillary study is that treatment with nutritional supplements of selenium or vitamin E will significantly reduce the prevalence of colorectal adenomas and cancers. The ACP study design is illustrated in Fig. 1. The outcome of power calculations described below was that the study hypothesis could be satisfactorily tested in a 14,500-individual sample of the total 35,533 SELECT population. Analysis of SELECT accrual indicated that a 14,500-individual sample could be assembled using just the top 75 highest accruing sites of the total of 427 clinics.

SELECT participants who underwent colonoscopy were identified through a questionnaire administered at the twice-yearly clinic visits attended by all participants while taking study medication. At each visit, individuals who stated they had undergone sigmoidoscopy or colonoscopy since their previous SELECT clinic visit were asked to provide informed consent and a Medical

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Release for the collection of procedure report(s) and any associated pathology reports. At the time SELECT was terminated prematurely on the basis of a planned interim analysis (see below), approximately 60% of the participants required for the ancillary study had been enrolled. The study protocol was amended, with IRB approval, in July 2011 to allow ancillary study recruitment to be completed subsequently by centralized follow-up (CFU) staff. During the CFU phase of recruitment, participants were sent a questionnaire annually asking whether they had undergone a lower endoscopy. Those who reported on the questionnaire having undergone a lower endoscopy in the previous 12 months or who reported an earlier procedure, but were from a site that had not previously participated in ACP, were sent further materials. These included informed consent to be registered to the study and a Medical Release for study staff to obtain relevant lower endoscopy and pathology reports.

ACP study eligibility and exclusion criteria

All active participants in SELECT who underwent lower endoscopy (colonoscopy or flexible sigmoidoscopy) after randomization to SELECT and gave their informed consent to participate in the ACP ancillary study and for the release to ACP staff of their medical records were eligible. There were no exclusion criteria.

All SELECT participant data except for ACP ancillary study-related lower endoscopy and pathology reports were collected, managed, and archived at the SWOG Statistical Center (Seattle, WA). Lower endoscopy and pathology data were obtained, managed, and archived at the University of Arizona Cancer Center (Tucson, AZ). The University of Arizona Institutional Review Board (IRB) provided regulatory oversight of the ACP ancillary study. Conduct of the trial was in accordance with requirements of local IRBs at each study clinic site. Written informed consent was obtained from all participants.

Outcomes and objectives

The primary outcome was any colorectal adenoma detected at a lower endoscopy performed, in order that study interventions might take effect, at least 1 year after randomization in SELECT. The primary objective of the study was to measure the effect of selenium supplementation on colorectal adenoma prevalence in SELECT participants. Adenoma number, location, size, and histology were abstracted from endoscopic and pathology reports. Secondary outcomes included occurrences of multiple (>2) or advanced neoplasia, defined as adenomas with a diameter of $\geq$1 cm, or any adenoma with villous features or high-grade dysplasia, or colorectal cancer. Secondary objectives were to measure the effect of vitamin E supplementation on colorectal adenoma prevalence in SELECT participants and to measure the effect of the selenium and vitamin E interventions on colorectal adenoma incidence, that is, in participants undergoing more than one colonoscopy while on study, the development of new (metachronous) adenomas. Exploratory objectives were to measure effect modification of the primary outcome by concomitant use of aspirin, body mass index (BMI), or a family history of colorectal cancer, defined as having 1 or more first-degree relatives (FDR) previously diagnosed with the disease.

