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Design and baseline characteristics of participants in a phase III randomized trial of celecoxib and selenium for colorectal adenoma prevention

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Abstract

Cyclooxygenase (COX) inhibitors reduce colorectal adenoma recurrence by up to 45% and selenium supplementation may prevent colorectal cancer. Following colonoscopic adenoma resection, 1,600 men and women aged 40-80 years were randomized to celecoxib (400 mg daily), a selective COX-2 inhibitor, and/or selenium (200 μg daily as selenized yeast), or double placebo. The trial was initiated in November, 2001. The primary trial endpoint is adenoma recurrence in each intervention group compared to placebo, as determined by surveillance colonoscopy performed 3-5 years after baseline. Randomization was stratified by use of low-dose aspirin (81 mg) and clinic site. Following reports of cardiovascular toxicity associated with COX-2 inhibitors, the celecoxib arm was discontinued in December, 2004 when 824 participants had been randomized. Accrual continued with randomization to selenium alone or placebo. Randomization of the originally planned cohort (n=1,621) was completed in November, 2008. A further 200 patients with 1+ advanced adenomas (denoting increased risk for colorectal cancer) were accrued to enhance statistical power for determining intervention efficacy in this higher-risk subgroup. Accrual of the total cohort (n=1,824) was completed in January, 2011. Baseline cohort characteristics include: mean age 62.9 years; 65% male; BMI 29.1 ±5.1; 47% taking low-dose aspirin while on trial; 20% with 3+ adenomas; and 38% with advanced adenomas. Intervention effects on adenoma recurrence will be determined, and their modification by genetic background

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and baseline selenium level. The effect of selenium supplementation on risk for type 2 diabetes will also be reported (Funded by the National Cancer Institute; ClinicalTrials.gov number, NCT00078897.)

Keywords

colorectal adenoma; celecoxib; selenium; randomized trial

Introduction

Approximately 143,000 new cases and 52,000 deaths from colorectal cancer are expected in 2012 in the United States, a cancer morbidity and mortality that is second only to that of lung cancer (1). Implementation of screening is considered an important factor in the decline of incidence and mortality from colorectal cancer over recent decades. However, the proportion of colorectal cancer deaths that can be prevented by screening is unclear with estimated mortality reductions ranging from approximately 20% to more than 50% (2-5). Among screening modalities, colonoscopy has yielded the largest mortality reductions. However, a limitation of colonoscopic screening is that it may be less effective for reducing risk (6) and mortality (7, 8) of right-sided than left-sided colorectal cancers. Incomplete compliance with guidelines, regardless of the modality, may also limit what can be achieved by screening alone; prevalence of colorectal cancer screening in U.S. adults combined, African Americans, Hispanics and uninsured individuals, respectively, was reported recently as 53.2%, 48.9%, 37.2% and 19.5% (9). Thus, to optimize reductions in colorectal cancer incidence and mortality, additional effective interventions that are safe, easy to use and inexpensive are needed to complement screening.

Chemoprevention has been advocated as a potential adjunct to screening for reducing colorectal cancer morbidity and mortality (10). In randomized chemoprevention trials, calcium supplementation (11) and the non-steroidal anti-inflammatory drug (NSAID) aspirin (12, 13) were shown to reduce colorectal adenoma risk by 15-35%; aspirin yielded a greater 41% reduction in risk (12) for adenomas with advanced pathology, which are associated with a high risk of subsequent neoplasia (14-16). Recently, in a meta-analysis of cardiovascular prevention trials, aspirin reduced colon cancer risk and mortality, respectively, by 24% and 35% (17) and colorectal cancer risk was reduced by 44% in Lynch syndrome patients receiving aspirin for a mean of 56 months (18).

The anti-neoplastic actions of aspirin are attributed at least in part to inhibition of cyclooxygenase (COX) (19) but the level of gastrointestinal toxicity caused by aspirin and other NSAIDS (20) has restrained enthusiasm for their use as cancer preventive agents. Because inhibition of the COX-1 isoform is thought to be responsible for NSAID-related gastrointestinal toxicity, immense effort was directed to the development of selective COX-2 inhibitors (coxibs), such as celecoxib and rofecoxib, that would, hypothetically, conserve the beneficial effects of NSAIDs and minimize their toxicity. Although in randomized trials celecoxib and rofecoxib reduced colorectal adenoma risk by 24 – 45% (14, 16, 21), an associated increased risk of serious cardiovascular events with both agents prohibited the subsequent clinical use of coxibs for chemoprevention.

Selenium is an essential micronutrient with antioxidant activity and chemopreventive potential (22-24). It is incorporated into specialized selenocysteine-containing selenoproteins (25) that mediate redox-dependent and other cellular functions (24, 26, 27). Evidence that selenium might help to prevent colorectal cancer came from the Nutritional Prevention of Cancer (NPC) Trial, a randomized controlled trial of selenium 200 μg daily as

selenized yeast for the prevention of skin cancer (28). Although the intervention had no effect on the incidence of basal or squamous cell cancers, in planned secondary analyses there was a significant reduction of colorectal cancer incidence, which attenuated over time (29). In a subsequent pooled analysis of data from three colorectal adenoma recurrence trials, participants' baseline blood selenium levels were inversely related to risk for developing metachronous (recurrent) colorectal adenomas (30). Selenium interventions were of significant benefit in four trials included in a Cochrane review of randomized controlled trials of antioxidant supplements administered for colorectal cancer prevention (31); there was some evidence that benefits of selenium were sustained in a later follow-up report (32). While finding the methodologies of these four trials suboptimal, the Cochrane review authors considered the evidence for a potential effect of selenium in preventing colorectal cancer sufficient to warrant randomized trials of this agent.

At the time the current study was designed, the majority of randomized trials for the chemoprevention of colorectal adenomas compared a single intervention to placebo. We hypothesized that combining relatively modest doses of two agents, each targeting a separate carcinogenesis pathway, would optimize efficacy while minimizing toxicity. The interventions we selected were celecoxib in a single daily dose of 400 mg and selenium as selenized yeast in a single daily dose of 200 μg. The 2×2 factorial design included each intervention alone, the combined interventions, and placebo. We report here the study design and baseline data of the complete trial cohort and an unavoidable modification to the study design—withdrawal of the celecoxib intervention—when the Federal Drug Administration terminated all coxib colorectal adenoma prevention trials because of unanticipated cardiotoxicity (33, 34). After the withdrawal of celecoxib, accrual to the trial was completed with randomization to selenium or placebo only. In this report we focus on methodological adjustments that enabled us to complete trial accrual. We believe that this experience may be helpful for the design of future cancer prevention trials and that dissemination of this experience need not be delayed until the trial results are reported after unblinding in late 2013.

