No Evidence for Post-Treatment Effects of Vitamin D and Calcium Supplementation on Risk of Colorectal Adenomas in a Randomized Trial

Audrey H. Calderwood, John A. Baron, Leila A. Mott, Dennis J. Ahnen, Roberd M. Bostick, Jane C. Figueiredo, Michael N. Passarelli, Judy R. Rees, Douglas J. Robertson, Elizabeth L. Barry

Affiliations:

AHC	Section of Gastroenterology and Hepatology, Department of Medicine, Geisel School of Medicine at Dartmouth, Hanover, NH, USA
JAB	Department of Epidemiology, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA Department of Medicine, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA University of North Carolina School of Medicine, Chapel Hill, NC, USA.
LAM	Department of Epidemiology, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA
DJA	Division of Gastroenterology and Hepatology, University of Colorado School of Medicine, Denver, CO, USA
RMB	Department of Epidemiology, Emory University, Atlanta, GA, USA Winship Cancer Institute, Emory University, Atlanta, GA, USA
JCF	Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA
MNP	Department of Epidemiology, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA
JRR	Department of Epidemiology, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA
DJR	VA Medical Center, White River Junction, VT, USA Section of Gastroenterology and Hepatology, Department of Medicine, Geisel School of Medicine at Dartmouth, Hanover, NH, USA
ELB	Department of Epidemiology, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

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Abbreviations: BMI, body mass index

Corresponding author:
Audrey H. Calderwood, MD, MS
Dartmouth-Hitchcock Medical Center
One Medical Center Drive
Lebanon, NH 03756
Tel: 603-650-5215
Fax: 603-650-5225
Email: audrey.h.calderwood@hitchcock.org

Abstract

Vitamin D and calcium supplementation are postulated to have chemopreventive effects against colorectal neoplasia, yet in our previously-reported randomized trial, there was no overall efficacy of calcium and/or vitamin D_3 against colorectal adenoma recurrence. It is possible vitamin D_3 and calcium chemopreventive effects are not detectable until beyond the 3-5 year follow-up captured in that trial. Accordingly, we explored possible vitamin D and calcium effects on post-treatment (observational) adenoma occurrence. In this secondary analysis of the observational follow-up phase of the Vitamin D/Calcium Polyp Prevention Study, participants who completed the treatment phase were invited to be followed for one additional surveillance colonoscopy cycle. We evaluated adenoma occurrence risk at surveillance colonoscopy, with a mean of 55 ± 15 months post-treatment follow-up, according to randomized treatment with vitamin D vs. no vitamin D, calcium vs. no calcium, and calcium plus vitamin D vs. calcium alone. Secondary outcomes included advanced and multiple adenomas. Among the 1121 participants with observational follow-up, the relative risk (95% confidence interval, CI) of any adenoma was 1.04 (0.93-1.17) for vitamin D vs. no vitamin D; 0.95 (0.84-1.08) for calcium vs. no calcium; 1.07 (0.91-1.25) for calcium plus vitamin D vs. calcium; and 0.96 (0.81-1.15) for calcium plus vitamin D vs. neither. Risks of advanced or multiple adenomas also did not differ by treatment. Our results do not support an association between supplemental calcium and/or vitamin D_3 for 3–5 years and risk of recurrent colorectal adenoma at an average of 4.6 years post-treatment.

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Introduction

Vitamin D[1,2] and calcium[3] have potential antineoplastic effects in the colorectum[4-14] and several randomized trials of calcium for colon adenoma prevention found reduced risks.[4-6] However, in our randomized, multi-center, double-blind, placebo-controlled trial of supplementation with calcium, vitamin D_3, or both (the Vitamin D/Calcium Polyp Prevention Study), we found no effect of 3- or 5-years of treatment on the prevention of new colorectal adenomas in persons with a recent history of adenomas.[15] Since adenomas can take approximately 10-25 years to develop and progress,[16] it is possible that the chemopreventive effects of vitamin D and calcium may not be detectable until beyond the initial 3-5 year follow-up. In our previous calcium trial, the chemopreventive effect of calcium on the risk of any adenoma appeared to be more pronounced during the 5 years *after* active treatment than during the active treatment period itself.[4,17,18] Accordingly, the goal for the post-treatment observational analysis reported here was to explore possible vitamin D and calcium effects on post-treatment adenoma occurrence.

Materials and Methods

Study Design – Treatment Phase

A detailed description of the design and treatment phase findings of the Vitamin D/Calcium Polyp Prevention Study (ClinicalTrials.gov number, NCT00153816) have been published previously.[15] Briefly, the Vitamin D/Calcium Polyp Prevention Study was a multi-center, randomized, double-blind, placebo-controlled trial of vitamin D and/or calcium supplements at 11 academic medical centers and associated medical practices in the US. Institutional review boards at each center approved the study, and all participants provided written informed consent.

Eligible participants were age 45-75 years with at least one colorectal adenoma ($\geq$ 0.2 cm) removed in the 4 months prior to study entry and no known remaining polyps in the colon after complete colonoscopy. All participants had blood calcium within the normal reference range, creatinine not exceeding 20% above the upper limit of normal, and 25-hydroxyvitamin D concentrations $\geq$ 12 ng/ml to $\leq$ 90 ng/ml at enrollment.

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Following eligibility screening and a 56-84 day placebo run-in period, 2259 participants were randomly assigned in a partial 2 x 2 factorial design to receive vitamin D_3 (1000 IU/day), calcium carbonate (1200 mg elemental calcium/day), both agents, or placebo only (full factorial randomization). Women could choose to be randomly assigned to receive either calcium or calcium plus vitamin D (two-group randomization). Randomization was completed between July 2004 and July 2008. At enrollment, participants were instructed not to take their own off-study calcium or vitamin D supplementation.

Participants completed telephone questionnaires every six months regarding adherence to study agents, use (dose and frequency) of medications and vitamin/mineral supplements, illnesses, hospitalizations, and dietary intake of calcium and vitamin D (using a targeted, 17-item dietary screener custom developed by NutritionQuest (Berkeley, CA) for this study). Blood concentrations of 25-hydroxyvitamin D were measured at baseline and at year 1, as well as at year 3 for participants with a 5-year surveillance cycle, and shortly before the end of treatment. For all major medical events, medical records were obtained and the event confirmed by a blinded study physician.

The primary endpoint was at least one adenoma detected on follow-up colonoscopy approximately either 3 or 5 years after qualifying colonoscopy, depending on the follow-up interval recommended by each participant's endoscopist. Data collection for the primary endpoint was completed in October 2013. All participants were unblinded to their study treatment assignment in November 2013, after treatment phase follow-up was ended study-wide.

