Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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ONLINE SUPPLEMENT

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Contents

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Investigators: Dartmouth-Hitchcock Medical Center, Lebanon, NH: A. Alrakawi, S. Bensen, A. Damianos, D. Howell, D. Rath, R. Thompson; Emory University: J. S. Mandel, R. Rutherford, M. Wehbi; University of Colorado: T. Byers, S. R. Freeman, J. S. Levine; University of Iowa: N.S. Dusdieker, J.R. Ewing, B. I. Leman, R. Lengeling, J. Piros, S. Reddy, W. Silverman, G. Weinman; University of Minnesota: J. I. Allen, J. H. Bond, K. D. Wilson; University of North Carolina: L. Gangarosa; University of Puerto Rico: H. Gonzalez, R. Mosquera, F. Ramos, D. Toro; University of Southern California: C. Conteas, D. Gerety, R.W. Haile, L. Laine, T. Lee, T. Zarchy; University of Texas: A. Dekovich, G. Raju, J. R. Stoehlein.

Study Coordinators and Staff: Cleveland Clinic: J. Bauman, H. Hasson; Dartmouth-Hitchcock Medical Center, Lebanon, NH: E. Belles, P. Doughty, T. George, P. Goralski, B. Hewitt, V. Kelly, L. Matchem, C. Swasey, L. Wettimann, K. Wood; Emory University: J. Brockman, J. Woodard; University of Colorado: L. Brandes, K. Camp, J. Cisek, T. Dunn, A. Rietema, E. Schleski, A. Therrian; University of Iowa: B. Musgrave, R. Thompson; University of Minnesota: P. Beckmann, D. Engelhard, P. Stout, J. Stromberg; University of North Carolina: K. Jeremiah, K. Lezama, J. Maloney, B. Schliebe; University of Puerto Rico: J. Hernandez; Consultants in Gastroenterology, West Columbia, SC: R. Caldwell, A. Dawan, K. Todd; University of Southern California: L. Gerstmann, Y. Perez, A. Rivera; University of Texas: J. Foreman, R. Holley, P. Robichaux, T. Smith, T. Tipps.

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University of California at Los Angeles, Nutrition Biomarker Laboratory: Susanne Henning

Data and Safety Monitoring Committee: W. Willett (Chairman; Harvard University, Boston, MA), F. Giardiello (John Hopkins University School of Medicine, Baltimore, MD), M. Holick (Boston University School of Medicine, Boston, MA), P. Holt (Rockefeller University, New York, NY), J. Neaton (University of Minnesota, Minneapolis, MN), G. Curhan (consultant; Harvard School of Public Health, Boston, MA), W. Malone (ex officio member; National Cancer Institute, Bethesda, MD), A. Umar (ex officio member; National Cancer Institute, Bethesda, MD).

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Statistical power and sample size considerations
For the primary endpoints, we originally planned to randomize 1966 participants to achieve 0.89 power for a vitamin D risk ratio of 0.80 (assuming a calcium risk ratio of 0.80), 0.79 for a calcium risk ratio of 0.80 (assuming a vitamin D risk of 0.75), and 0.85 for a risk ratio of 0.75 between vitamin D plus calcium *vs*. calcium alone, each comparison using $\alpha = 0.05$. Subsequently, we increased enrollment to increase representation of women, minorities, and high-risk participants (with ≥3 adenomas or an advanced adenoma at baseline).

Pathology procedures and rules
Excised tissue was classified as representing a "lesion", a "biopsy" or a "cluster." A lesion was defined as a relatively circumscribed area of abnormal-appearing mucosa, consistent with neoplasia. A biopsy was defined as tissue from an undirected excision of normal-appearing mucosa (as might be obtained for diagnosis of diarrhea) or directed at a broad area of abnormality (e.g. erythema, as might be obtained to investigate inflammation). Missing pathology for a biopsy was not considered missing with regard to lesion outcomes. A cluster was defined as a group of diminutive (<5mm), typically sessile, lesions in the distal colorectum. A cluster located in the rectum that had no tissue available for diagnosis was assumed to be comprised of hyperplastic polyps.