Materials and Methods

Trial design

Originally, this was a phase III randomized, parallel, 2×2 factorial design trial of celecoxib (active versus placebo) crossed with a selenium supplement (active versus placebo) for prevention of metachronous (recurrent) colorectal adenomas (Figure 1). The CONSORT 2010 guidelines for reporting randomized controlled trials (35) have been followed in the following description of completed accrual of the trial cohort.

Eligibility

Healthy male and female patients between the ages of 40 and 80 years who had undergone total colonoscopy and complete removal of one or more colorectal adenomas with a diameter of 3 mm or more within the six months prior to registration were eligible. Adenomas were categorized as non-advanced or advanced; the latter defined as adenomas with a diameter of 1+ cm, or any adenoma with villous features or high-grade dysplasia. Patients with 1 or more advanced adenomas or ≥3 non-advanced adenomas were classified in a "high-risk adenoma" category. Patients with a family history of familial adenomatous polyposis or Lynch syndrome and those diagnosed with invasive cancer within the previous five years were among those excluded. Patients taking low-dose aspirin, defined as a maximum dose of 81 mg daily, were eligible.

Study sites

Participants were recruited through clinical centers in Arizona, Colorado, Texas and New York (Table 1) following ambulatory colonoscopies performed at local high-volume endoscopy facilities. All study data and biospecimens are 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 and conduct of the trial was in accordance with requirements of the local IRB at each study site.

Interventions

Celecoxib (Celebrex®) 200 mg capsules and matching placebo were provided by Pfizer (New York, NY). The active intervention was celecoxib 400 mg taken as a single daily dose of two 200 mg capsules. The drug was stored at room temperature in a locked storage facility. Celecoxib content of the stored drug was assayed annually by high performance liquid chromatography in the University of Arizona Cancer Center Analytical Core Laboratory (36). The range of celecoxib content in these assays was 189 – 204 mg per capsule. Selenium as SelenoExcell High Selenium Yeast capsules (selenium 200 μg/capsule) and matching placebo are provided by Cypress Systems (Fresno, CA). The active intervention is selenium 200 μg as a single daily dose. The selenium content of stored intervention tablets as measured semi-annually by atomic absorption spectrophotometry in the University of Arizona Cancer Center Analytical Core Laboratory is within the range of 196 – 201 μg. Selenium plasma levels are measured at baseline and annually by atomic absorption spectrophotometry in all participants while on study.

Outcomes

The primary study outcome is colorectal adenoma recurrence. Recurrence rates are determined as the percentage of participants with metachronous adenomas diagnosed in each randomization group at surveillance colonoscopies, which are timed according to usual practice guidelines (37). The pre-specified primary outcome measures are recurrence rates with any (non-advanced or advanced) adenoma in participants taking celecoxib alone, selenium alone, celecoxib + selenium, or placebo. Additional planned analyses include the number, location and non-advanced/advanced/high-risk status of metachronous adenomas. A further pre-specified primary aim is to measure the type and incidence of adverse events occurring during prolonged treatment with celecoxib and selenium, given alone or in combination, with or without concomitant low-dose aspirin therapy in patients with colorectal adenomas.

Secondary outcome measures include: modification of the effects of the celecoxib or selenium interventions on colorectal adenoma risk by concomitant low-dose aspirin; modification of the effects of the selenium intervention by baseline blood selenium level; and modification of the effects of the selenium intervention by sequence variations of candidate selenoprotein genes.

Participant safety and outcomes are monitored by an External Data and Safety Monitoring Committee (EDSMC), which convenes semi-annually or more frequently if necessary. At each meeting, the EDSMC reviews unblinded safety and efficacy data in the context of newly reported information from other trials and studies as the basis for a recommendation on whether or not the trial should be continued, with or without modification.

Randomization

Potentially eligible patients were identified through screening of colonoscopy and pathology reports by study coordinators from the respective clinical sites. After implementation of the Health Insurance Portability and Accountability Act (HIPAA) in 2003, those patients who

were screened for possible eligibility gave written permission ("caregivers' consent") before their colonoscopy for: their records to be reviewed for this purpose by research staff after the procedure; and, if potentially eligible, for study staff then to contact them concerning possible participation in the study.

Patients who fulfilled all trial eligibility criteria were asked to provide written informed consent for participation, which included consent for isolation of their DNA to be used for analyses of sequence variations in selenoprotein genes. Those who consented to participate began a 4-week run-in assessment period of taking placebo medication for assessment of future compliance with taking study medication; they were blinded to the placebo nature of the run-in medication. The study intervention manager was notified of potential participants at the time a patient started run-in medication. Those who returned for clinic visits as scheduled and had taken at least 75% of the placebo medication doses were randomized into one of four groups, i.e. celecoxib + placebo, selenium + placebo, celecoxib + selenium, or double placebo (Figure 1).

Randomization was performed using a Structured Query Language function that first checked for previous randomization and a valid clinic identification number. Randomization was stratified by clinical center and for use of low-dose aspirin (≤81 mg/day). A block size of 4 was used for the factorial design.

After the randomization group was assigned, the information was sent to the Intervention Manager at the central study pharmacy, which dispatches study medication for all participants to their respective clinical centers. Only the intervention manager and designated backup and statistical center personnel responsible for randomization and preparation of unblinded reports for the EDSMC have access to the unblinded list of participant study identification numbers, treatment codes, and intervention identity.