Study Design – Observational Follow-up Phase

The aim of this post-treatment observational follow-up phase of the Vitamin D/Calcium Polyp Prevention Study was to investigate the effects of the study agents during the colonoscopic surveillance interval after cessation of active supplementation. All participants were invited to participate in the observational phase, and those who

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agreed provided written informed consent. Only participants who had a complete colonoscopy at the end of the treatment phase were included in this analysis. Participants were followed in the observational period for an additional colonoscopic surveillance cycle, the length of which was determined by their own physicians. Participants completed yearly telephone questionnaires that included use of medications and vitamin/mineral supplements and dietary intake of calcium and vitamin D, which were used to calculate daily average use and intake over the observational time period. We included outcomes identified during all procedures through the first colonoscopy at least 3 years after the end-of-treatment colonoscopy. If the surveillance colonoscopy was incomplete (e.g. inadequate bowel preparation) or there was a very short follow-up interval (i.e., < 6 months) to the next colonoscopy (e.g. for re-treatment of a polyp), the results of the later colonoscopy were also included. Observational follow-up ended for all participants in June 2016 due to discontinuation of study funding. For each colonoscopy, we obtained copies of the endoscopy and pathology reports. One study pathologist reviewed slides of each colon lesion removed to provide uniform review.

The primary endpoint for the current analysis was the occurrence of new adenomas in the interval between the colonoscopy at the end of study treatment and the colonoscopy at the end of observational follow-up. Secondary outcomes were the occurrence of advanced adenomas (defined as those with cancer, high-grade dysplasia, more than 25% villous features, or an estimated diameter of at least 1 cm as assessed by the endoscopist), and high-risk findings (any advanced adenoma and/or >2 adenomas). We also examined adenoma location. Proximal adenomas were defined as those occurring proximal to the splenic flexure and distal adenomas were defined as those occurring in, or distal to, the splenic flexure. Participants with at least one proximal and at least one distal adenoma were considered to have both a proximal and a distal adenoma in our analysis.

Statistical Analysis

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We used contingency tables and standard chi-square tests to compare the risk of having one or more adenomas at an observational follow-up surveillance colonoscopy according to randomized assignment to vitamin D vs. no vitamin D, calcium vs. no calcium, and calcium plus vitamin D vs. calcium alone. Adjusted risk ratios (termed “relative risk” through the paper) and 95% confidence intervals were estimated using a Poisson log-linear model with adjustment for under/overdispersion. The models included relevant patient characteristics (age, sex, number of baseline adenomas) and variables used in the randomization stratification (clinical center, two-group vs. full factorial randomization, and treatment phase surveillance interval specified at baseline [3 vs. 5 year]). When data were sparse, we grouped clinical centers geographically into southeast (Georgia, North Carolina, South Carolina, and Puerto Rico), north (Ohio, New Hampshire, Iowa, and Minnesota), and west (Colorado, Texas, and California).

We performed subgroup analyses to compare potential delayed effects of vitamin D and calcium according to baseline characteristics, including sex, body mass index (BMI in kg/m^2: normal <25, overweight 25-29.9, obese ≥30), and alcohol use (0, 0.1-1, >1/day); and end-of-treatment characteristics, including cigarette smoking (never/former vs. current), serum 25-hydroxyvitamin D concentrations (below vs. above median of 28.1 ng/ml), dietary calcium (above or below median of 794 mg/day), calcium supplementation (<400 mgs/day vs. ≥400 mgs/day), vitamin D supplementation (<400 IU/day vs. ≥400 IU/day), non-steroidal anti-inflammatory drug (NSAID)/aspirin use (<4 days vs. ≥4 days/week), and adenoma at end-of-treatment colonoscopy (no/yes). Analyses of Vitamin D vs. no vitamin D included all randomized participants; analyses of calcium vs. no calcium and of both Vitamin D and calcium vs. neither agent were restricted to full factorial participants; analyses of Vitamin D and calcium vs. calcium alone excluded full factorial participants randomized to placebo or vitamin D alone. Subgroup heterogeneity was tested using the Wald test by including interaction terms in the regression models.

Last, we evaluated the occurrence of clinical events (i.e., death, myocardial infarction, stroke, cancer, urolithiasis, and fractures), by treatment assignment, during the observational follow-up phase and in the treatment and observational phase together. Observational phase clinical events occurred between 30 days after exiting the

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treatment phase and the first colonoscopy at least three years after end-of-treatment colonoscopy or exit from the observational study.

All statistical tests were two-sided. P values ≤ 0.05 or 95% confidence intervals that excluded 1.0 were considered statistically significant. Stata 9 software (StataCorp, College Station, TX) and SAS 9.4 (Cary, NC) were used to perform all analyses.

Results

Of the 2259 randomized participants, 2087 had colonoscopy information from an end-of-treatment examination; of these, 1986 (95.2%) agreed to observational follow-up. Among these 1986 eligible participants, 1121 (56.4%) had a surveillance colonoscopy before the observational follow-up phase of the study ended, and were included in analyses (**Figure 1**). Participants who did not have a colonoscopy in the observational period (N=865) tended to have been enrolled later (45% enrolled in the last 2 years of enrollment vs. 23% in the subjects who had an observational colonoscopy; $p<0.0001$). In addition, those without an observational colonoscopy were less likely to have adenomas at the end-of-treatment colonoscopy (38% vs. 47%; $p<0.0001$) and therefore had longer expected surveillance intervals after the end-of-treatment exam (58 months in those without colonoscopy vs. 51 months for those with an observational colonoscopy; $p<0.0001$). The percentage of participants with and without an observational colonoscopy did not differ by treatment group (data not shown).

The study population was 64.0% male and 89.4% white, with a mean age of 58.1 years. The characteristics of the participants across the four arms of the full factorial randomization were similar, as were the two arms in the two-group randomization (**Table 1**)**.** All baseline comparisons were statistically non-significant. Some end-of-treatment comparisons suggested differences by randomization assignment (serum 25-hydroxyvitamin D concentrations for full factorial and for 2 group, and alcohol for 2 group). Adherence to study treatment was similar across all groups during the active treatment phase of the study (data not shown).

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The overall mean ± SD observational follow-up was 55 ± 15 months (range 6-100); this did not vary substantially by treatment assignment (p=0.86; **Table 2**). Four hundred twelve participants (37%) had observational phase colonoscopy before participants were unblinded; this proportion did not differ by treatment group (data not shown).

Vitamin D and/or calcium supplement use during the observational phase was similar across all randomized treatment assignment groups (**Table 2**). During the observational phase, very few participants (N=16) reported supplemental calcium intake of ≥1200 mg/day. Overall vitamin D supplementation use of ≥1000 IU/day was also modest (18.2%), with overall higher use among the 2-group (Vitamin D only) randomization participants.