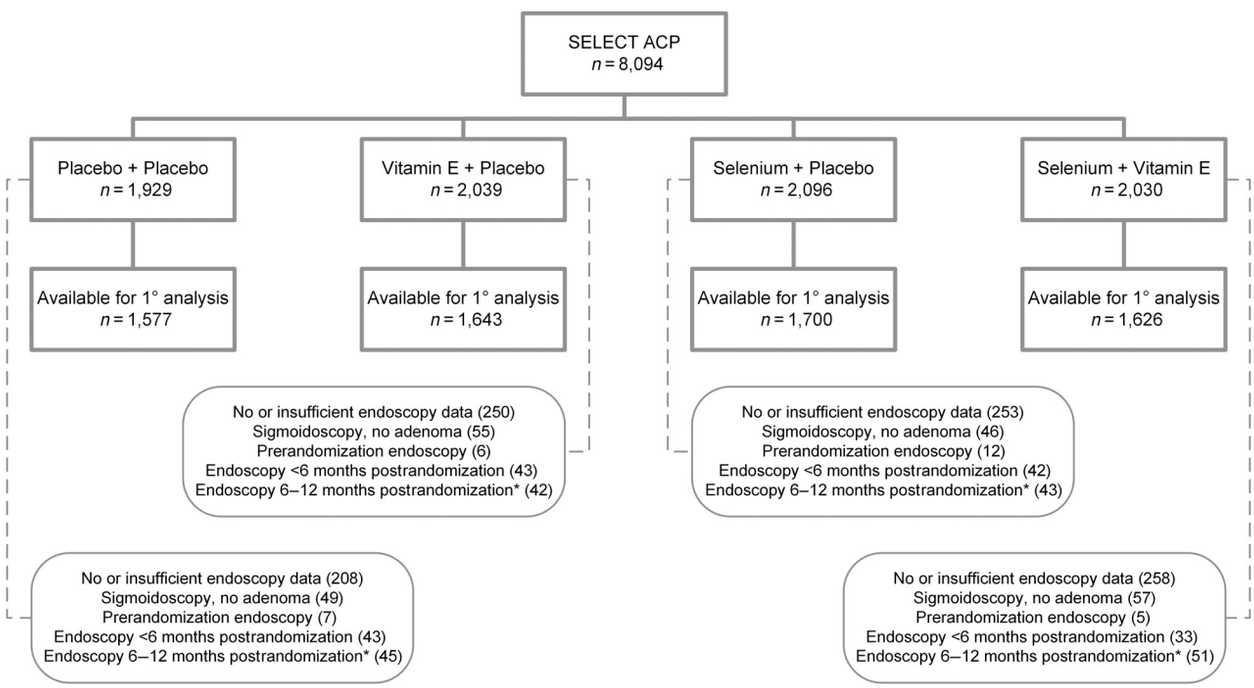

Figure 2.

Participant flow by SELECT intervention group. Rounded rectangles, categories of exclusion from primary analysis (1°) with numbers of cases in parentheses. *Participants undergoing lower endoscopy from 6 to 12 months postrandomization were included in a sensitivity analysis. Se, selenium; Vit. E, vitamin E; CRA, colorectal adenoma.

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Table 1. Baseline characteristics of SELECT ACP participants by treatment arm

	Placebo + Placebo ($n = 1,577$)	Vitamin E + Placebo ($n = 1,643$)	Selenium + Placebo ($n = 1,700$)	Selenium + Vitamin E ($n = 1,626$)
Age, y				
Median (IQR)	62.0 (58.0–67.0)	61.0 (58.0–66.0)	62.0 (58.0–66.0)	62.0 (58.0–67.0)
50–54	52 (3.3)	60 (3.7)	59 (3.5)	49 (3.0)
55–64	933 (59.2)	1,025 (62.4)	1,045 (61.5)	1,002 (61.6)
65–74	524 (33.2)	494 (30.1)	538 (31.7)	516 (31.7)
≥75	68 (4.3)	64 (3.9)	58 (3.4)	59 (3.6)
Race/ethnicity				
White	1,374 (87.1)	1,411 (85.9)	1,445 (85.0)	1,412 (86.8)
African American	160 (10.2)	181 (11.0)	187 (11.0)	167 (10.3)
Hispanic, not African American	25 (1.6)	30 (1.8)	30 (1.8)	32 (2.0)
Hispanic, African American	0 (0.0)	2 (0.1)	1 (0.1)	1 (0.1)
Aboriginal	7 (0.4)	2 (0.1)	8 (0.5)	1 (0.1)
Asian/Pacific Islander	9 (0.6)	12 (0.7)	22 (1.3)	11 (0.7)
Other	2 (0.1)	5 (0.3)	7 (0.4)	2 (0.1)
Education				
≤High school/GED	263 (16.7)	263 (16.1)	264 (15.6)	226 (14.0)
Some college/vocational	378 (24.1)	432 (26.4)	447 (26.4)	397 (24.6)
≥College graduate	931 (59.2)	944 (57.6)	980 (58.0)	992 (61.4)
Missing	5	4	9	11
Smoking status				
Never	711 (45.1)	729 (44.4)	785 (46.2)	726 (44.7)
Current	97 (6.2)	87 (5.3)	98 (5.8)	99 (6.1)
Former	767 (48.7)	826 (50.3)	815 (48.0)	800 (49.2)
Missing	2	1	2	1
BMI, kg/m^2				
Median (IQR)	28.0 (25.4–30.8)	27.8 (25.7–31.2)	28.0 (25.4–30.9)	27.8 (25.6–30.9)
Normal or underweight (≤25)	324 (20.6)	293 (17.9)	355 (20.9)	327 (20.2)
Overweight (>25 to 30)	764 (48.6)	818 (49.9)	795 (46.9)	800 (49.4)
Obese (>30)	484 (30.8)	528 (32.2)	545 (32.2)	492 (30.4)
Missing	5	4	5	7
Personal history of				
Cancer	30 (1.9)	38 (2.3)	32 (1.9)	35 (2.2)
CRC	5 (0.3)	7 (0.4)	7 (0.4)	7 (0.4)
Colon polyps	355 (22.5)	355 (21.6)	347 (20.4)	339 (20.9)
Diverticulitis	110 (7.0)	128 (7.8)	103 (6.1)	121 (7.4)
Diabetes	148 (9.4)	138 (8.4)	126 (7.4)	126 (7.8)
Number of FDRs with CRC				
0	1,279 (85.2)	1,347 (86.4)	1,393 (86.2)	1,350 (86.9)
1	196 (13.1)	185 (11.9)	198 (12.2)	181 (11.7)
2 or more	26 (1.7)	28 (1.8)	26 (1.6)	23 (1.5)
Missing	76	83	83	72
Medication use				
Aspirin	736 (46.7)	756 (46.0)	769 (45.2)	775 (47.7)
Cox II inhibitors	77 (4.9)	91 (5.5)	85 (5.0)	92 (5.7)
Missing	2	2	3	2
Other NSAIDs	168 (10.7)	173 (10.5)	175 (10.3)	164 (10.1)
Missing	1	2	2	0
Statins	284 (29.7)	280 (28.2)	297 (28.3)	283 (28.2)
Not asked/missing	622	651	650	621