Design changes after commencement

On September 30, 2004, Merck (Whitehouse Station, NJ) announced the world-wide withdrawal of rofecoxib (VIOXX®), like celecoxib a coxib-class selective COX-2 inhibitor, because of an increased relative risk of adverse cardiovascular events in patients taking rofecoxib compared to placebo in a colorectal adenoma prevention trial. On December 17, 2004, the National Institutes of Health announced that it had suspended a second selective COX-2 inhibitor colorectal adenoma prevention trial because of an increased risk of cardiotoxicity associated with the drug: celecoxib was the agent in this trial. The EDSMC recommended permanent suspension of the celecoxib arm of our trial on December 20, 2004. On December 23, 2004, the Food and Drug Administration (FDA) placed the trial on clinical hold. However, when informed that the celecoxib arm of the trial had already been permanently suspended by the EDSMC, the same day the FDA authorized uninterrupted continuation of the selenium arm of the trial. With the withdrawal of celecoxib, the study was modified to a randomized parallel two-group design, comparing selenium to placebo. Participants previously randomized to celecoxib with or without placebo were retained in the appropriate selenium or placebo arm (Figure 2).

As noted, adenomas with advanced pathology are those at greatest risk for progression to colorectal cancer (38). It was apparent as accrual of the originally planned cohort of 1,600 individuals approached completion that 25-30% of randomized participants had one or more advanced adenomas at baseline. To enhance study power for demonstrating intervention effects in this higher risk subpopulation, recruitment of an additional 200 participants with one or more advanced adenomas was undertaken after recruitment of the original 1,600 participant cohort was completed. Because surveillance colonoscopy is indicated after three years in patients with an advanced adenoma rather than the five year interval for patients

with non-advanced adenomas, this modification did not lengthen the total duration of the trial. EDSMC and National Cancer Institute approval was obtained for the change in design, which was implemented without any modification to the trial's original primary aims.

Sample size

The sample size selected for the factorial design was 400 participants per cell, thus requiring randomization of a total of 1,600 participants. The sample size justification assumed a separate test of each intervention (celecoxib or selenium) without adjustment for multiple comparisons. The power calculations were based on a Poisson regression analysis, with an estimated adenoma recurrence rate of 0.25 polyps per year. This estimate was originally based on results from the National Polyp Study (39) and our own Wheat Bran Fiber (WBF) Study (40). Based on the level of compliance in the WBF study, we assumed at least 90% compliance with obtaining the endpoint colonoscopy, resulting in a sample size of 360 per group. Our statistical power was 99% to detect a 25% reduction in the recurrence rate due to celecoxib and 95% to detect a 20% reduction in the recurrence rate due to selenium, assuming no negative interaction between celecoxib and selenium (two-sided 0.05 level of significance). Even with a negative interaction of up to 20%, estimated power for detecting effects of celecoxib and selenium, respectively, was 96% and 78%.

Withdrawal of the celecoxib intervention did not alter the total sample size required. The statistical power was reassessed in light of data from our Ursodeoxycholic Acid (UDCA) colorectal adenoma prevention trial (41). Forty two percent of participants had a recurrent adenoma during the three-year follow-up period of the UDCA trial; this implied an annual hazard of recurrence of 0.182. Based on results of other studies, we were interested in the power to detect a 25% reduction in adenoma recurrence rate due to selenium. Given new guidelines that patients with non-advanced adenomas should undergo colonoscopic surveillance after 5 rather than 3 years (37), we assumed an average follow-up of 4 years. This resulted in 94% statistical power to detect a 25% reduction due to selenium, based on a two-group test of proportions at a 2-sided 0.05 level of significance.

Results from the UDCA trial (41) showed a 49% recurrence of non-advanced or advanced adenomas for those who had an advanced adenoma at baseline. The statistical power would have been 73% to detect a 33% reduction in the recurrence rate in those with advanced adenomas at baseline with the originally planned sample size. One hundred additional participants per group with one or more advanced adenomas were therefore added so that the statistical power increased to approximately 87%. This subset analysis was planned without regard to outcome data in the original 1,600 participants and so is not subject to the limitations of a data derived subset analysis.

Results and Discussion

Screening for eligibility and recruitment processes

Study coordinators attempted to contact a total of 20,436 patients who had recently undergone colonoscopic polypectomy for a preliminary assessment of potential study eligibility (Figure 3). Successful phone contact was made with 12,430 patients, of whom 3,461 came for a clinic visit and 1,824 were randomized.

Accrual phases

The first participant to the "Full Factorial Cohort" (Table 1; celecoxib vs. selenium vs. celecoxib + selenium vs. placebo) was randomized on November 27, 2001. A total of 824 participants were randomized to the Full Factorial Cohort, including 414 to celecoxib, before the EDSMC recommended termination of the celecoxib intervention on December

20, 2004; the last participant in the Full Factorial Cohort was randomized on December 16, 2004. The 414 participants receiving celecoxib took the agent for a median of 14.0 (25^{th} percentile, 4.9; 75^{th} percentile, 22.8) months.

Adverse event data from the 824 participants randomized to either celecoxib or placebo were contributed to a pooled analysis of adjudicated data for cardiovascular risk (the combination of cardiovascular death, myocardial infarction, stroke, heart failure, or thromboembolic event) in 7,950 participants from six placebo-controlled trials comparing celecoxib with placebo for conditions other than arthritis (42). Of note, the risk was lowest (hazard ratio, 1.1; 95% CI, 0.6 to 2.0) for the 400-mg-daily dose of celecoxib, which was the dose used in our trial.

Participants in the Full Factorial Cohort continued active participation after the withdrawal of celecoxib, taking selenium or placebo, until their endpoint colonoscopy. Timing of the latter was not altered by termination of the trial's celecoxib arm. The effect of celecoxib on adenoma recurrence will be analyzed as originally planned, albeit with less statistical power than originally estimated. In secondary analyses, the length of time for which celecoxib was taken, the duration of any celecoxib effect after the intervention's termination, and modification of any selenium effects by celecoxib will be considered.

After withdrawal of celecoxib, a further 797 participants with non-advanced or advanced adenomas were randomized to selenium or placebo (Table 1, "Selenium Cohort") for a total of 1,621 participants in the originally planned cohort. The last of these 1,621 participants was randomized on November 26, 2008. Following completion of the original 1,621-participant cohort, an additional 203 participants with one or more advanced adenomas (Table 1, "Advanced Adenoma Cohort") were randomized to selenium or placebo, the last of them on January 19, 2011.