The proportions of participants with any adenoma, advanced adenomas, and high risk findings during the observational follow-up were 51.4%, 9.3%, and 19.7%, respectively. Adjusted relative risks did not differ substantially or statistically significantly by randomized treatment assignment (**Table 3**), though there was a non-significant increase in the risk of advanced adenomas among participants randomized to Vitamin D plus calcium in comparison to those given calcium alone. These null effects did not differ by anatomic site (proximal or distal) (**Supplemental Table 1**).

The results of the subgroup analyses are shown in **Table 4**. There were no significant differences in the post-treatment effect of vitamin D on risk of any adenoma when comparing participants with baseline serum 25-hydroxyvitamin D concentrations below the overall median (RR 0.96 (0.81-1.13)) and those with 25-hydroxyvitamin D concentrations above the overall median (RR 1.14 (0.96-1.34); p for interaction = 0.13) (**Table 4**). For any adenoma, there was also no evidence of treatment effect modification by other characteristics measured before the start of treatment (e.g., sex, BMI, alcohol use) or characteristics measured at the end-of-treatment (smoking status, dietary calcium intake, calcium and vitamin D supplement use, NSAID/aspirin use, or adenoma on colonoscopy). However, vitamin D appeared to increase the risk of high risk findings among

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participants with NSAID or aspirin use ≥4 days/week at end-of-treatment (RR 1.42 (1.01-2.00)) compared to those with less frequent use (RR 0.81 (0.57-1.14); p for interaction = 0.03).

The post-treatment effect of calcium treatment appeared to be modified by sex, with a trend toward an increase in the delayed risk of adenomas in women (RR 1.46 (0.95-2.25)), but not in men (RR 0.89 (0.78-1.01); p for interaction = 0.01) (Table 4). Use of calcium supplements outside the study seemed to modify the post-treatment calcium effect: the RR among participants who were using ≥400 mg of calcium supplementation at the end-of-treatment was 2.47 (0.77-7.89), while that among those who were not was 0.91 (0.81-1.03) (p for interaction = 0.02). However, there was (weaker) evidence of an interaction (p = 0.10) in the opposition direction for dietary calcium intake and advanced adenomas (Table 4). In the calcium treatment group, there was a marginally significant interaction with vitamin D supplementation for advanced and high risk findings (p for interaction = 0.04 and 0.05, respectively). The effect of calcium was not modified by BMI.

Overall, there were no substantial or statistically significant differences in the occurrence of adverse events across treatment assignment groups during the observational phase or overall (combined treatment and observational follow-up phases) (**Table 5)**.

Discussion

In this observational follow-up of the randomized Vitamin D/Calcium Polyp Prevention Study, neither 1000 IU of Vitamin D_3 nor 1200 mg of calcium, taken daily alone or in combination for 3 or 5 years during the active treatment phase, were associated with risk of new colorectal adenomas during a mean of 4.6 years of additional post-treatment observational follow-up. This was true even among participants with serum 25-hydroxyvitamin D concentrations and dietary calcium intake below the median at the end-of-treatment. Our findings in relation to risk of high-risk findings were also null. Overall, there was also no post-treatment effect of vitamin D or calcium on the risk of adenomas within participant subgroups. Although there were some nominally statistically significant interactions, because of the number of subgroups examined, these are likely due to chance. While in the

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randomized active treatment phase of the study BMI appeared to modify the effects of calcium on adenoma risk, such that the lower the BMI, the greater the protection with calcium supplementation,[15,19] there was no evidence for continued benefit of calcium treatment in participants with a low BMI during observational follow-up.

In our previous randomized trial of calcium (the Calcium Poly Prevention Study), recurrent adenoma risks among participants treated with 1200 mg of elemental calcium relative to those on placebo was reduced (RR 0.85 (0.74-0.98)),[4] and the effect appeared to be more pronounced for advanced adenomas (RR 0.65 (0.46-0.93)).[17] Another, smaller randomized trial found a modest but statistically non-significant reduction in recurrent adenomas with treatment with 2000 mg of elemental calcium (OR 0.66 (0.38-1.17)).[5] A small feasibility study by Chu et al. found a reduction in adenoma recurrence among those taking 1800 mg/d of calcium carbonate compared to placebo (odds ratio 0.47 (0.27- 0.84)).[6]

During the treatment phase of the Vitamin D/Calcium Polyp Prevention Study trial, we saw non-statistically significant findings that suggested that longer calcium or vitamin D treatment and follow-up might reduce adenoma recurrence.[15] For example, among participants with an intended 3-year follow-up, the RRs (95% confidence intervals) for calcium and vitamin D were 0.98 (0.84-114) and 1.04 (0.90-1.19), respectively. Among those with an intended 5-year follow-up, they were 0.90 (0.77-1.05) and 0.93 (0.80-1.08), respectively. However, the current results do not support post-treatment delayed effects with longer follow-up, and differ with those from our previous calcium trial,[4] in which the chemopreventive effect of 1200 mg calcium per day on risk of any adenoma appeared to be more pronounced during the 5 years *after* active treatment than during the active treatment period itself.[18]

Calcium treatment might alter the colorectal mucosa to impede the development of new adenomas, however the underlying mechanism is unknown. One hypothesis is that calcium binds and precipitates bile acids and other free fatty acids in the gut lumen, thus inhibiting mucosal inflammation and proliferation.[20,21] A second proposed

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mechanism is a direct effect of calcium through a calcium sensing receptor (CaSR) that is expressed on colonocytes.[22,23] Regardless of potential mechanism, we did not find a substantive chemopreventive effect of calcium, vitamin D or calcium plus vitamin D either during active treatment[15] or now in observational follow-up.

Given the small number of adverse events, it is not surprising that vitamin D and calcium supplementation was not associated with the development of important clinical events, including fractures and cardiovascular diseases, during and/or after the active treatment phase of the randomized trial. However, the current study was not powered to investigate these events specifically in the observational follow-up.

Our study has several strengths. Our analysis was based on randomized treatment, there was excellent adherence to study treatment during the treatment phase, and a large number of participants were still alive and agreed to participate in the observational phase of the trial. We were able to assess calcium and vitamin D supplementation during the post-treatment observational follow-up period via yearly questionnaires. All histopathological slides collected from colonoscopies during both the treatment and observational periods underwent a standardized review.