Abbreviations: CRC, colorectal cancer; GED, General Educational Development Test; IQR, interquartile range; NSAIDS, nonsteroidal anti-inflammatory drugs.

Sample size

The proposed sample size for this ancillary study was 8,000 participants who had undergone lower endoscopy. The proposed sample size would result in 4,000 participants randomized to selenium (with and without vitamin E) and 4,000 participants not randomized to selenium (with and without vitamin E). Power calculations assumed that 27% of those without intervention would have one or more colorectal adenomas and that 10% of those without intervention would have one or more advanced colorectal adenomas. The proposed sample size provided 98% statistical power to detect a 15% reduction in the selenium group (i.e., 27% vs. 23%, RR = 0.85), assuming no effect of vitamin E (two-sided alpha level of 0.05). In addition, the proposed sample size provided 87% statistical power to detect a 20% reduction in the occurrence of advanced adenomas (i.e., 10% vs. 8%, RR = 0.80) in the absence of a vitamin E effect. Sensitivity analyses for testing the selenium effect, allowing for a 15% reduction due to vitamin E, continued to yield 98% power for the prevalence of any adenoma and 84% power for the prevalence of any advanced adenoma under the assumptions discussed above.

Statistical analysis

All analyses were performed based on the randomized treatment assignment (intent-to-treat). Statistical analysis was based on the factorial design and compared the presence of selenium (selenium alone and selenium + vitamin E groups) versus the

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Table 2. Duration of intervention, follow-up time, and number of follow-up endoscopies, by individual treatment arm

	Placebo + Placebo (n = 1,577)	Vitamin E + Placebo (n = 1,643)	Selenium + Placebo (n = 1,700)	Selenium + Vitamin E (n = 1,626)
Duration of intervention, years	4.7 (3.3–5.8)	4.7 (3.2–5.9)	4.6 (3.2–5.8)	4.6 (3.1–5.9)
Follow-up time from randomization to last follow-up endoscopy, years	5.2 (3.6–6.8)	5.3 (3.7–6.8)	5.2 (3.6–6.9)	5.3 (3.5–6.9)
Number of follow-up endoscopies				
1	1,277 (81.0)	1,295 (78.8)	1,386 (81.5)	1,298 (79.8)
2	252 (16.0)	302 (18.4)	274 (16.1)	271 (16.7)
3	35 (2.2)	36 (2.2)	33 (1.9)	42 (2.6)
4	11 (0.7)	5 (0.3)	7 (0.4)	10 (0.6)
5	1 (0.1)	5 (0.3)	0 (0.0)	5 (0.3)
8	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

NOTE: Median (25th percentile–75th percentile); count (%).

absence (double placebo and vitamin E alone groups). Comparison of the presence versus the absence of vitamin E was assessed as a secondary outcome. Log-binomial regression was used to generate RR estimates and 95% confidence intervals (CI). The initial models included the effects of selenium and vitamin E and their interaction; interaction was tested using a likelihood ratio test (LRT), comparing a model with and without the interaction term. In the absence of interaction, the selenium and vitamin E effects were estimated with the interaction terms excluded.

For a small number of participants, information regarding adenoma size, location, or number was missing from the endoscopy report. This occurred for advanced colorectal neoplasia ($n = 147$), colonic adenomas ($n = 144$), rectal adenomas ($n = 144$), and multiple adenomas ($n = 61$). The intervention duration was missing for 8 participants. Participants just listed, for whom data were missing, were omitted from corresponding analyses.

Exploratory outcomes included assessment of the selenium effect in prespecified patient subgroups. Initially, the model including the three-way interaction between the subgroups with selenium and vitamin E was compared with a model excluding the three-way interaction in an LRT. If the three-way interaction was significant at $P < 0.10$, then analyses stratified by subgroup are presented. In the absence of a significant three-way interaction, the removal of all two-way interactions was assessed simultaneously. If the P value from this test was significant at $P < 0.10$, then the analyses stratified by subgroup are also presented. For completeness, all stratified results are provided. However, only those that passed this sequential testing protocol are discussed.