Participant characteristics at baseline

Baseline characteristics of the participants in the respective cohorts differed in some respects (Table 1). Mean age of the Full Factorial Cohort (62.9 years) was older than the Advanced Adenoma Cohort (60.5 years). The percentage of female participants increased from 32.2 in the Full Factorial Cohort to 37.6 and 39.4, respectively, in the Selenium and Advanced Adenoma Cohorts. The percentages of participants on regular low-dose aspirin (≤81 mg daily) in the Full Factorial, Selenium and Advanced Adenoma Cohorts, respectively, were 48.7, 46.5 and 37.9. The percentages of participants with a prior history of colorectal polyps in the Full Factorial, Selenium and Advanced Adenoma Cohorts, respectively, were 28.8, 34.5 and 39.6. Overall, an almost 60% majority of participants reported having ever smoked cigarettes.

Adenoma characteristics

Characteristics of participants' colorectal adenomas at baseline, including anatomic location, size and histological category, are shown in Table 2. Overall, 675 participants (37.9%) had one or more advanced adenomas and 366 (20.1%) had more than two adenomas. Adenomas from 202 of 203 participants in the Advanced Adenoma Cohort were ≥1 cm in size; the remaining participant qualified for the Advanced Adenoma Cohort by having an adenoma with villous histology. Of the 366 participants with more than two adenomas, 199 had at least one advanced adenoma and 164 did not. Thus, a total of 842 participants (47.2%) were in a high risk category by virtue of having one or two advanced adenomas (n=476) (37), or three or more non-advanced adenomas (n=167) (43), or three or more adenomas of which at least one was an advanced adenoma (n=199); the 167 participants with three or more non-

advanced adenomas includes three in whom it is unknown whether the adenomas were advanced or non-advanced.

Concomitant low-dose aspirin

Approaching 50% of participants continued low-dose aspirin during the trial. As described, our sample size provides 94% statistical power to detect a 25% reduction due to the selenium intervention averaged across non-aspirin and low-dose aspirin users. As a secondary endpoint, we will also have adequate power to assess whether low-dose aspirin modifies the effect of selenium. The power calculation for the latter analysis assumes an adenoma recurrence rate of 49%, a marginal OR of 0.6 due to selenium (a 25% reduction in the recurrence rate), and a marginal OR for low-dose aspirin of 0.8 (a 10% reduction in the recurrence rate). We will have >80% power to detect an interaction odds ratio of ≤0.5 (a combined 33% reduction in the adenoma recurrence rate from selenium + low-dose aspirin).

Selenium plasma levels

Median baseline plasma selenium levels (interquartile range) in the Full Factorial, Selenium and Advanced Adenoma Cohorts, respectively, were 134.3 (120.4 – 149.8), 137.6 (122.0 – 157.7) and 133.4 (121.9 – 147.8) ng/ml (Table 3). In the Nutritional Prevention of Cancer (NPC) trial of selenized yeast, reductions in overall cancer risk with the selenium intervention were confined to participants whose baseline selenium levels were in the lowest two tertiles (<121.6 ng/ml) (28). Chemoprevention trials in which nutritional supplements, including selenium (44), have been administered to already-replete study populations have been criticized because supplementation of a given intervention above a certain preexisting threshold may confer no additional protection against the neoplastic condition in question (45). The median baseline plasma selenium level of the study population in the current trial was in the replete range. As noted, modification of the effects of the selenium intervention by baseline plasma selenium level will be analyzed.

Accrual period

Recruitment of the originally planned 1,600 participants extended over seven years from November, 2001 until November, 2008. The length of the recruitment period, which was much longer than was required in our earlier WBF (40) and UDCA (41) colorectal adenoma prevention trials, was unanticipated. Several factors contributed. Prior to the Health Insurance Portability and Accountability Act (HIPAA), potential participants could be identified and contacted concerning possible participation simply from perusal of endoscopy unit and pathology department logs. The introduction of HIPAA in April, 2003 necessitated developing lengthier processes with additional steps protecting patient confidentiality before study staff could directly contact potential participants. The modified recruitment practices had to be tailored to each study site. Just as post-HIPAA modifications to recruitment strategies were taking effect and recruitment was gathering pace again, adverse events associated with rofecoxib (VIOXX) were announced in graphic terms in the national media. This slowed recruitment to a trial that included celecoxib, an agent from the same class—the coxibs—as rofecoxib, even before the FDA compulsorily withdrew celecoxib and all other coxibs in December, 2004.

Causes for consideration of early termination

Results from two other selenium chemoprevention trials that were published during accrual to the current trial compelled us to consider early termination. The first was a report that supplementation with selenized yeast was associated with increased risk for type 2 diabetes (T2D) (46) and the second was the early termination, for lack of any effect, of the SELECT Trial of selenium and vitamin E for prostate cancer prevention (47).

In a secondary analysis of the NPC trial (28) that was published in 2007, a positive association was reported between selenium supplementation and self-reported diagnoses of T2D during the blinded phase of the trial (46). Participants were followed for an average of 7.7 years and the hazard ratio for development of T2D in those randomized to selenized yeast compared to placebo was 1.55 (95% CI, 1.03 to 2.33). Reports of diabetes came from three sources: self-report at clinic visits, reported use of drugs for diabetes, and reports in medical record documents. Medical record requests were then sent to the primary physicians for every patient with a report of diabetes.

In our ongoing selenium trial, fasting blood specimens for plasma glucose and other measurements are drawn from all participants at baseline and annually thereafter during the blinded phase of the trial. The EDSMC conducted an unblinded analysis of fasting plasma glucose data in our trial after the report of selenium-related increased risk for T2D in NPC trial participants; the investigators remained blinded. After this analysis, the Principal Investigator was instructed by the EDSMC to continue the trial without modification. The fasting blood specimens available for the complete trial cohort will provide a unique opportunity to compare the incidence of T2D in the selenium and placebo groups based on plasma glucose levels and other analyses that are planned.

As noted, the SELECT Trial of the effects of selenium (200 μg daily as selenomethionine) and vitamin E (400 IU daily), alone or in combination, on the risk of prostate cancer in 35,533 men (48) was terminated in October, 2009 before completion. The reason for early termination was the result of a planned interim analysis by an independent data and safety monitoring committee. This showed that neither selenium nor vitamin E had any effect on prostate cancer incidence (47). In light of the early termination of SELECT, the EDSMC for our selenium trial requested a futility analysis in November, 2009. The committee recommended continuation of the trial without modification on the basis of the results of this analysis.