We acknowledge some study limitations. Dietary assessment of calcium and vitamin D were obtained from a brief survey instrument and may be inexact. Information on supplement use during the observational period relied on participant self-report, which has inherent limitations. There was no uniform interval between the end of active treatment and the first post-treatment colonoscopy. However, the timing of follow-up colonoscopy was left to the discretion of the treating physician, so reflects real clinical practice conditions. Only 56.4% of eligible participants in the clinical trial had colonoscopies during the observational follow-up period, since many participants had anticipated colonoscopies after the end of follow-up. However, the participant characteristics among those who did have observational phase colonoscopies remained balanced across the randomized treatment assignment groups. Nonetheless, the limited number of participants with observational phase colonoscopies reduced our statistical power to identify potential associations and for less common outcomes like advanced adenomas. The

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length of observational follow up was relatively short, and may still have been insufficient for detecting potential longer-term effects of the treatment. Another limitation is that observational follow-up averaged 55 months and therefore favored the inclusion of individuals whose prescribed surveillance interval was shorter (indicating the likely presence of a lesion at the end of treatment); if a delayed effect takes longer than this period to develop, we would not have identified it.

In summary, the results of our study do not support that supplemental calcium and/or vitamin D_3 for 3 – 5 years is associated with risk for recurrent colorectal adenoma over a mean of 55 months after the end of active preventive treatment with these agents.

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Table 1: Characteristics of post-treatment observational follow-up phase participants

	All participants consented to observational phase	Participants with observational phase adenoma outcome data						
			Treatment assignment					
			Full factorial randomization				Two-group randomization[a]	
		Overall	Placebo	Calcium	Vitamin D	Calcium + vitamin D	Calcium + placebo	Calcium + vitamin D
Baseline characteristics	N (%) or mean ± SD	N (%) or mean ± SD	N (%) or mean ± SD	N (%) or mean ± SD	N (%) or mean ± SD	N (%) or mean ± SD	N (%) or mean ± SD	N (%) or mean ± SD
N	1986	1121	210	215	213	224	132	127
Sex								
Female	715 (36.0)	375 (33.5)	25 (11.9)	28 (13.0)	28 (13.2)	35 (15.6)	132 (100)	127 (100)
Male	1271 (64.0)	746 (66.6)	185 (88.1)	187 (87.0)	185 (86.9)	189 (84.4)	0	0
Age (years)	58.1 ± 6.7	57.8 ± 6.4	58.3 ± 6.7	58.5 ± 6.7	57.6 ± 6.6	58.1 ± 6.4	57.2 ± 5.6	56.3 ± 6.1
Race								
Caucasian	1708 (89.4)	975 (89.8)	189 (92.2)	186 (87.7)	194 (94.2)	200 (90.1)	102 (84.3)	104 (86.7)
African American	138 (7.2)	83 (7.6)	14 (6.8)	17 (8.0)	7 (3.4)	20 (9.0)	13 (10.7)	12 (10.0)
Asian/Pacific Islander	48 (2.5)	20 (1.8)	1 (0.5)	5 (2.4)	4 (1.9)	1 (0.5)	6 (5.0)	3 (2.5)
Other	17 (0.9)	8 (0.7)	1 (0.5)	4 (1.9)	1 (0.5)	1 (0.5)	0	1 (0.8)
BMI (kg/m^2)	28.9 ± 5.1	29.0 ± 5.0	29.1 ± 4.9	29.6 ± 5.0	29.1 ± 4.4	28.6 ± 4.6	28.8 ± 5.9	28.3 ± 5.4
< 25	459 (23.1)	242 (21.6)	39 (18.6)	33 (15.4)	36 (16.9)	51 (22.8)	39 (29.6)	44 (34.7)
25 - 29.9	818 (41.2)	471 (42.0)	95 (45.2)	97 (45.1)	95 (44.6)	99 (44.2)	43 (32.6)	42 (33.1)
≥ 30	708 (35.7)	408 (36.4)	76 (36.2)	85 (39.5)	82 (38.5)	74 (33.0)	50 (37.9)	41 (32.3)
Alcohol intake (drinks/day)	0.78 ± 1.01	0.79 ± 1.02	0.89 ± 1.11	0.88 ± 1.04	0.92 ± 1.11	0.94 ± 1.11	0.31 ± 0.52	0.53 ± 0.69
End-of-treatment characteristics								
Smoking status								
Never	1061 (53.4)	578 (51.6)	87 (41.4)	112 (52.1)	102 (47.9)	110 (49.1)	88 (66.7)	79 (62.2)
Former	805 (40.5)	471 (42.0)	112 (53.3)	91 (42.3)	103 (48.4)	94 (42.0)	37 (28.0)	34 (26.8)
Current	120 (6.0)	72 (6.4)	11 (5.2)	12 (5.6)	8 (3.8)	20 (8.9)	7 (5.3)	14 (11.0)
Dietary calcium intake (mg/day)	814 ± 140	817 ± 138	850 ± 132	854 ± 149	834 ± 120	843 ± 133	720 ± 109	725 ± 103
Dietary vitamin D intake (IU/day)	74 ± 70	75 ± 71	82 ± 77	81 ± 73	70 ± 68	77 ± 69	68 ± 69	64 ± 66
Supplemental calcium[b] (mg/day)								
< 400	1887 (95.6)	1062 (95.0)	201 (96.2)	210 (97.7)	201 (94.4)	215 (96.9)	121 (92.4)	114 (89.8)
≥ 400	86 (4.4)	55 (4.9)	8 (3.8)	5 (2.3)	12 (5.6)	7 (3.2)	10 (7.6)	13 (10.2)
Supplemental vitamin D (IU/day)								
< 400	1679 (85.1)	961 (86.0)	190 (90.9)	185 (86.1)	183 (85.9)	196 (88.3)	107 (81.7)	100 (78.7)
≥ 400	294 (14.9)	156 (14.0)	19 (9.1)	30 (14.0)	30 (14.1)	26 (11.7)	24 (18.3)	27 (21.3)
Serum 25-hydroxy-vitamin D (ng/ml)[c]	29.1 ± 10.4	28.6 ± 10.3	24.1 ± 8.3	24.6 ± 9.0	31.3 ± 8.8	33.6 ± 10.9	25.0 ± 9.8	33.2 ± 10.1
Aspirin use								
< 4 days/week	1074 (54.7)	611 (54.9)	107 (51.4)	101 (47.2)	105 (49.3)	117 (52.7)	89 (67.9)	92 (73.0)
≥ 4 days/week	890 (45.3)	503 (45.2)	101 (48.6)	113 (52.8)	108 (50.7)	105 (47.3)	42 (32.1)	34 (27.0)
NSAID use (non-aspirin)								
< 4 days/week	1755 (89.8)	1006 (90.6)	188 (90.4)	199 (93.0)	190 (90.1)	204 (92.3)	109 (83.9)	116 (91.3)

≥ 4 days/week	199 (10.2)	105 (9.5)	20 (9.6)	15 (7.0)	21 (10.0)	17 (7.7)	21 (16.2)	11 (8.7)
Adenoma at end-of-treatment colonoscopy								
No	1115 (57.3)	587 (53.4)	112 (54.1)	108 (51.4)	97 (46.6)	114 (51.8)	81 (62.8)	75 (60.0)
Yes	830 (42.7)	512 (46.6)	95 (45.9)	102 (48.6)	111 (53.4)	106 (48.2)	48 (37.2)	50 (40.0)
Advanced adenoma at end-of-treatment colonoscopy								
No	1775 (90.6)	974 (88.1)	183 (88.8)	181 (85.4)	181 (86.2)	197 (88.3)	120 (92.3)	112 (89.6)
Yes	185 (9.4)	132 (11.9)	23 (11.2)	31 (14.6)	29 (13.8)	26 (11.7)	10 (7.7)	13 (10.4)

Numbers for some characteristics may not sum to total N due to missing data. Abbreviations: SD, standard deviation; BMI, body mass index

[a] Participants not randomized to calcium but were given calcium; offered to women who wanted to take calcium.