Size and location information for colorectal lesions was generally taken from the endoscopy reports. If not recorded there, these data were taken from the pathology report where possible. If size was reported as a range, the midpoint of the range was recorded. If location was given in distance from the anus, ≤15 cm was assumed to be in the rectum, 16-40 cm in the sigmoid or descending colon (indeterminate as to which) and >40 cm an unknown location. The lesion diagnosis from the local pathologist was taken from the pathology report. If the degree of dysplasia for an adenoma was not reported, it was assumed to be mild/moderate. If a polyp was reported on more than one colonoscopy, the largest size and the most aggressive histological diagnosis for that polyp was used in analyses.

In this study, advanced adenomas were virtually always relatively large: Among lesions with available tissue, only 2% of those less than 0.6 cm in estimated size were advanced adenomas. Therefore, when there was no tissue available from a lesion less than 0.6 cm, it was assumed the lesion was *not* an advanced adenoma (but could have been a tubular adenoma or a serrated polyp).

The study pathologist reviewed all available tissue removed from the large bowel and classified each lesion as an adenoma, serrated polyp, or other (non-neoplastic) lesion. In the event of a diagnostic disagreement with the local pathologist, the study pathologist performed a second blinded read as specified in the table below. The second read by the study pathologist was taken as the final diagnosis unless it differed from both the local diagnosis and the first read by the study pathologist. In this case, a third unblinded reading was conducted by the study pathologist to adjudicate the diagnosis. In all cases, the study pathologist read the same slides as those seen by the local pathologists, if possible.

In the case of disagreement between the local pathologist and the study pathologist, actions described in the following table were taken.

Table S1. Resolution of disagreements between the study pathologist and local pathologists

	Study Pathologist				
Local Pathologist	**Serrated Polyp**	**Adenoma/ Cancer**	**Mixed***	**Other†**	**Slides available only to local pathologist**
Serrated Polyp	No disagreement	Obtain second read‡ by study pathologist	Obtain 2nd read by study pathologist	If study pathologist saw only 1 tissue level, use local diagnosis; otherwise obtain 2nd read by study pathologist	Use local diagnosis
Adenoma/ Cancer	Obtain 2nd read by study pathologist	No disagreement	Use study pathologist diagnosis	If study pathologist saw only 1 tissue level, use local diagnosis; otherwise obtain 2nd read by study pathologist	Use local diagnosis
Mixed	Obtain 2nd read by study pathologist	Obtain 2nd read by study pathologist	No disagreement	Obtain 2nd read by study pathologist	Use local diagnosis
Other	Use study pathologist diagnosis	Use study pathologist diagnosis	Obtain 2nd read by study pathologist	No disagreement	Use local diagnosis

*Two distinct histological diagnoses (e.g. tubular adenoma and hyperplastic polyp -- in current terminology, a sessile serrated adenoma with conventional dysplasia).

†Non-neoplastic diagnosis: normal mucosa, inflammation, lymphoid aggregate, etc.

‡The second read by the study pathologist is conducted blinded to knowledge of the first diagnosis.

Measurement of serum calcium, creatinine and 25-OH Vitamin D

Calcium and creatinine were assayed using standard procedures at laboratories associated with the clinical centers. 25-OH-vitamin D was assayed centrally using the IDS (Fountain Hills, AZ) liquid phase radioimmunoassay which has a sensitivity of 5 ng/l. The inter-assay CVs were 4.3% (at 12.9 ng/ml), 10.3% (at 21.1 ng/ml), and 4.5% (at 57.6 ng/ml). Blinded aliquots from a large pooled sample, sent with most sample shipments, yielded a between-batch CV of 4.1%.

Computation of seasonally adjusted serum 25-OH Vitamin D

To obtain baseline season-adjusted 25-OH-vitamin D levels, we first calculated separate means for each month of blood draw. For each participant, we calculated the difference between the 25-OH-vitamin D level and the appropriate monthly mean. This residual was then added to the overall mean of all participants in all months. Year 1, year 3 and end of treatment seasonally-adjusted levels were calculated separately by Vitamin D treatment in a similar manner.

Semiannual estimation of dietary calcium and vitamin D intake

To monitor participants' calcium and vitamin D intakes, a calcium and vitamin D dietary screener was used at enrollment and every semiannual interview. This brief screening tool was developed from the NHANES 1999-2001 dietary recall data by Nutritionquest (Berkeley, CA). It includes 25 food intake questions, without portion size responses.