There are several important respects in which our ongoing selenium colorectal adenoma prevention trial differs from the SELECT trial and could, therefore, have a positive outcome. First, selenium may have tissue-specific effects and the target organ for our trial is the colorectum, not the prostate. Second, the endpoint in our trial is adenoma recurrence as opposed to invasive cancer in SELECT, and it is possible that selenium may prevent or reverse premalignant earlier adenoma stages of colorectal carcinogenesis. Finally, selenized yeast, the intervention in our trial, contains additional selenium compounds (49) to selenomethionine and one or more of these compounds may have additional actions with chemopreventive potential to those of the selenomethionine-only intervention used in SELECT.

In summary, while accrual to our trial took longer than expected and administration of the celecoxib intervention was necessarily abbreviated, we are on schedule to unblind trial results for the full study cohort of 1,824 participants in 2013. Close involvement of a vigilant EDSMC enabled us to sustain the trial without compromising patient safety when first celecoxib was withdrawn and then the possibility that selenium supplementation may be associated with increased T2D risk arose. An interactive trial infrastructure involving study physicians, biostatisticians and other key investigators, EDSMC and the funding agency enabled us to enhance accrual of a high-risk group—patients with advanced adenomas—without delaying completion of the trial. Most importantly, the study will answer in the setting of a randomized trial the previously unanswered question of whether a selenized yeast intervention prevents the development of premalignant colorectal adenomas. We will add to the existing body of information on coxib colorectal adenoma chemoprevention. Finally, we will provide detailed novel data of high public health

significance on the potential adverse effects of selenium supplementation on glucoregulatory function and risk for T2D.

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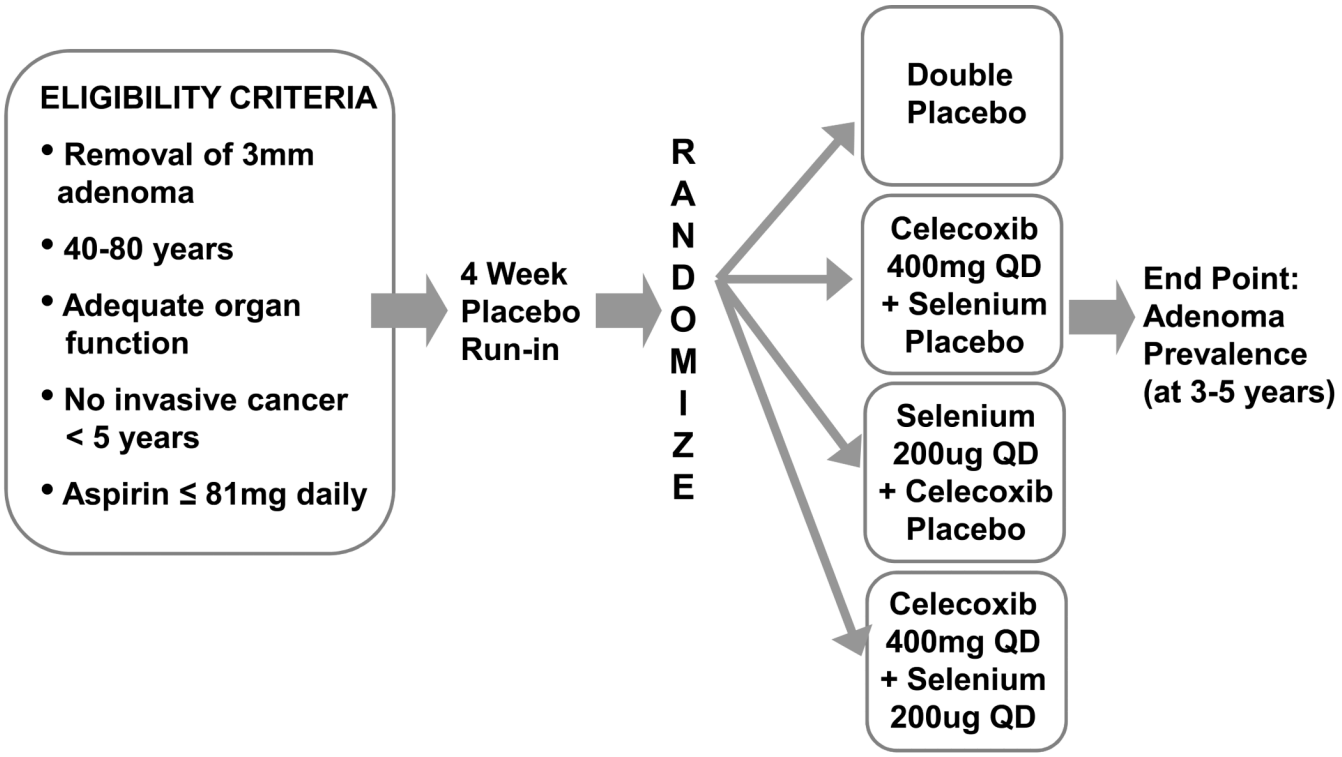

