Published OnlineFirst March 4, 2019; DOI: 10.1158/1940-6207.CAPR-19-0023

Research Article

Cancer Prevention Research

# No Evidence for Posttreatment Effects of Vitamin D and Calcium Supplementation on Risk of Colorectal Adenomas in a Randomized Trial

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## 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- to 5-year follow-up captured in that trial. Accordingly, we explored possible vitamin D and calcium effects on posttreatment (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 $\pm$ 15 months after treatment follow-up, according to randomized treatment with vitamin D versus no vitamin D, calcium versus no calcium, and calcium plus vitamin D versus calcium alone. Secondary outcomes included advanced and multiple adenomas. Among the 1,121 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 versus no vitamin D; 0.95 (0.84–1.08) for calcium versus no calcium; 1.07 (0.91–1.25) for calcium plus vitamin D versus calcium; and 0.96 (0.81–1.15) for calcium plus vitamin D versus 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 to 5 years and risk of recurrent colorectal adenoma at an average of 4.6 years after treatment.

## 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, multicenter, 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). Because adenomas can take approximately 10 to 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- to 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 posttreatment observational analysis reported here was to explore possible

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**Note:** Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

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**doi:** 10.1158/1940-6207.CAPR-19-0023

Published OnlineFirst March 4, 2019; DOI: 10.1158/1940-6207.CAPR-19-0023



vitamin D and calcium effects on posttreatment 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) has been published previously (15). Briefly, the Vitamin D/Calcium Polyp Prevention Study was a multicenter, randomized, double-blind, placebo-controlled trial of vitamin D and/or calcium supplements at 11 academic medical centers and associated medical practices in the United States. Institutional review boards at each center approved the study, and all participants provided written informed consent.

Eligible participants were age 45 to 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.

Following eligibility screening and a 56- to 84-day placebo run-in period, 2,259 participants were randomly assigned in a partial 2 $\times$ 2 factorial design to receive vitamin $D_3$ (1000 IU/day), calcium carbonate (1,200 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 6 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 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 was 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.

***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 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 retreatment 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

We used contingency tables and standard $\chi^2$ 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 versus no vitamin D, calcium versus no calcium, and calcium plus vitamin D versus calcium alone. Adjusted risk ratios (termed "relative risk" throughout the paper) and 95% confidence intervals were estimated using a Poisson log-linear model with adjustment for under/overdispersion.

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The models included relevant patient characteristics (age, sex, number of baseline adenomas) and variables used in the randomization stratification (clinical center, two-group versus 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 mg/day vs. ≥400 mg/day), vitamin D supplementation (<400 IU/day vs. ≥400 IU/day), nonsteroidal 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 versus no vitamin D included all randomized participants; analyses of calcium versus no calcium and of both vitamin D and calcium versus neither agent were restricted to full factorial participants; analyses of vitamin D and calcium versus 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 treatment phase and the first colonoscopy at least 3 years after end-of-treatment colonoscopy or exit from the observational study.

All statistical tests were two-sided. $P$ values $\leq 0.05$ or 95% confidence intervals that excluded 1.0 were considered statistically significant. Stata 9 software (StataCorp) and SAS 9.4 were used to perform all analyses.

## Results

Of the 2,259 randomized participants, 2,087 had colonoscopy information from an end-of-treatment examination; of these, 1,986 (95.2%) agreed to observational follow-up. Among these 1,986 eligible participants, 1,121 (56.4%) had a surveillance colonoscopy before the observational follow-up phase of the study ended, and were included in analyses (Fig. 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 versus 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