The primary analyses included the results of endoscopies that occurred at least 1 year after randomization to allow time for the active interventions to have an effect. A sensitivity analysis, which added participants with endoscopies between 6 months and 1 year after randomization, yielded similar results (data not shown). Another sensitivity analysis, which truncated follow-up at 6 months after the off-treatment date, also yielded similar results (data not shown). No adjustment for multiple comparisons was performed.

Results

Randomization of the 35,533 SELECT participants began on August 22, 2001, and was completed on June 24, 2004 (13). On September 15, 2008, the SELECT Data and Safety Monitoring Committee recommended discontinuation of the trial on the basis of a planned interim analysis that demonstrated no evidence of any beneficial effect from either selenium or vitamin E in preventing prostate cancer ($P < 0.0001$) and no possibility of benefit with additional follow-up. The median overall follow-up was 5.46 years. As previously reported (13, 14), there were no significant differences among the treatment groups in preplanned analyses for cancers other than prostate; the hazard ratio (HR) for colorectal cancer in the selenium and selenium + vitamin E groups, respectively, was 1.05 (99% CI, 0.66–1.67; $n = 63$) and 1.28 (99% CI, 0.82–2.00; $n = 77$) compared with placebo ($n = 60$).

A total of 8,094 participants who underwent lower endoscopy during the trial consented to participate in the ancillary study (Fig. 2). Endoscopy information sufficient for ascertainment of essential study data was available for 6,546 of these participants, of whom 2,286 had 1 or more adenomas. Colorectal cancer occurred in 36 participants (0.5%), of whom 6 (0.4%) were in the double placebo group, 11 (0.6%) were in the selenium group, 10 (0.6%) were in the vitamin E group, and 9 (0.6%) were in the selenium + vitamin E group. ACP ancillary study participant characteristics at baseline were well balanced among the four treatment groups (Table 1). Median age across the treatment arms was 61 to 62 years. An 85% to 87% majority was white and 10% to 11% were African American. A little over 50% of participants were current or former smokers. The median BMI was 28 kg/m^2 and just over 30% of participants were obese. Approximately 14% reported having 1 or more FDRs who had previously been diagnosed with colorectal cancer. Depending on the treatment group, 45% to 47% of participants reported aspirin use at baseline.

ACP study participant characteristics were also well balanced across the treatment groups for the length of time taking SELECT medication (4.6–4.7 years) and the follow-up time from randomization to the last lower endoscopy (5.2–5.3 years; Table 2). The lower endoscopies that yielded adenomas included 21 flexible sigmoidoscopies, and all the other procedures were colonoscopies. The last endoscopy occurred on or before the off-treatment date in 55.4% of participants, and after in 44.6%. The median time off intervention for the latter group was 1.5 years (interquartile range = 0.7–2.7 years). The combined cohort of ACP participants did differ from the remainder of the SELECT population who did not participate in the ACP ancillary study in several respects (Table 3). A higher percentage of ACP participants were white. ACP participants were more highly educated than non-ACP participants, and a higher proportion had never smoked, were using aspirin at baseline, and had a previous history of colorectal polyps.

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Table 3. Comparison of ACP subset to non-ACP participants and total SELECT sample

	ACP participants ($n = 8,094$)	Non-ACP participants ($n = 26,793$)	All of SELECT ($n = 34,887$)
Age, y			
Median (IQR)	62.0 (58.0–67.0)	62.0 (58.0–68.0)	62.0 (58.0–67.0)
50–54	284 (3.5)	1,199 (4.5)	1,483 (4.3)
55–64	4,937 (61.0)	15,408 (57.5)	20,345 (58.3)
65–74	2,563 (31.7)	8,244 (30.8)	10,807 (31.0)
≥75	310 (3.8)	1,942 (7.3)	2,252 (6.5)
Race/ethnicity			
White	6,883 (85.0)	20,688 (77.2)	27,571 (79.0)
African American	935 (11.6)	3,383 (12.6)	4,318 (12.4)
Hispanic, not African American	150 (1.9)	1,790 (6.7)	1,940 (5.6)
Hispanic, African American	6 (0.1)	355 (1.3)	361 (1.0)
Aboriginal	24 (0.3)	95 (0.4)	119 (0.3)
Asian/Pacific Islander	72 (0.9)	400 (1.5)	472 (1.4)
Other	24 (0.3)	82 (0.3)	106 (0.3)
Education			
≤High school/GED	1,267 (15.7)	6,415 (24.2)	7,682 (22.2)
Some college/vocational	2,048 (25.4)	7,307 (27.6)	9,355 (27.1)
≥College graduate	4,740 (58.9)	12,775 (48.2)	17,515 (50.7)
Missing	39	296	335
Smoking status			
Never	3,646 (45.1)	11,235 (41.9)	14,882 (42.7)
Current	481 (6.0)	2,201 (8.2)	2,682 (7.7)
Former	3,957 (48.9)	13,200 (49.3)	17,156 (49.2)
Missing	10	157	167
BMI, kg/m^2			
Median (IQR)	27.8 (25.5–30.9)	28.0 (25.5–31.0)	28.0 (25.5–31.0)
Normal or underweight (≤25)	1,630 (20.1)	5,413 (20.3)	7,043 (20.3)
Overweight (>25–30)	3,930 (48.7)	12,726 (47.8)	16,656 (48.0)
Obese (>30)	2,505 (30.9)	8,497 (31.9)	11,002 (31.7)
Missing	29	157	186
Personal history of			
Cancer	170 (2.1)	576 (2.2)	746 (2.1)
CRC	33 (0.4)	110 (0.4)	143 (0.4)
Colon polyps	1,646 (20.3)	3,639 (13.6)	5,285 (15.2)
Diverticulitis	547 (6.8)	1,365 (5.1)	1,912 (5.5)
Diabetes	680 (8.4)	2,945 (11.0)	3,625 (10.4)
Number of FDRs with CRC			
0	6,685 (86.7)	22,390 (88.9)	29,075 (88.4)
1	907 (11.8)	2,525 (10.0)	3,432 (10.4)
2 or more	116 (1.5)	286 (1.1)	402 (1.2)
Missing	386	1,592	1,978
Medication use			
Aspirin	3,731 (46.1)	10,288 (38.4)	14,019 (40.2)
Missing	0	12	12
Cox II inhibitors	424 (5.2)	1,414 (5.3)	1,838 (5.3)
Missing	10	36	46
Other NSAIDs	868 (10.7)	2,308 (8.6)	3,176 (9.1)
Missing	5	36	41
Statins	1,463 (28.6)	4,439 (25.2)	5,902 (26.0)
Not asked/missing	2,975	9,165	12,140