[b] Supplemental values in elemental mg/day and include separate supplements and multivitamins. Participants were asked to cease these supplements at enrollment as a condition of study entry.

[c] Seasonally adjusted serum 25(OH) vitamin D concentration

Table 2. Follow-up data on participants with post-treatment observational follow-up phase adenoma outcome data (N = 1121)

Characteristic	Full-factorial randomization					Two-group randomization		
	Placebo (N = 210)	Calcium (N = 215)	Vitamin D (N = 213)	Vitamin D + calcium (N = 224)	P-value	Calcium + placebo (N = 132)	Calcium + vitamin D (N = 127)	P-value
	N (%)	N (%)	N (%)	N (%)		N (%)	N (%)	
Total months in observational phase, mean ± SD	55.3 ± 15.8	53.7 ± 15.7	54.9 ± 15.4	54.2 ± 14.8	0.72	55.5 ± 15.0	54.9 ± 13.7	0.74
Dietary calcium during observational follow-up phase[a]					0.92			0.72
0 - 699 mg/day	15 (7.2)	17 (7.9)	20 (9.4)	20 (9.0)		69 (52.3)	61 (48.0)	
700 - 799 mg/day	68 (32.5)	67 (31.2)	69 (32.4)	71 (32.0)		33 (25.0)	40 (31.5)	
800 - 899 mg/day	67 (32.1)	72 (33.5)	77 (36.2)	69 (31.1)		22 (16.7)	19 (15.0)	
900+ mg/day	59 (28.2)	59 (27.4)	47 (22.1)	62 (27.9)		8 (6.1)	7 (5.5)	
Missing	1	0	0	2		0	0	
Calcium supplemental use during observational follow-up phase					0.58			0.67
0 mg/day	146 (71.9)	155 (75.2)	158 (76.3)	163 (74.4)		40 (33.3)	35 (28.5)	
1 - 399 mg/day	40 (19.7)	32 (15.5)	26 (12.6)	33 (15.1)		26 (21.7)	33 (26.8)	
400 - 1199 mg/day	15 (7.4)	17 (8.3)	23 (11.1)	21 (9.6)		50 (41.7)	49 (39.8)	
1,200+ mg/day	2 (1.0)	2 (1.0)	0 (0.0)	2 (0.9)		4 (3.3)	6 (4.9)	
Missing	7	9	6	5		12	4	
Dietary vitamin D during observational follow-up phase[a]					0.17			0.52
0 - 19.9 IU/day	30 (14.4)	39 (18.1)	53 (24.9)	51 (23.0)		44 (33.3)	37 (29.1)	
20 - 49.9 IU/day	62 (29.7)	55 (25.6)	55 (25.8)	47 (21.2)		25 (18.9)	34 (26.8)	
50 - 99.9 IU/day	56 (26.8)	50 (23.3)	49 (23.0)	56 (25.2)		28 (21.2)	25 (19.7)	
100+ IU/day	61 (29.2)	71 (33.0)	56 (26.3)	68 (30.6)		35 (26.5)	31 (24.4)	
Missing	1	0	0	2		0	0	
Vitamin D supplement use during observational follow-up phase					0.99			0.36
0 - 399 IU/day	139 (68.8)	144 (69.6)	137 (68.8)	144 (67.0)		54 (44.6)	48 (40.7)	
400 - 999 IU/day	36 (17.8)	32 (15.5)	33 (16.6)	37 (17.2)		28 (23.1)	37 (31.4)	
1000+ IU/day	27 (13.4)	31 (15.0)	29 (14.6)	34 (15.8)		39 (32.2)	33 (28.0)	
Missing	8	8	14	9		11	9	

[a] Assessed as the average of the annual dietary screener estimate

Table 3. Association of treatment assignment with recurrent colorectal adenoma risk in the post-treatment observational follow-up phase (N = 1121)

Treatment assignment	**Any adenoma**		**Advanced adenoma**		**High risk findings**[a]	
	No. of patients/Total No. (%)	**Adjusted Relative Risk (95% CI)**[b]	**No. of patients/Total No. (%)**	**Adjusted Relative Risk (95% CI)**[b]	**No. of patients/Total No. (%)**	**Adjusted Relative Risk (95% CI)**[b]
Total N	569/1108 (51.4)		104/1113 (9.3)		216/1096 (19.7)	
Vitamin D vs. no vitamin D						
No vitamin D	275/552 (49.8)	Ref	45/552 (8.2)	Ref	103/545 (18.9)	Ref
Vitamin D	294/556 (52.9)	1.04 (0.93-1.17)	59/561 (10.5)	1.30 (0.89-1.88)	113/551 (20.5)	1.05 (0.83-1.34)
Calcium vs. no calcium						
No calcium	238/421 (56.5)	Ref	40/421 (9.5)	Ref	87/413 (21.1)	Ref
Calcium	231/429 (53.9)	0.95 (0.84-1.08)	45/433 (10.4)	1.07 (0.71-1.61)	91/425 (21.4)	1.01 (0.77-1.31)
Calcium plus vitamin D vs. calcium						
Calcium	158/342 (46.2)	Ref	25/344 (7.3)	Ref	60/340 (17.7)	Ref
Calcium plus vitamin D	173/345 (50.1)	1.07 (0.91-1.25)	39/348 (11.2)	1.55 (0.97-2.49)	69/343 (20.1)	1.11 (0.81-1.51)
Calcium plus vitamin D vs. neither						
Neither	117/210 (55.7)	Ref	20/208 (9.6)	Ref	43/205 (21.0)	Ref
Calcium plus vitamin D	119/219 (54.3)	0.96 (0.81-1.15)	27/221 (12.2)	1.22 (0.69-2.13)	50/217 (23.0)	1.05 (0.72-1.52)

Analyses of no vitamin D *vs.* vitamin D included all randomized participants; analyses of calcium *vs.* no calcium and of both agents *vs.* neither agent were restricted to full factorial participants; analyses of calcium *vs.* both agents excluded full factorial participants randomized to placebo or vitamin D alone.