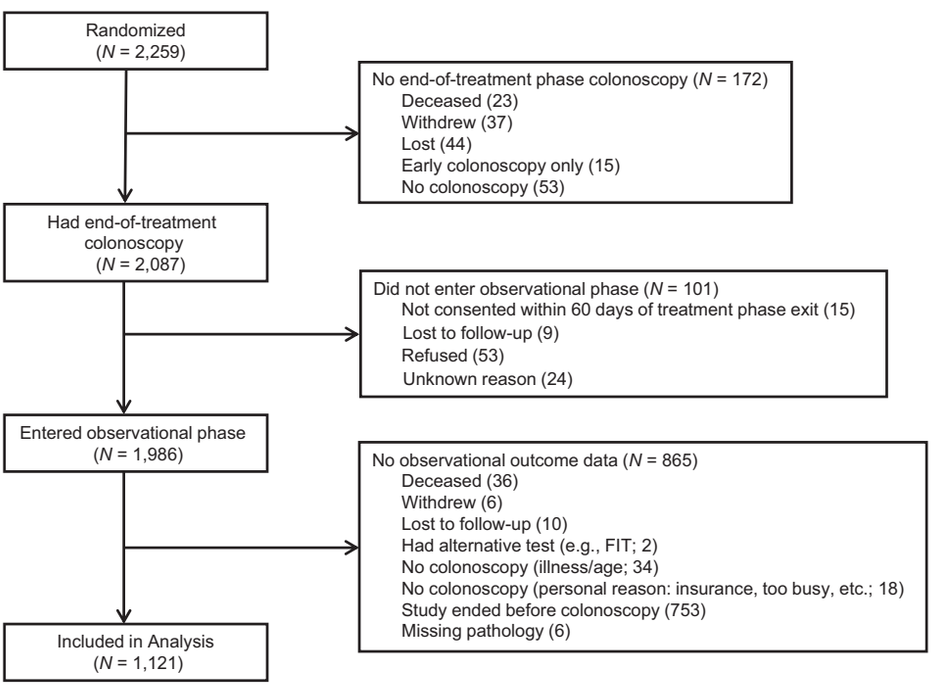


**Figure 1.**
Flow diagram for the posttreatment observational follow-up phase of the Vitamin D/Calcium Polyp Prevention Study.

Published OnlineFirst March 4, 2019; DOI: 10.1158/1940-6207.CAPR-19-0023



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 nonsignificant. 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).

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 ≥1,200 mg/day. Overall vitamin D supplementation use of ≥1,000 IU/day was also modest (18.2%), with overall higher use among the two-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 nonsignificant increase in the risk of advanced adenomas among participants randomized to vitamin D plus calcium in comparison with those given calcium alone. These null effects did not differ by anatomic site (proximal or distal; Supplementary Table S1).

The results of the subgroup analyses are shown in Table 4. There were no significant differences in the posttreatment 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 participants with NSAID or aspirin use ≥4 days/week at end-of-treatment (RR 1.42; 1.01–2.00) compared with those with less frequent use (RR 0.81; 0.57–1.14; $P$ for interaction $= 0.03$).

The posttreatment 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 posttreatment 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 opposite 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 1,000 IU of vitamin $D_3$ nor 1,200 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 posttreatment 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 posttreatment 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. Although in the 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

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**Table 1.** Characteristics of posttreatment 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* | 1,986 | 1,121 | 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 | 1,271 (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 | 1,708 (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 | 1,061 (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 | 1,887 (95.6) | 1,062 (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 | 1,679 (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 | 1,074 (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 (nonaspirin) | | | | | | | | |
| <4 days/week | 1,755 (89.8) | 1,006 (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 | 1,115 (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 | 1,775 (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) |

NOTE: 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.

Published OnlineFirst March 4, 2019; DOI: 10.1158/1940-6207.CAPR-19-0023



**Table 2.** Follow-up data on participants with posttreatment observational follow-up phase adenoma outcome data ($N = 1{,}121$)

| | Full factorial randomization | | | | | Two-group randomization | | |
|---|---|---|---|---|---|---|---|---|
| **Characteristic** | **Placebo ($N = 210$) *N* (%)** | **Calcium ($N = 215$) *N* (%)** | **Vitamin D ($N = 213$) *N* (%)** | **Vitamin D + calcium ($N = 224$) *N* (%)** | ***P*** | **Calcium + placebo ($N = 132$) *N* (%)** | **Calcium + vitamin D ($N = 127$) *N* (%)** | ***P*** |
| 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) | |
| 400–1,199 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.