Figure 1. Original study schema—Celecoxib/Selenium Trial

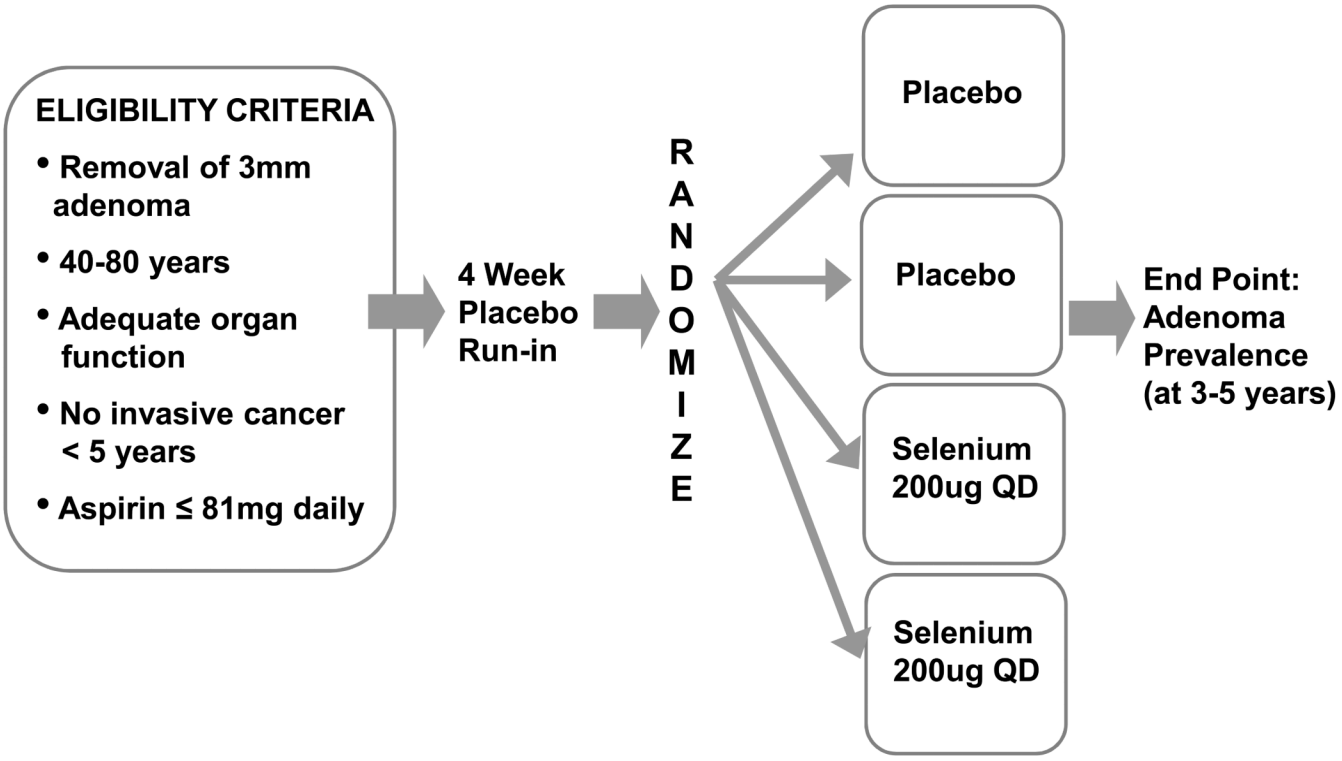

Figure 2. Revised study schema—Selenium Trial

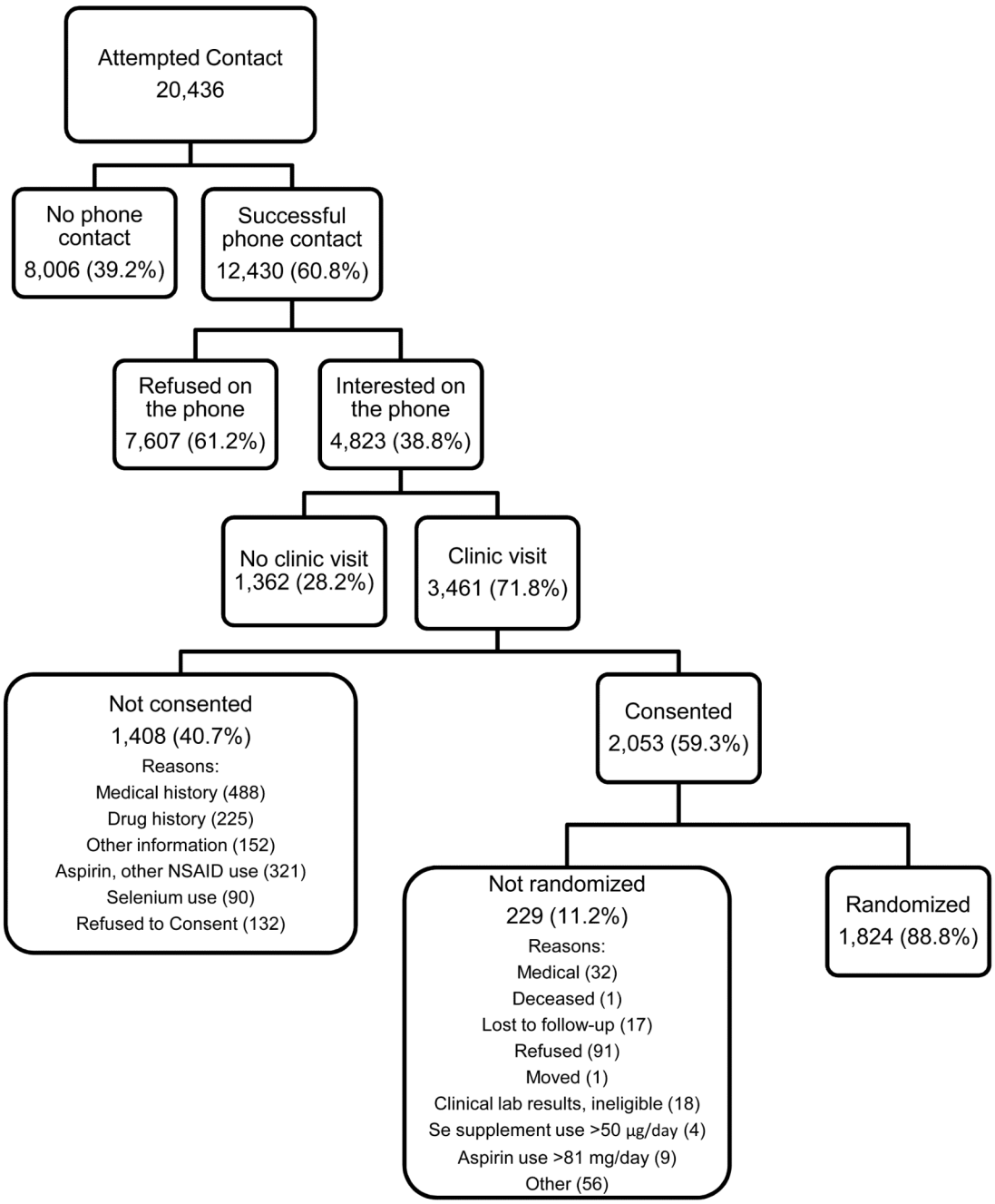

Figure 3. Flow diagram of patient enrollment, consenting and randomization

Table 1

Baseline Participant Characteristics

		Full Factorial Cohort[1] (n=824)		Selenium Cohort[2] (n=797)		Advanced Adenoma Cohort[3] (n=203)		Total (n=1824)	
Clinic									
	Baylor	2	(0.2)	100	(12.5)	21	(10.3)	123	(6.7)
	Colorado	183	(22.2)	100	(12.5)	40	(19.7)	323	(17.7)
	Mayo	6	(0.7)	49	(6.1)	9	(4.4)	64	(3.5)
	Phoenix	461	(55.9)	457	(57.3)	86	(42.4)	1004	(55.0)
	Tucson	172	(20.9)	91	(11.4)	16	(7.9)	279	(15.3)
	Western New York	0	(0.0)	0	(0.0)	31	(15.3)	31	(1.7)
Mean age ± SD		62.9	± 9.3	63.5	± 8.6	60.5	± 8.7	62.9	± 9.0
Age Group									
	<50 y	55	(6.7)	28	(3.5)	16	(7.9)	99	(5.4)
	50-59 y	234	(28.4)	249	(31.2)	77	(37.9)	560	(30.7)
	60-69 y	323	(39.2)	298	(37.4)	71	(35.0)	692	(37.9)
	≥ 70 y	212	(25.7)	222	(27.9)	39	(19.2)	473	(25.9)
Sex									
	Male	559	(67.8)	497	(62.4)	123	(60.6)	1179	(64.6)
	Female	265	(32.2)	300	(37.6)	80	(39.4)	645	(35.4)
Race[4]									
	White	778	(94.6)	742	(93.2)	188	(93.1)	1708	(93.8)
	Black/African	16	(1.9)	32	(4.0)	7	(3.5)	55	(3.0)
	Asian	12	(1.5)	4	(0.5)	3	(1.5)	19	(1.0)
	American Indian/Alaskan	4	(0.5)	4	(0.5)	1	(0.5)	9	(0.5)
	Other/Mixed	12	(1.5)	14	(1.8)	3	(1.5)	29	(1.6)
	Unknown	2		1		1		4	
Hispanic/Latino									
	Yes	42	(5.1)	41	(5.2)	7	(3.5)	90	(4.9)
	No	782	(94.9)	754	(94.8)	195	(96.5)	1731	(95.1)

		Full Factorial Cohort[1] (n=824)		Selenium Cohort[2] (n=797)		Advanced Adenoma Cohort[3] (n=203)		Total (n=1824)	
	Unknown	0		2		1		3	
Education									
	< High School	18	(2.2)	14	(1.8)	3	(1.5)	35	(1.9)
	High School or GED	156	(18.9)	154	(19.4)	43	(21.2)	353	(19.4)
	Some college	253	(30.7)	242	(30.4)	46	(22.7)	541	(29.7)
	Bachelor's Degree	168	(20.4)	158	(19.9)	55	(27.1)	381	(20.9)
	Graduate/Professional	229	(27.8)	227	(28.6)	56	(27.6)	512	(28.1)
	Unknown	0		2		0		2	
Mean BMI[5] ± SD		29.1	± 4.9	29.0	± 5.3	29.2	± 5.2	29.1	± 5.1
	BMI unknown	0		2		0		2	
Cigarette smoking status									