Randomization of Ineligible Participants

Fifteen ineligible participants were randomized. All were retained in the analysis if follow-up information was available.

Four participants had a documented history of urolithiasis despite having given negative reports during recruitment. (One of these was an incidental finding on CT scan that might not have been communicated to the patient.) Two participants had completed treatment when the urolithiasis history was discovered; two were removed from treatment. None had a recurrence during study participation.

Five participants did not have an adenoma at baseline. In each case, the local pathology report noted adenomatous tissue in a polyp coexisting with serrated tissue. These would now be labeled a sessile serrated adenoma/polyp with dysplasia. A covariate in our analyses is number of baseline adenomas; for this variable, these participants are considered to have 1 adenoma at baseline.

Four participants did not have all polyps removed from the large bowel. In each case one or more small rectal polyps remained.

Transcription errors led to randomization of two participants despite baseline blood calcium levels outside the normal range. The true values were 10.3 mg/dL (upper limit of normal 10.2 mg/dL), and 8.4 mg/dL (lower limit of normal 8.5 mg/dL). These participants were retained on study treatment.

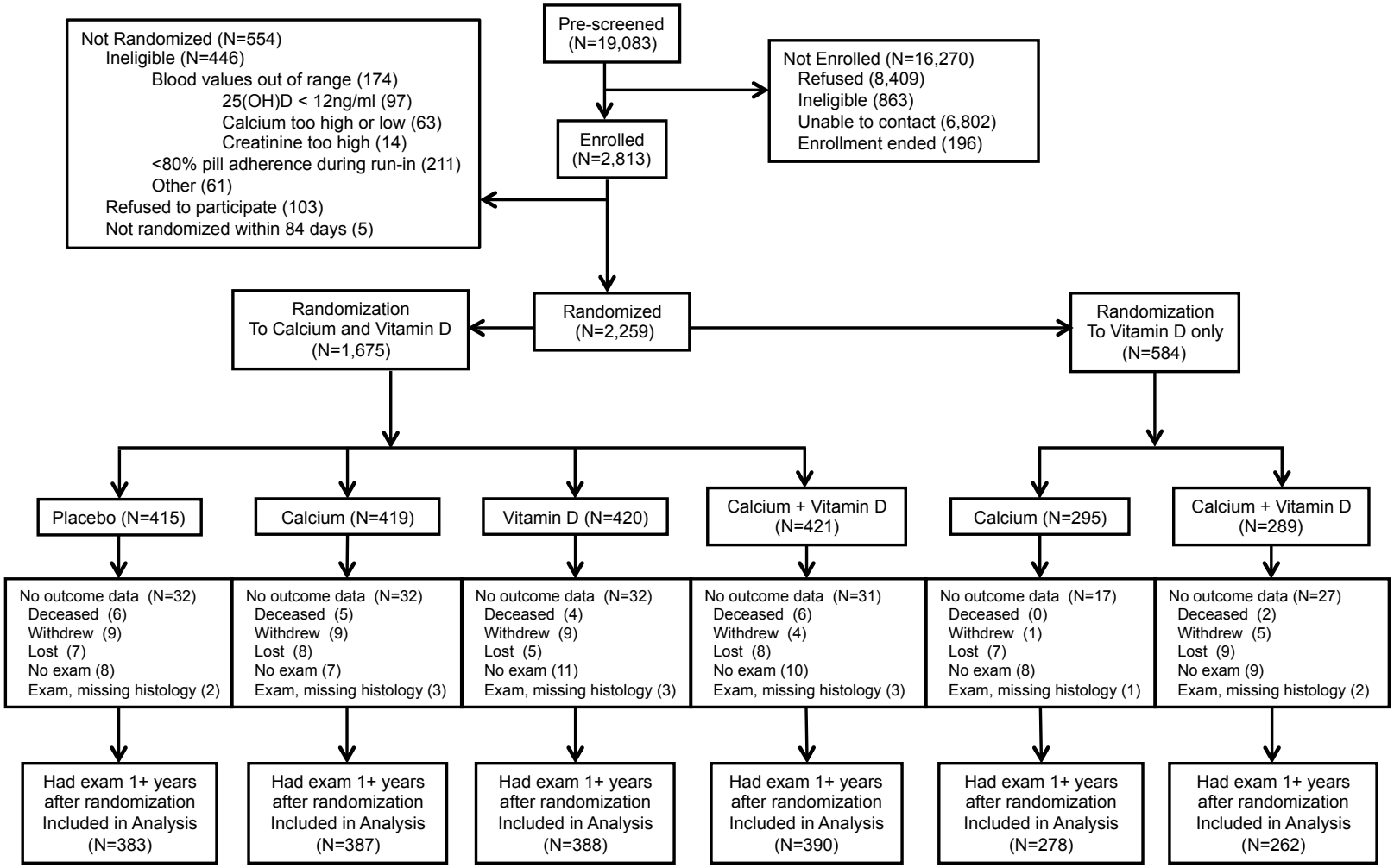

Figure S1. Consort Diagram

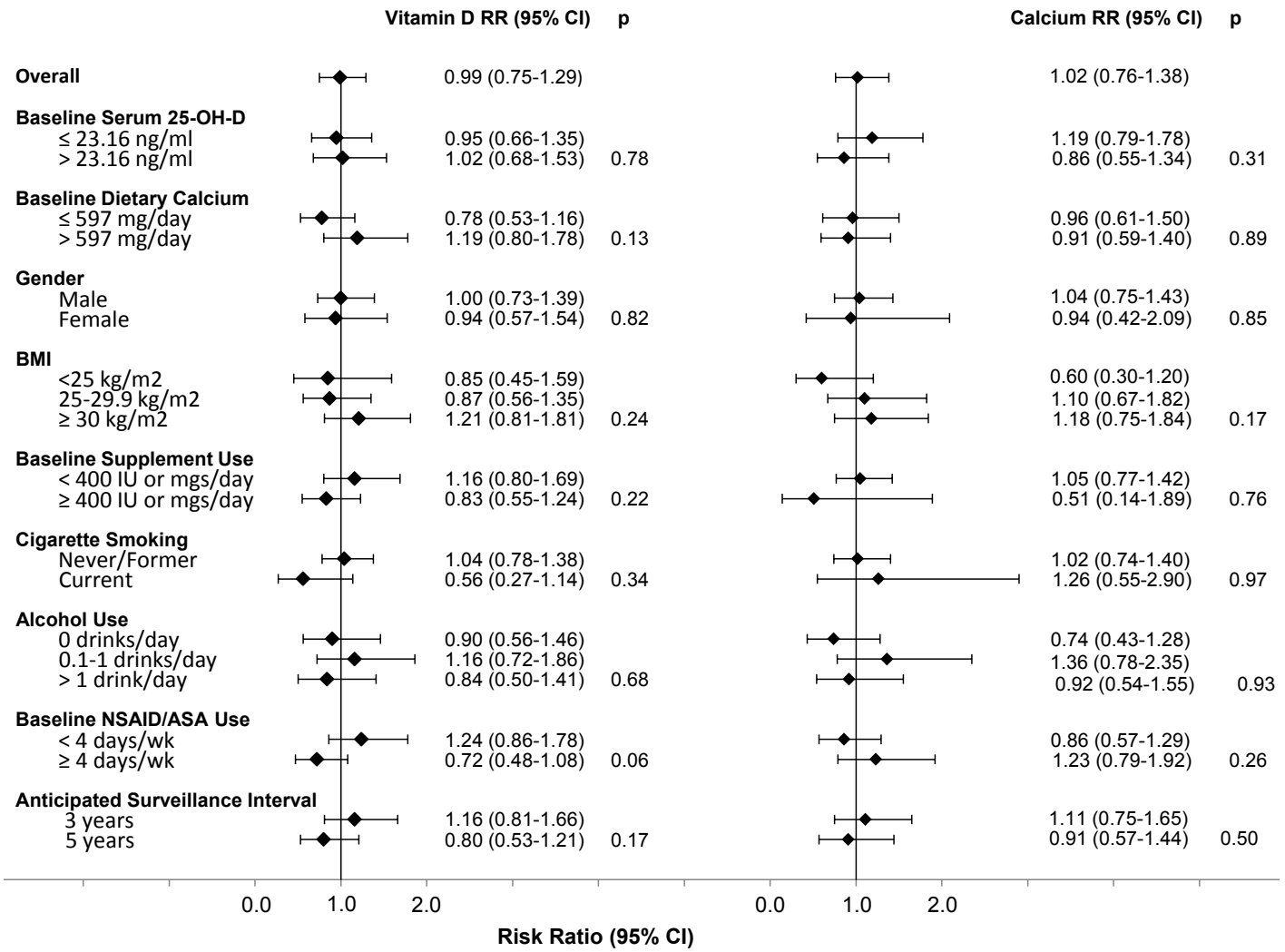

Figure S2. Subgroup Treatment Effects for Supplementation with Calcium or Vitamin D: One or More Advanced Adenomas