Abbreviations: CRC, colorectal cancer; GED, General Educational Development Test; IQR, interquartile range; NSAIDS, nonsteroidal anti-inflammatory drugs.

Effect of selenium on prevalent adenomas

Overall, adenomas diagnosed at least 12 months after randomization occurred in 34.2% and 35.7%, respectively, of participants who received selenium or placebo (Table 4). Compared with placebo, the RR for adenoma occurrence was 0.96 (95% CI, 0.90–1.02; $P = 0.193$) after adjusting for randomization to vitamin E. The selenium intervention had no effect on subsite adenomas of the colon or rectum or on advanced or multiple adenomas (Table 4).

Effect of vitamin E on prevalent adenomas

In secondary analyses and after adjusting for selenium, vitamin E had no effect on overall adenoma occurrence (RR = 1.03; 95% CI, 0.96–1.10; $P = 0.38$), adenoma location, or on advanced or multiple adenomas (Table 4).

Subgroup analyses

Results from the full factorial analysis of any adenoma in subgroups defined by potential effect modifiers (Table 5) demonstrated statistically significant interactions between selenium and vitamin E with BMI ($P = 0.013$) and the existence of FDRs with colorectal cancer ($P = 0.075$). For BMI, there was a statistically significant interaction between selenium and vitamin E in obese individuals (RR = 0.77; 95% CI, 0.61–0.97; $P = 0.028$), which attenuated the combination toward the null compared with either agent alone (Table 5). Although there was a significant

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Table 4. Prevalent colorectal adenoma outcomes in ACP participants

	Selenium					Vitamin E				
	Active ($n = 3,326$) Number (%)	Placebo ($n = 3,220$) Number (%)	RR	95% CI	*P*	Active ($n = 3,269$) Number (%)	Placebo ($n = 3,277$) Number (%)	RR	95% CI	*P*
Colorectal adenoma (primary)	1,136 (34.2)	1,150 (35.7)	0.96	0.90–1.02	0.19	1,159 (35.5)	1,127 (34.4)	1.03	0.96–1.10	0.38
Advanced colorectal neoplasia	269 (8.3)	282 (9.0)	0.92	0.78–1.08	0.32	280 (8.8)	271 (8.4)	1.04	0.88–1.22	0.66
Adenoma in the colon	1,004 (30.8)	997 (31.8)	0.97	0.90–1.04	0.41	1,014 (31.8)	987 (30.7)	1.04	0.96–1.11	0.34
Adenoma in the rectum	132 (4.0)	137 (4.4)	0.93	0.73–1.17	0.52	130 (4.1)	139 (4.3)	0.94	0.74–1.19	0.62
Multiple (3+) adenomas	258 (7.8)	276 (8.7)	0.91	0.77–1.07	0.24	276 (8.5)	258 (7.9)	1.07	0.91–1.26	0.84

interaction for the existence of FDRs, neither selenium nor vitamin E was statistically significantly related to adenoma occurrence for either subgroup (0 vs. >1). Although the three-way interaction with age was not statistically significant ($P = 0.601$), there was a statistically significant overall test of all two-way interactions ($P = 0.082$). Specifically, there was a statistically significant selenium effect in men aged <63 years (RR = 0.91; 95% CI, 0.83–1.00; $P = 0.042$).