[a] High risk findings include advanced adenomas and/or ≥2 adenomas

[b] Adjusted for age, clinical center, anticipated surveillance interval (3 or 5 years), 3-level variable for sex and randomization arm (male, 2-arm female, full-factorial female), number of baseline adenomas (0, 1, 2+)

Table 4. Associations or treatment assignment with recurrent colorectal adenoma risk, according to selected participant characteristics, in the post-treatment observational follow-up phase (N = 1121)

	Any adenoma				Advanced adenoma				High risk finding[a]			
	Vitamin D[b] N = 1108		Calcium[c] N = 850		Vitamin D N = 1113		Calcium N = 854		Vitamin D N = 1096		Calcium N = 838	
	# events/N (%)	RR (95% CI)	# events/N (%)	RR (95% CI)	# events/N (%)	RR (95% CI)	# events/N (%)	RR (95% CI)	# events/N (%)	RR (95% CI)	# events/N (%)	RR (95% CI)
Baseline characteristics												
Sex		p_{int} = 0.47		p_{int} = 0.01		p_{int} = 0.95		p_{int} = 0.74		p_{int} = 0.72		p_{int} = 0.73
Male	415/735 (56.5)	1.01 (0.89-1.15)	415/735 (56.5)	0.89 (0.78-1.01)	72/738 (9.8)	1.33 (0.84-2.10)	72/738 (9.8)	1.06 (0.68-1.64)	157/724 (21.7)	1.09 (0.82-1.45)	157/724 (21.7)	1.03 (0.78-1.36)
Female	154/373 (41.3)	1.12 (0.87-1.44)	54/115 (47.0)	1.46 (0.95-2.25)	32/375 (8.5)	1.37 (0.75-2.52)	13/116 (11.2)	1.25 (0.53-2.96)	59/372 (15.9)	0.98 (0.61-1.57)	21/114 (18.4)	0.80 (0.37-1.74)
BMI		p_{int} = 0.27		p_{int} = 0.94		p_{int} = 0.31		p_{int} = 0.20		p_{int} = 0.21		p_{int} = 0.17
< 25 kg/m^2	113/240 (47.1)	1.18 (0.89-1.57)	81/158 (51.3)	0.84 (0.60-1.17)	26/241 (10.8)	1.64 (0.74-3.63)	19/158 (12.0)	1.77 (0.66-4.76)	39/239 (16.3)	1.15 (0.62-2.16)	28/157 (17.8)	1.25 (0.60-2.61)
25 - 29.9 kg/m^2	245/466 (52.6)	1.08 (0.90-1.29)	209/381 (54.9)	1.03 (0.85-1.25)	31/467 (6.6)	1.45 (0.70-3.01)	27/382 (7.1)	1.23 (0.58-2.61)	85/460 (18.5)	1.22 (0.82-1.81)	72/375 (19.2)	1.16 (0.75-1.79)
≥ 30 kg/m^2	211/402 (52.5)	0.97 (0.80-1.18)	179/311 (57.6)	0.91 (0.75-1.11)	47/405 (11.6)	1.10 (0.64-1.91)	39/314 (12.4)	0.84 (0.46-1.52)	92/397 (23.2)	0.87 (0.60-1.27)	78/306 (25.5)	0.83 (0.55-1.24)
Alcohol use		p_{int} = 0.39		p_{int} = 0.52		p_{int} = 0.72		p_{int} = 0.55		p_{int} = 0.28		p_{int} = 1.00
0 drinks/day	171/326 (52.5)	1.01 (0.81-1.25)	129/218 (59.2)	0.86 (0.68-1.09)	35/325 (10.8)	0.97 (0.50-1.88)	25/217 (11.5)	0.99 (0.44-2.26)	60/325 (18.5)	0.77 (0.47-1.25)	46/217 (21.2)	1.02 (0.58-1.79)
0.1 - 1 drinks/day	208/423 (49.2)	1.21 (0.99-1.48)	175/321 (54.5)	1.02 (0.83-1.26)	32/425 (7.5)	1.96 (0.99-3.91)	27/323 (8.4)	1.64 (0.77-3.50)	76/415 (18.3)	1.08 (0.71-1.64)	63/313 (20.1)	1.22 (0.76-1.95)
> 1 drink/day	154/288 (53.5)	0.95 (0.75-1.19)	136/253 (53.8)	0.97 (0.76-1.23)	28/290 (9.7)	1.08 (0.53-2.18)	26/254 (10.2)	0.91 (0.44-1.86)	67/286 (23.4)	1.26 (0.80-1.98)	59/251 (23.5)	1.0 (0.63-1.60)
Serum 25-hydroxy-vitamin D[d]		p_{int} = 0.13		p_{int} = 0.38		p_{int} = 0.93		p_{int} = 0.42		p_{int} = 0.86		p_{int} = 0.10
≤ 23.16 ng/ml	275/533 (51.6)	0.96 (0.81-1.13)	225/406 (55.4)	0.90 (0.75-1.08)	51/534 (9.6)	1.23 (0.72-2.10)	40/406 (9.9)	0.93 (0.51-1.70)	103/529 (19.5)	1.01 (0.71-1.44)	82/402 (20.4)	0.80 (0.53-1.19)
> 23.16 ng/ml	294/575 (51.1)	1.14 (0.96-1.34)	244/444 (55.0)	1.00 (0.84-1.19)	53/579 (9.2)	1.31 (0.77-2.22)	45/448 (10.0)	1.26 (0.72-2.20)	113/567 (19.9)	1.07 (0.76-1.51)	96/436 (22.0)	1.23 (0.85-1.77)
End-of-treatment characteristics												
Smoking status		p_{int} = 0.35		p_{int} = 0.68		p_{int} = 0.15		p_{int} = 0.83		p_{int} = 0.45		p_{int} = 0.15
Never/former	526/1036 (50.8)	1.02 (0.90-1.15)	436/799 (54.6)	0.95 (0.84-1.08)	95/1043 (9.1)	1.41 (0.95-2.08)	78/805 (9.7)	1.05 (0.69-1.60)	201/1026 (19.6)	1.09 (0.87-1.40)	167/789 (21.2)	1.06 (0.81-1.39)
Current	43/72 (59.7)	1.39 (0.80-2.41)	33/51 (64.7)	0.86 (0.48-1.53)	9/70 (12.9)	0.56 (0.09-3.62)	7/49 (14.3)	0.85 (0.17-4.30)	15/70 (21.4)	0.70 (0.23-2.11)	11/49 (22.5)	0.38 (0.10-1.40)
Dietary calcium		p_{int} = 0.28		p_{int} = 0.82		p_{int} = 0.40		p_{int} = 0.10		p_{int} = 0.34		p_{int} = 0.80
< 794 mg/day	269/530 (50.8)	1.10 (0.93-1.31)	190/331 (57.4)	0.94 (0.78-1.14)	53/531 (10.0)	1.08 (0.65-1.80)	39/332 (11.8)	1.64 (0.89-3.02)	96/523 (18.4)	0.93 (0.64-1.35)	67/324 (20.7)	0.98 (0.64-1.52)
≥ 794 mg/day	298/575 (51.8)	0.97 (0.82-1.14)	277/516 (53.7)	0.96 (0.82-1.14)	51/579 (8.8)	1.68 (1.00-2.85)	46/519 (8.9)	0.83 (0.48-1.41)	120/570 (21.1)	1.22 (0.87-1.70)	111/511 (21.7)	1.03 (0.74-1.45)
Calcium		p_{int} = 0.37		p_{int} = 0.02		N/A		N/A		p_{int} = 0.46		N/A