Table S2. Years from Randomization to Final Colonoscopy				
Study treatment	**N**	**Mean**	**Std Error**	**Median**
Full Factorial Participants:				
Calcium + Placebo	387	3.73	0.06	3.57
Calcium + Vitamin D	390	3.76	0.06	3.49
Placebo + Placebo	383	3.73	0.06	3.46
Placebo + Vitamin D	388	3.76	0.06	3.49
2-Arm Participants:				
Vitamin D	262	3.79	0.07	3.84
Placebo	278	3.79	0.07	3.91

P for difference between the 6 groups: 0.81.
P for difference between no vitamin Dz *vs.* vitamin D: 0.38.
P for difference between no calcium *vs.* calcium: 0.84.
P for difference between vitamin D+calcium *vs.* calcium: 0.33.
P for difference between vitamin D+calcium *vs.* neither: 0.34.

80.4% of participants with a recommended 3-year surveillance interval had a colonoscopy within 6 months of the anticipated time (9% earlier and 11% later). 72.8% of participants with a recommended 5-year surveillance interval had a colonoscopy within 6 months of the anticipated time (20% earlier and 7% later).

Table S3. Adenoma Risk Ratios By Anatomic Location

Event	Left (Splenic Flexure through Rectum)		Right (Cecum through Transverse Colon)	
	Events/N (%)	**Risk Ratio* (95% CI)**	**Events/N (%)**	**Risk Ratio* (95% CI)**
One or More Adenomas				
No Vitamin D	181/1024 (17.7)	reference	322/1034 (31.1)	reference
Vitamin D	205/1013 (20.2)	1.13 (0.94-1.35)	324/1035 (31.3)	0.98 (0.87-1.12)
No Calcium	159/752 (21.1)	reference	270/769 (35.1)	reference
Calcium	159/750 (21.2)	1.00 (0.82-1.22)	255/764 (33.4)	0.94 (0.82-1.08)
Calcium	109/649 (16.8)	reference	186/653 (28.5)	reference
Vitamin D + Calcium	118/636 (18.6)	1.09 (0.86-1.38)	190/647 (29.4)	1.01 (0.85-1.20)
Neither Vitamin D nor Calcium	72/375 (19.2)	reference	136/381 (35.7)	reference
Vitamin D + Calcium	83/377 (22.0)	1.12 (0.84-1.49)	128/386 (33.2)	0.90 (0.74-1.10)
One or More Advanced Adenomas†				
No Vitamin D	40/1045 (3.8)	reference	65/1047 (6.2)	reference
Vitamin D	38/1035 (3.7)	0.95 (0.61-1.47)	63/1039 (6.1)	0.94 (0.67-1.31)
No Calcium	33/768 (4.3)	reference	53/771 (6.9)	reference
Calcium	27/773 (3.5)	0.81 (0.49-1.34)	55/776 (7.1)	1.00 (0.69-1.44)
Calcium	24/663 (3.6)	reference	41/664 (6.2)	reference
Vitamin D + Calcium	21/649 (3.2)	0.88 (0.49-1.57)	34/651 (5.2)	0.81 (0.52-1.26)
Neither Vitamin D nor Calcium	16/382 (4.2)	reference	24/383 (6.3)	reference
Vitamin D + Calcium	12/388 (3.1)	0.70 (0.33-1.47)	25/389 (6.4)	0.96 (0.55-1.67)

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

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

†Denominators may differ between adenomas and advanced adenomas due to missing lesion size and an assumption that small lesions (<6mm) with missing pathology data are not advanced adenomas (see Pathology Procedures and Rules above).