In the subgroup with advanced adenomas, there was a statistically significant interaction between selenium and vitamin E with the existence of FDRs with colorectal cancer ($P = 0.001$). There was also a significant two-way interaction between the selenium and vitamin E interventions in participants who reported no FDRs with colorectal cancer (RR = 0.65; 95% CI, 0.45–0.94; $P = 0.021$), which attenuated the combination toward the null (Table 5). Similarly, among those reporting 1+ FDRs, the combination also was attenuated toward the null compared with either agent alone (RR = 3.14; 95% CI, 1.38–7.13; $P = 0.006$; Table 5).

Effects of selenium and vitamin E on incident adenomas

Adenoma incidence was assessed in the 658 participants undergoing more than 1 colonoscopy during their SELECT participation (Table 6). Of these, 224 were found to have incident adenomas at their latest colonoscopy. For these 224 participants, 64 (28.6%) had not had previous adenomas and 64 (67.9%) reported previous adenomas or colorectal cancer; whether or not they had had previous adenomas was unknown for 8 (3.6%) participants. The RR for incident adenomas with selenium was 1.18 (95% CI, 0.096–1.46; $P = 0.121$) and with vitamin E was 0.81 (95% CI, 0.66–1.00; $P = 0.053$). There were no statistically significant interactions between selenium and vitamin E for any subgroups.

Discussion

In answer to the primary objective of the ACP SELECT ancillary study, and contradicting earlier NPCT evidence that selenium supplementation might prevent colorectal neoplasia, we found no evidence for any effect of selenium supplementation on overall colorectal adenoma occurrence. The primary outcome in the current study, colorectal adenoma, is a surrogate for colorectal cancer, which was the colorectal outcome of interest in the NPCT. It is possible that although selenium might not prevent adenoma development, it could inhibit colorectal carcinogenesis in the later stages of adenoma progression to cancer. However, in the parent SELECT, albeit with modest statistical power, there was no evidence that the selenium intervention reduced new diagnoses of or deaths from colorectal cancer compared with placebo (14).

A limitation of the study is that the analysis was restricted to men who reported having undergone lower endoscopy while participating in SELECT. An effect of either intervention on adenoma occurrence in men who harbored adenomas but did not undergo lower endoscopy cannot be excluded. Furthermore, the profile of SELECT participants in the ACP ancillary study differed somewhat from the entire SELECT population; a higher percentage was white, had never smoked, used aspirin, and reported previous colorectal polyps in the ACP subpopulation. Thus, a small intervention effect in the entire SELECT population could have been missed in the ACP study.

It has been argued that supplementation of selenium and other micronutrients may only benefit individuals who are relatively depleted for the micronutrient(s) in question (15). Reductions in cancer risk attributed to selenium in the NPCT were restricted to the two thirds of participants with baseline serum selenium levels ≤121.6 ng/mL (16). Median baseline selenium levels in the placebo and selenium groups of SELECT, respectively, were 137.6 and 135.0 ng/mL, indicating that the study population was largely replete for selenium; assessment of baseline selenium status in the SELECT study population by measurement of toenail levels confirmed this (17). Our negative outcome is generalizable only to selenium-replete individuals.

In SELECT, the selenium intervention was selenomethionine (selenium 200 μg/d), whereas in the NPCT, selenized yeast (selenium 200 μg/d) was the intervention. Although selenomethionine is the major selenium-containing compound, selenized yeast also includes multiple other selenium compounds (18), one or more of which could have colorectal adenoma–preventing activity that selenomethionine lacks (19). We recently reported a randomized, placebo-controlled trial of selenium 200 μg/d as selenized yeast for colorectal adenoma prevention in 1,621 participants (20). New adenomas developed in 42.8% and 44.1%, respectively, of participants randomized to selenium or placebo after median periods of 33.6 and 33.0 months (RR = 1.03; 95% CI, 0.91–1.16). Thus, neither selenomethionine nor selenized yeast prevented adenoma development in the setting of a randomized trial.

In answer to the secondary and exploratory objectives of the study, our finding was that vitamin E as α-tocopherol had no effect on overall adenoma occurrence. This is consistent with the, at best, equivocal role for vitamin E, especially as α-tocopherol, in preventing colorectal neoplasia (6, 10, 21–23). However, certain secondary and exploratory analyses produced statistically significant results. Thus, the RR of colorectal adenomas for men under the study cohort median age of 63 years was 0.91 (95% CI, 0.83–1.00), and among participants reporting 1+ relatives with colorectal cancer, the combination of selenium and vitamin E negated

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Table 5. Prevalent colorectal adenoma outcomes, by subgroup