supplementation												
< 400 mgs/day	548/1049 (52.2)	1.04 (0.94-1.19)	457/815 (56.1)	0.91 (0.81-1.03)	100/1054 (9.5)	1.34 (0.91-1.95)	84/819 (10.3)	1.09 (0.72-1.63)	206/1037 (19.9)	1.09 (0.85-1.39)	175/803 (21.8)	1.00 (0.77-1.31)
≥ 400 mgs/day	19/55 (34.6)	0.77 (0.33-1.79)	10/32 (31.3)	2.47 (0.77-7.89)	4/55 (7.3)	RR not estimable[e]	1/32 (3.1)	RR not estimable[e]	10/55 (18.2)	0.49 (0.14-1.65)	3/32 (9.4)	RR not estimable[e]
Vitamin D supplementation		p_{int} = 0.73		p_{int} = 0.83		p_{int} = 0.10		p_{int} = 0.04		p_{int} = 0.93		p_{int} = 0.05
< 400 IU/day	497/950 (52.3)	1.05 (0.93-1.19)	412/744 (55.4)	0.94 (0.82-1.07)	91/954 (9.5)	1.47 (0.98-2.19)	76/747 (10.2)	1.27 (0.82-1.95)	187/939 (19.9)	1.06 (0.82-1.37)	157/733 (21.4)	1.11 (0.84-1.47)
≥ 400 IU/day	70/154 (45.5)	1.04 (0.72-1.49)	55/103 (53.4)	0.96 (0.65-1.42)	13/155 (8.4)	0.60 (0.20-1.83)	9/104 (8.7)	0.23 (0.05-1.14)	29/153 (19.0)	1.21 (0.61-2.40)	21/102 (20.6)	0.48 (0.21-1.13)
NSAID/aspirin use		p_{int} = 0.55		p_{int} = 0.12		p_{int} = 0.14		p_{int} = 0.40		p_{int} = 0.03		p_{int} = 0.51
< 4 days/wk	266/549 (48.5)	1.01 (0.84-1.20)	207/386 (53.6)	0.85 (0.70-1.03)	51/554 (9.2)	0.98 (0.58-1.66)	43/390 (11.0)	0.88 (0.49-1.56)	107/543 (19.7)	0.81 (0.57-1.14)	84/380 (22.1)	0.91 (0.62-1.34)
≥ 4 days/wk	300/555 (54.1)	1.08 (0.92-1.26)	260/461 (56.4)	1.04 (0.88-1.22)	53/555 (9.6)	1.75 (1.03-2.96)	42/461 (9.1)	1.30 (0.72-2.34)	109/549 (19.9)	1.42 (1.01-2.00)	94/455 (20.7)	1.12 (0.78-1.61)
Adenoma at end-of-treatment colonoscopy		p_{int} = 0.94		p_{int} = 0.32		p_{int} = 0.11		p_{int} = 0.74		p_{int} = 0.40		p_{int} = 0.44
No	254/580 (43.8)	1.03 (0.86-1.25)	204/425 (48.0)	0.89 (0.73-1.09)	37/587 (6.3)	1.88 (0.96-3.68)	29/431 (6.7)	0.98 (0.48-1.98)	81/576 (14.1)	1.16 (0.77-1.74)	69/421 (16.4)	1.15 (0.75-1.79)
Yes	303/506 (59.9)	1.04 (0.90-1.21)	257/408 (63.0)	1.01 (0.87-1.18)	67/504 (13.3)	1.01 (0.63-1.58)	56/406 (13.8)	1.14 (0.69-1.87)	131/498 (26.3)	0.95 (0.71-1.28)	106/400 (26.5)	0.93 (0.67-1.30)

Interactions were assessed with the use of Wald Test and multiplicative interaction terms. The P-values shown are for the interaction between the (vitamin D or calcium) treatment effects and the participant characteristics listed.

Analyses of no vitamin D vs. vitamin D included all randomized participants; analyses of calcium vs. no calcium and of both agents vs. neither agent were restricted to full factorial participants; analyses of calcium vs. both agents excluded full factorial participants randomized to placebo or vitamin D alone.

All models adjusted for age, center, sex (where appropriate), treatment arm, number of baseline adenomas, surveillance interval (where appropriate)

[a] High risk findings include advanced adenomas and/or ≥2 adenomas.

[b] # of events is total number of subjects with the outcome in the subgroup, N is the number of subjects in the subgroup, RR is the relative risk for vitamin D vs. no vitamin D within the subgroup, p is the p-value for interaction between the subgroup variable and vitamin D treatment

[c] # of events is total number of subjects with the outcome in the subgroup, N is the number of subjects in the subgroup, RR is the relative risk for calcium vs. no calcium within the subgroup in the full factorial randomization subjects, p is the p-value for interaction between the subgroup characteristic and calcium treatment.

[d] Seasonally adjusted serum 25(OH)D concentration

[e] Data are too sparse to allow estimation of adjusted relative risk

Table 5. Clinical events, overall and during the post-treatment observational follow-up phase, by randomized treatment assignment (N = 2259)