	Ever[6]	484	(60.1)	440	(57.1)	108	(57.1)	1032	(58.5)
	Current	79	(9.8)	66	(8.6)	26	(13.8)	171	(9.7)
	Previous	405	(50.3)	374	(48.6)	82	(43.4)	861	(48.8)
	Never	321	(39.9)	330	(42.9)	81	(42.9)	732	(41.5)
	Unknown	19		27		14		60	
History of colorectal polyps[7]									
	Yes	233	(28.8)	271	(34.5)	78	(39.6)	582	(32.5)
	No	575	(71.2)	514	(65.5)	119	(60.4)	1208	(67.5)
	Unknown	16		12		6		34	
Family History of CRC[8]									
	Yes	160	(20.6)	140	(18.3)	37	(19.1)	337	(19.4)
	No	617	(79.4)	623	(81.7)	157	(80.9)	1397	(80.6)
	Unknown	47		34		9		90	
Diabetes									
	Yes	61	(7.4)	88	(11.1)	23	(11.3)	172	(9.4)
	No	763	(92.6)	708	(88.9)	180	(88.7)	1651	(90.6)
	Unknown	0		1		0		1	

		Full Factorial Cohort[1] (n=824)		Selenium Cohort[2] (n=797)		Advanced Adenoma Cohort[3] (n=203)		Total (n=1824)	
Personal history of cancer[9]									
	Yes	49	(5.9)	47	(5.9)	9	(4.4)	105	(5.8)
	No	775	(94.1)	749	(94.1)	194	(95.6)	1718	(94.2)
	Unknown	0		1		0		1	
Personal history of skin cancer[10]									
	Yes	117	(14.2)	141	(17.7)	28	(13.8)	286	(15.7)
	No	707	(85.8)	655	(82.3)	175	(86.2)	1537	(84.3)
	Unknown	0		1		0		1	
Aspirin use in the past 20 years[11]									
	< 1 year	481	(58.4)	411	(51.8)	122	(60.1)	1014	(55.7)
	1 to <5 years	174	(21.1)	170	(21.4)	36	(17.7)	380	(20.9)
	5 to <10 years	73	(8.9)	90	(11.3)	14	(6.9)	177	(9.7)
	≥ 10 years	96	(11.7)	123	(15.5)	31	(15.3)	250	(13.7)
	Unknown	0		3		0		3	
Aspirin use at randomization									
	0 mg/d	423	(51.3)	426	(53.5)	126	(62.1)	975	(53.5)
	1-81 mg/d	401	(48.7)	371	(46.5)	77	(37.9)	849	(46.5)
NSAID use in the past 20 years[12]									
	< 1 year	739	(89.7)	699	(88.0)	180	(88.7)	1618	(88.9)
	1 to <5 years	53	(6.4)	58	(7.3)	13	(6.4)	124	(6.8)
	5 to <10 years	16	(1.9)	17	(2.1)	3	(1.5)	36	(2.0)
	≥ 10 years	16	(1.9)	20	(2.5)	7	(3.4)	43	(2.4)
	Unknown	0		3		0		3	
Supplement User									
	Yes	537	(68.4)	521	(69.7)	123	(63.7)	1181	(68.4)
	No	248	(31.6)	227	(30.3)	70	(36.3)	545	(31.6)
	Unknown	39		49		10		98	

Note: Counts and percentages for categorical variables; mean ± standard deviation for continuous variables. Percentages are calculated from non-missing data.