	Selenium					Vitamin E				
	Active number (%)	**Placebo number (%)**	**RR**	**95% CI**	***P***	**Active number (%)**	**Placebo number (%)**	**RR**	**95% CI**	***P***
Colorectal adenoma										
Aspirin										
Nonusers	597 (33.5)	629 (36.4)	0.92	0.84–1.01	0.07	600 (34.5)	626 (35.3)	0.97	0.89–1.07	0.55
Users	539 (34.9)	521 (34.9)	1.00	0.91–1.10	0.98	559 (36.5)	501 (33.3)	1.10	1.00–1.21	0.06
P 3-way = 0.104										
P all 2-way = 0.204										
BMI										
Normal	206 (30.2)	194 (31.4)	0.96	0.82–1.13	0.62	187 (30.2)	213 (31.4)	0.96	0.82–1.13	0.63
Overweight	562 (35.2)	578 (36.5)	0.97	0.88–1.06	0.47	596 (36.8)	544 (34.9)	1.05	0.96–1.16	0.26
Obese[a]	365 (35.2)	374 (37.0)	1.09	0.92–1.28	0.32	372 (36.5)	367 (35.7)	1.16	0.99–1.37	0.07
P 3-way = 0.013										
P all 2-way = not tested										
FDRs with CRC										
0	921 (33.6)	937 (35.7)	0.94	0.88–1.01	0.11	963 (35.7)	895 (33.5)	1.07	0.99–1.15	0.09
≥1	159 (37.2)	147 (33.8)	1.09	0.91–1.31	0.34	138 (33.1)	168 (37.7)	0.88	0.74–1.06	0.18
P 3-way = 0.075										
P all 2-way = not tested										
Race/ethnicity										
White	973 (34.1)	992 (35.6)	0.96	0.89–1.03	0.22	994 (35.2)	971 (34.4)	1.02	0.95–1.10	0.59
African American	126 (35.6)	119 (34.9)	1.03	0.84–1.26	0.76	130 (37.4)	115 (33.1)	1.13	0.92–1.38	0.24
Hispanic	22 (35.5)	21 (38.2)	0.93	0.58–1.49	0.76	25 (40.3)	18 (32.7)	1.23	0.76–2.00	0.40
P 3-way = 0.467										
P all 2-way = 0.933										
Age										
<63 years	**566 (31.6)**	**609 (34.9)**	**0.91**	**0.83–1.00**	**0.04**	**631 (34.8)**	**544 (31.6)**	**1.10**	**1.00–1.21**	**0.05**
≥63 years	570 (37.2)	541 (36.6)	1.01	0.92–1.11	0.77	528 (36.2)	583 (37.5)	0.97	0.88–1.06	0.45
P 3-way = 0.601										
P all 2-way = 0.082										
Advanced colorectal neoplasia										
Aspirin										
Nonusers	158 (9.0)	163 (9.7)	0.94	0.76–1.15	0.52	161 (9.4)	160 (9.2)	1.02	0.83–1.26	0.84
Users	111 (7.4)	119 (8.2)	0.90	0.70–1.16	0.42	119 (8.0)	111 (7.5)	1.06	0.83–1.36	0.63
P 3-way = 0.137										
P all 2-way = 0.743										
BMI										
Normal	44 (6.6)	41 (6.8)	0.97	0.64–1.46	0.87	44 (7.2)	41 (6.2)	1.17	0.77–1.76	0.46
Overweight	133 (8.5)	146 (9.5)	0.90	0.72–1.13	0.36	141 (9.0)	138 (9.1)	0.99	0.79–1.23	0.91
Obese	92 (9.1)	92 (9.3)	0.98	0.74–1.29	0.86	94 (9.5)	90 (8.9)	1.06	0.80–1.40	0.68
P 3-way = 0.870										
P all 2-way = 0.578										
FDRs with CRC										
0[b]	213 (7.9)	213 (8.3)	1.20	0.92–1.56	0.18	**222 (8.4)**	**204 (7.8)**	**1.34**	**1.04–1.75**	**0.03**
≥1[c]	**39 (9.4)**	**51 (12.0)**	**0.46**	**0.26–0.81**	**0.01**	**40 (9.8)**	**50 (11.6)**	**0.51**	**0.29–0.88**	**0.02**
P 3-way = 0.001										
P all 2-way = not tested										
Race/ethnicity										
White	229 (8.2)	245 (9.0)	0.91	0.76–1.08	0.28	244 (8.9)	230 (8.3)	1.06	0.89–1.26	0.50
African American	31 (8.9)	31 (9.3)	0.95	0.59–1.53	0.84	30 (8.8)	32 (9.4)	0.94	0.58–1.51	0.79
Hispanic	7 (11.5)	5 (9.3)	1.23	0.42–3.64	0.71	5 (8.2)	7 (13.0)	0.64	0.21–1.88	0.41
P 3-way = 0.672										
P all 2-way = 0.870										
Age										
<63 years	129 (7.3)	146 (8.5)	0.86	0.68–1.08	0.18	138 (7.8)	137 (8.1)	0.96	0.76–1.20	0.70
≥63 years	140 (9.4)	136 (9.5)	0.99	0.79–1.24	0.91	142 (10.0)	134 (8.9)	1.13	0.91–1.42	0.28
P 3-way = 0.494										
P all 2-way = 0.371										

NOTE: Bold signifies a statistically significant effect within the subgroup ($P < 0.05$)

Abbreviations: CRC, colorectal cancer; *P* 3-way, *P* from the test of the 3-way interaction term; *P* all 2-way, *P* from the simultaneous test of all 2-way interaction terms.