	Observational phase						Overall					
	No vitamin D	Vitamin D		No calcium	Calcium		No vitamin D	Vitamin D		No calcium	Calcium	
	N = 1,014	N = 1,014		N = 745	N = 760		N = 1129	N = 1130		N = 835	N = 840	
	N (%)	N (%)	p-value	N (%)	N (%)	p-value	N (%)	N (%)	p-value	N (%)	N (%)	p-value
Death	21 (2.1)	15 (1.5)	0.31	16 (2.2)	15 (2.0)	0.81	33 (2.9)	30 (2.7)	0.70	28 (3.4)	28 (3.3)	0.98
Myocardial Infarction with or without coronary revascularization	10 (1.0)	8 (0.8)	0.64	6 (0.8)	9 (1.2)	0.46	17 (1.5)	15 (1.3)	0.72	14 (1.7)	11 (1.3)	0.54
Coronary revascularization without myocardial infarction	12 (1.2)	14 (1.4)	0.69	12 (1.6)	12 (1.6)	0.96	23 (2.0)	26 (2.3)	0.67	20 (2.4)	24 (2.9)	0.55
Stroke	9 (0.9)	11 (1.1)	0.65	13 (1.7)	7 (0.9)	0.16	14 (1.2)	20 (1.8)	0.30	18 (2.2)	10 (1.2)	0.12
Transient ischemic attack	2 (0.2)	4 (0.4)	0.69	1 (0.1)	5 (0.7)	0.22	3 (0.3)	7 (0.6)	0.34	4 (0.5)	5 (0.6)	1.00
Cancer												
Any	56 (5.5)	59 (5.8)	0.77	46 (6.2)	45 (5.9)	0.84	112 (9.9)	107 (9.5)	0.72	89 (10.7)	90 (10.7)	0.97
Colorectal	6 (0.6)	3 (0.3)	0.51	3 (0.4)	4 (0.5)	1.00	8 (0.7)	6 (0.5)	0.59	3 (0.4)	6 (0.7)	0.51
Breast	6 (0.6)	6 (0.6)	1.00	2 (0.3)	1 (0.1)	0.62	11 (1.0)	8 (0.7)	0.49	3 (0.4)	4 (0.5)	1.00
Prostate	10 (1.0)	15 (1.5)	0.31	13 (1.7)	12 (1.6)	0.80	36 (3.2)	35 (3.1)	0.90	39 (4.7)	32 (3.8)	0.38
Melanoma	4 (0.4)	6 (0.6)	0.53	5 (0.7)	2 (0.3)	0.28	9 (0.8)	7 (0.6)	0.61	7 (0.8)	5 (0.6)	0.56
Urolithiasis	18 (1.8)	19 (1.9)	0.87	14 (1.9)	16 (2.1)	0.75	44 (3.9)	37 (3.3)	0.43	29 (3.5)	35 (4.2)	0.46
Fracture	52 (5.1)	48 (4.7)	0.68	31 (4.2)	37 (4.9)	0.51	111 (9.8)	101 (8.9)	0.47	72 (8.6)	71 (8.5)	0.90

Observational phase events are those that occurred in participants who consented to the observational phase, regardless of the presence of an end-of-treatment colonoscopy. Data are the numbers of participants who had one or more occurrences of an adverse event and their percentage among all participants who were randomly assigned to the given group.

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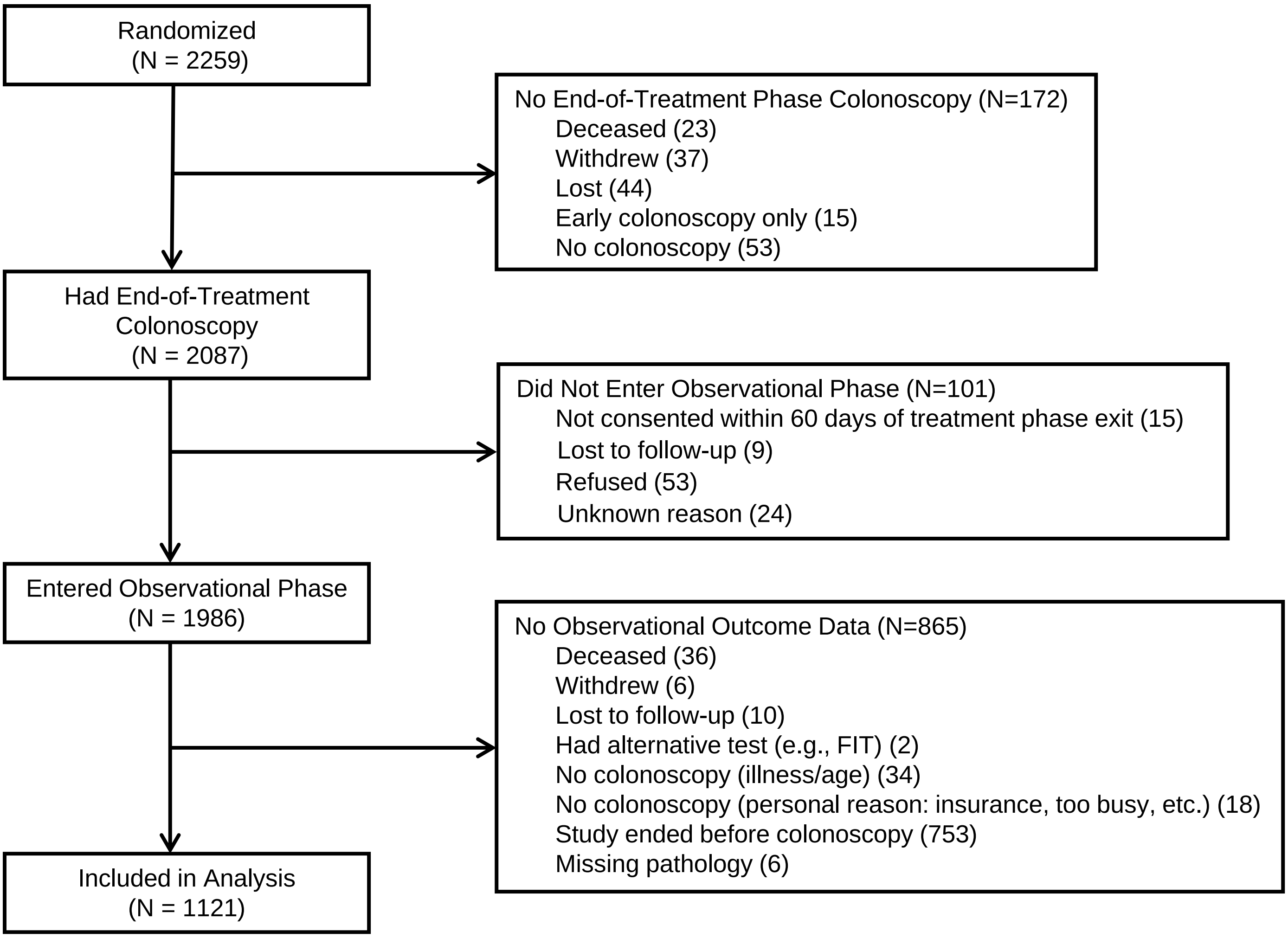
Figure Legends

Figure 1. Flow Diagram for the Post-Treatment Observational Follow-Up Phase of the Vitamin D/Calcium Polyp Prevention Study

Figure 1. Flow Diagram for the Post-Treatment Observational Phase of the Vitamin D/Calcium Polyp Prevention Study



American Association for Cancer Research

Cancer Prevention Research

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