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 1,200 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; ref. 17). Another, smaller randomized trial found a modest but statistically nonsignificant reduction in recurrent adenomas with treatment with 2,000 mg of elemental calcium

**Table 3.** Association of treatment assignment with recurrent colorectal adenoma risk in the posttreatment observational follow-up phase ($N = 1{,}121$)

| | Any adenoma | | Advanced adenoma | | High-risk findings[a] | |
|---|---|---|---|---|---|---|
| **Treatment assignment** | **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* | 569/1,108 (51.4) | | 104/1,113 (9.3) | | 216/1,096 (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) |

NOTE: 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), three-level variable for sex and randomization arm (male, two-arm female, full factorial female), number of baseline adenomas (0, 1, 2+).

**Table 4.** Associations of treatment assignment with recurrent colorectal adenoma risk, according to selected participant characteristics, in the posttreatment observational follow-up phase ($N = 1{,}121$)

| | Any adenoma | | | | Advanced adenoma | | | | High-risk finding[a] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Vitamin D[b] $N = 1{,}108$ | | Calcium[c] $N = 850$ | | Vitamin D $N = 1{,}113$ | | Calcium $N = 854$ | | Vitamin D $N = 1{,}096$ | | 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) | (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 supplementation | | $P_{int} = 0.37$ | | $P_{int} = 0.02$ | | N/A | | N/A | | $P_{int} = 0.46$ | | N/A |
| < 400 mg/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 mg/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/week | 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/week | 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) |

NOTE: 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]Number of events is the 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]Number of events is the 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.

Published OnlineFirst March 4, 2019; DOI: 10.1158/1940-6207.CAPR-19-0023



**Table 5.** Clinical events, overall and during the posttreatment observational follow-up phase, by randomized treatment assignment ($N = 2,259$)

| | Observational phase | | | | | | Overall | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No vitamin D $N = 1,014$ | Vitamin D $N = 1,014$ | | No calcium $N = 745$ | Calcium $N = 760$ | | No vitamin D $N = 1,129$ | Vitamin D $N = 1,130$ | | No calcium $N = 835$ | Calcium $N = 840$ | |
| | *N* (%) | *N* (%) | *P* | *N* (%) | *N* (%) | *P* | *N* (%) | *N* (%) | *P* | *N* (%) | *N* (%) | *P* |
| 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 |

NOTE: 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.

(OR 0.66; 0.38–1.17; ref. 5). A small feasibility study by Chu and colleagues found a reduction in adenoma recurrence among those taking 1,800 mg/d of calcium carbonate compared with placebo (odds ratio 0.47; 0.27– 0.84; ref. 6).

During the treatment phase of the Vitamin D/Calcium Polyp Prevention Study trial, we saw nonstatistically 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 posttreatment delayed effects with longer follow-up, and differ with those from our previous calcium trial (4), in which the chemopreventive effect of 1,200 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 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 posttreatment observational follow-up period via yearly questionnaires. All histopathologic 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 posttreatment 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, because many

Published OnlineFirst March 4, 2019; DOI: 10.1158/1940-6207.CAPR-19-0023



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 such as advanced adenomas. The 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 to 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.

## Disclosure of Potential Conflicts of Interest

J.A. Baron has ownership interest in a patent for chemopreventive use of calcium, held with Dartmouth College (not currently licensed). D.J. Ahnen is a consultant/advisory board member for Cancer Prevention Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

## Authors' Contributions

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## Acknowledgments

This study was supported by the NIH, NCI (CA098286, to J.A. Baron).

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Received January 10, 2019; revised February 25, 2019; accepted February 25, 2019; published first March 4, 2019.

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Published OnlineFirst March 4, 2019; DOI: 10.1158/1940-6207.CAPR-19-0023



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Published OnlineFirst March 4, 2019; DOI: 10.1158/1940-6207.CAPR-19-0023



Cancer Prevention Research

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*Cancer Prev Res* 2019;12:295-304. Published OnlineFirst March 4, 2019.