[a]Statistically significant interaction between selenium and vitamin E treatment assignment: RR = 0.77; 95% CI, 0.61–0.97; $P = 0.028$.

[b]Statistically significant interaction between selenium and vitamin E treatment assignment: RR = 0.65; 95% CI, 0.45–0.94; $P = 0.021$.

[c]Statistically significant interaction between selenium and vitamin E treatment assignment: RR = 3.14; 95% CI, 1.38–7.13; $P = 0.006$.

the effect of either agent alone on the occurrence of advanced colorectal neoplasia. In the absence of any effect on overall adenoma risk with either selenium or vitamin E, these secondary and exploratory results are most likely artefacts of testing multiple subgroups and unlikely to be of preventive or therapeutic consequence (24, 25).

In summary, neither selenomethionine nor vitamin E affected colorectal adenoma prevalence in SELECT participants taking part

Table 6. Incident colorectal adenoma outcomes in ACP participants undergoing >1 colonoscopy and by subgroup

	Selenium					Vitamin E				
	Active ($n = 313$)	**Placebo ($n = 345$)**				**Active ($n = 346$)**	**Placebo ($n = 312$)**			
	Number (%)	**Number (%)**	**RR**	**95% CI**	***P***	**Number (%)**	**Number (%)**	**RR**	**95% CI**	***P***
Incident colorectal adenoma	116 (37.1)	108 (31.3)	1.18	0.96–1.46	0.12	106 (30.6)	118 (37.8)	0.81	0.66–1.00	0.05
Subgroups										
Aspirin										
Nonusers	63 (38.0)	59 (33.2)	1.13	0.85–1.50	0.40	52 (31.0)	70 (39.8)	0.78	0.59–1.05	0.10
Users	53 (36.0)	49 (29.3)	1.24	0.90–1.70	0.19	54 (30.3)	48 (35.3)	0.85	0.62–1.17	0.32
P 3-way = 0.454										
P all 2-way = 0.933										
BMI										
Normal	22 (31.9)	16 (29.6)	1.10	0.64–1.88	0.74	17 (28.8)	21 (32.8)	0.87	0.51–1.48	0.60
Overweight	52 (36.9)	54 (31.6)	1.16	0.85–1.58	0.34	56 (31.8)	50 (36.8)	0.87	0.64–1.18	0.38
Obese	42 (40.8)	38 (31.9)	1.26	0.89–1.79	0.19	33 (29.7)	47 (42.3)	0.71	0.50–1.01	0.06
P 3-way = 0.381										
P all 2-way = 0.974										
FDRs with CRC										
0	93 (38.9)	83 (31.2)	1.25	0.98–1.58	0.07	**85 (30.7)**	**91 (39.9)**	**0.77**	**0.61–0.98**	**0.03**
≥1	16 (29.1)	19 (30.2)	0.97	0.55–1.69	0.90	16 (31.3)	19 (28.4)	1.10	0.63–1.93	0.72
P 3-way = 0.208										
P all 2-way = 0.549										
Race/ethnicity										
White	103 (35.9)	94 (30.6)	1.17	0.93–1.47	0.17	96 (30.7)	101 (35.9)	0.85	0.68–1.07	0.17
African American	11 (52.3)	11 (39.3)	1.20	0.65–2.21	0.57	9 (34.6)	13 (56.5)	0.64	0.33–1.23	0.18
Hispanic	1 (33.3)	3 (50.0)				1 (20.0)	3 (75.0)			
P 3-way = 0.201										
P all 2-way = 0.860										
Age										
<63 years	50 (33.6)	56 (30.9)	1.10	0.81–1.50	0.53	**47 (26.3)**	**59 (39.1)**	**0.67**	**0.49–0.92**	**0.01**
≥63 years	66 (40.2)	52 (31.7)	1.27	0.95–1.70	0.11	59 (35.3)	59 (36.6)	0.98	0.73–1.30	0.86
P 3-way = 0.793										
P all 2-way = 0.312										

NOTE: Bold signifies a statistically significant effect within the subgroup ($P < 0.05$)

Abbreviations: CRC, colorectal cancer; *P* 3-way, *P* from the test of the 3-way interaction term; *P* all 2-way, *P* from the simultaneous test of all 2-way interaction terms.

in the ACP ancillary study. Taken together with our recently reported negative trial of selenized yeast for adenoma prevention, the definitive conclusion is that neither selenium nor vitamin E supplementation can be recommended for colorectal adenoma prevention.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Conception and design: P. Lance, D.S. Alberts, P.A. Thompson, I.M. Thompson
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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P. Lance, P.A. Thompson, F. Wang, E.T. Jacobs, P.J. Goodman, D.J. Roe
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Colorectal Adenomas in Participants of the SELECT Randomized Trial of Selenium and Vitamin E for Prostate Cancer Prevention

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