[1] Full Factorial Cohort: Celecoxib vs Selenium vs Combination vs Placebo, 11/27/2001-12/16/2004

[2] Selenium Cohort: Selenium vs Placebo, 02/02/2005-11/26/2008

[3] Advanced Adenoma Cohort: Selenium vs Placebo among participants selected for advanced adenoma at qualification, 07/30/2008-01/19/2011

[4] 25 participants marked more than one race, including 22 who selected a race they identified with primarily (and classified accordingly), and 3 who were unable to identify with one group (classified as Mixed).

[5] Body Mass Index, calculated as 703*(weight in pounds)/(height in inches)^2.

[6] Ever smoker defined as 100 or more cigarettes.

[7] History of colorectal polyp(s) on prior occasion to baseline colonoscopy with polypectomy that determined study eligibility

[8] Family history of colorectal cancer in a first degree relative

[9] Excluding non-melanoma skin cancer

[10] Including basal cell, squamous cell, and skin cancer of unknown type

[11] 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.

[12] Number of years in total within the past twenty years taking a non-steroidal anti-inflammatory drug (NSAID), excluding aspirin, either over-the-counter or prescription at least twice a week for at least six consecutive months.

Table 2

Baseline Adenoma Characteristics

	Full Factorial Cohort[1] (n=824)		Selenium Cohort[2] (n=797)		Advanced Adenoma Cohort[3] (n=203)		Total (n=1824)	
Number of adenomas								
1	499	(60.6)	471	(59.1)	83	(40.9)	1053	(57.7)
2	182	(22.1)	170	(21.3)	53	(26.1)	405	(22.2)
3+	143	(17.4)	156	(19.6)	67	(33.0)	366	(20.1)
Proximal adenoma								
No	294	(38.5)	250	(32.1)	61	(30.5)	605	(34.7)
Yes	470	(61.5)	528	(67.9)	139	(69.5)	1137	(65.3)
Unknown	60		19		3		82	
Distal/Rectal adenoma								
No	323	(42.3)	360	(46.3)	80	(40.0)	763	(43.8)
Yes	441	(57.7)	418	(53.7)	120	(60.0)	979	(56.2)
Unknown	60		19		3		82	
Largest adenoma								
<1cm	569	(71.8)	590	(75.7)	1	(0.5)	1160	(65.4)
≥1cm	224	(28.3)	189	(24.3)	202	(99.5)	615	(34.6)
Unknown	31		18		0		49	
Histology (most severe)								
Tubular, or Adenoma, NOS	717	(87.0)	709	(89.0)	156	(76.8)	1582	(86.7)
Tubulovillous or Villous	107	(13.0)	87	(10.9)	47	(23.2)	241	(13.2)
Invasive Cancer[4]	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)
High Grade Dysplasia								
No	808	(98.1)	785	(98.5)	196	(96.6)	1789	(98.1)
Yes	16	(1.9)	12	(1.5)	7	(3.4)	35	(1.9)
Advanced Adenoma[5]								
No	540	(67.7)	567	(72.6)	0	(0.0)	1107	(62.1)
Yes	258	(32.3)	214	(27.4)	203	(100.0)	675	(37.9)

	Full Factorial Cohort[1] (n=824)		Selenium Cohort[2] (n=797)		Advanced Adenoma Cohort[3] (n=203)		Total (n=1824)	
Unknown due to unknown size	26		16		0		42	
High Risk[6]								
No	477	(59.6)	466	(59.6)	0	(0.0)	943	(52.8)
Yes	323	(40.4)	316	(40.4)	203	(100.0)	842	(47.2)
Unknown due to unknown size	24		15		0		39	

Note: Counts and percentages of non-missing data.

[1]Full Factorial Cohort: Celebrex vs Selenium vs Combination vs Placebo, 11/27/2001-12/16/2004

[2]Selenium Cohort: Selenium vs Placebo, 02/02/2005-11/26/2008

[3]Advanced Adenoma Cohort: Selenium vs Placebo among participants selected for advanced adenoma at qualification, 07/30/2008-01/19/2011

[4]One participant was diagnosed with CRC less than 6 months after randomization. This is classified as a baseline event (i.e. not endpoint).

[5]Advanced adenoma defined as having one or more of the following features: adenoma ≥1cm, with tubulovillous or villous histology, and/or with high grade dysplasia.

[6]High risk defined as having an advanced adenoma or ≥3 adenomas.

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Table 3

Baseline Selenium Intake and Plasma levels

		Full Factorial Cohort[1] (n=824)		Selenium Cohort[2] (n=797)		Advanced Adenoma Cohort[3] (n=203)		Total (n=1824)	
Selenium supplement use at recruitment									
	0 μg	366	(44.4)	383	(48.1)	103	(50.7)	852	(46.7)
	1-50 μg	356	(43.2)	329	(41.3)	43	(21.2)	728	(39.9)
	51-199 μg	68	(8.3)	62	(7.8)	50	(24.6)	180	(9.9)
	≥200 μg	34	(4.1)	23	(2.9)	7	(3.4)	64	(3.5)
Selenium supplement use at randomization									
	0 μg	283	(42.2)	410	(51.4)	117	(57.6)	810	(48.5)
	1-50 μg	387	(57.8)	387	(48.6)	86	(42.4)	860	(51.5)
	Missing[4]	154		0		0		154	
Selenium Intake from food (μg), median (IQR)		94.5 (70.5-127.6)		92.8 (68.7-123.5)		91.0 (67.9-129.8)		93.4 (69.1-125.7)	
	Missing[5]	39		49		10		98	
Selenium (ng/ml) measured in plasma, median (IQR)		134.3 (120.4-149.8)		137.6 (122.0-157.7)		133.4 (121.9-147.8)		135.3 (121.3-152.7)	
	Missing[6]	7		5		2		14	

Note: Counts and percentages of non-missing data unless otherwise noted. IQR=Interquartile Range

[1] Full Factorial Cohort: Celebrex vs Selenium vs Combination vs Placebo, 11/27/2001-12/16/2004

[2] Selenium Cohort: Selenium vs Placebo, 02/02/2005-11/26/2008

[3] Advanced Adenoma Cohort: Selenium vs Placebo among participants selected for advanced adenoma at qualification, 07/30/2008-01/19/2011

[4] Missing data in the original cohort because the first version of the form omitted this question.

[5] Some participants refused to fill out the food frequency questionnaire.

[6] Selenium sample not obtained due to blood draw difficulties