Table S4. Adenoma Risk Ratios by Baseline Supplement Use

	Treatment			
Supplement use at baseline	**Events/N (%)**	**Events/N (%)**	**Risk Ratio* (95% CI)**	
Vitamin D supplement	No Vitamin D	Vitamin D		
0	204/450 (45.3)	190/438 (43.4)	0.95 (0.82-1.11)	
1-400 IU	171/415 (41.2)	169/400 (42.3)	0.99 (0.84-1.17)	
>400 IU	28/74 (37.8)	39/90 (43.3)	1.16 (0.77-1.75)	P for trend† = 0.37
Calcium supplement	No calcium	Calcium		
0	179/365 (49.0)	164/380 (43.2)	0.87 (0.74-1.02)	
1-399 mg	138/309 (44.7)	139/297 (46.8)	1.04 (0.87-1.24)	
≥400 mg	20/39 (51.3)	21/41 (51.2)	0.87 (0.51-1.48)	P for trend = 0.34
Vitamin D supplement	Calcium	Calcium + Vitamin D		
0	112/266 (42.1)	100/253 (39.5)	0.93 (0.75-1.15)	
1-400 IU	97/255 (38.0)	104/246 (42.3)	1.04 (0.83-1.29)	
>400 IU	21/61 (34.4)	26/68 (38.2)	1.16 (0.68-1.97)	P for trend = 0.26
Calcium & Vitamin D supplements	Neither	Calcium + Vitamin D		
No calcium and no Vitamin D	89/180 (49.4)	77/189 (40.7)	0.83 (0.65-1.05)	
<400 mg calcium and ≤ 400 IU Vitamin D	68/146 (46.6)	72/142 (50.7)	1.05 (0.82-1.35)	
≥400 mg calcium or > 400 IU Vitamin D	15/26 (57.7)	14/27 (51.9)	0.79 (0.40-1.57)	P for heterogeneity = 0.55

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

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

†P for trend obtained using midpoints of the supplement categories (vitamin D: 0, 400, 600; calcium: 0, 200, 700).

Table S5. Advanced Adenoma Risk Ratios by Baseline Supplement Use

	Treatment			
Supplement use at baseline	**Events/N (%)**	**Events/N (%)**	**Risk Ratio* (95% CI)**	
Baseline Vitamin D supplement	No Vitamin D	Vitamin D		
0	44/450 (9.8)	53/445 (11.9)	1.19 (0.81-1.73)	
1-400 IU	43/422 (10.2)	27/400 (6.8)	0.65 (0.41-1.03)	
>400 IU	6/72 (8.3)	11/92 (12.0)	1.46 (0.55-3.89)	P for trend† = 0.27
Baseline Calcium supplement	No calcium	Calcium		
0	43/367 (11.7)	43/385 (11.2)	0.95 (0.64-1.42)	
1-399 mg	27/309 (8.7)	32/303 (10.6)	1.20 (0.73-1.97)	
≥400 mg	5/40 (12.5)	5/42 (11.9)	0.51 (0.14-1.89)	P for trend = 0.87
Baseline Vitamin D supplement	Calcium	Calcium + Vitamin D		
0	28/266 (10.5)	26/258 (10.1)	0.95 (0.57-1.58)	
1-400 IU	27/262 (10.3)	16/247 (6.5)	0.59 (0.33-1.08)	
>400 IU	3/59 (5.1)	9/68 (13.2)	2.78 (0.74-10.35)	P for trend = 0.78
Baseline Calcium and Vitamin D supplement	Neither	Calcium + Vitamin D		
No calcium and no Vitamin D	16/180 (8.9)	20/194 (10.3)	1.12 (0.59-2.11)	
<400 mg calcium and ≤ 400 IU Vitamin D	15/146 (10.3)	13/145 (9.0)	0.85 (0.42-1.73)	
≥400 mg calcium or > 400 IU Vitamin D	4/26 (15.4)	3/26 (11.5)	0.53 (0.11-2.58)	P for heterogeneity = 0.75

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

*Adjusted for age, clinical center, anticipated surveillance interval (3 or 5 years), 3 level variable for sex and arm of randomization (male, 2-arm female, full factorial female), number of baseline adenomas (1, 2, 3+). Due to sparse data for advanced adenomas, clinical center is adjusted for using geographically grouped centers (southeast: Georgia, North Carolina, South Carolina, Puerto Rico vs north: Ohio, New Hampshire, Iowa, Minnesota vs west: Colorado, Texas, California).

†P for trend obtained using midpoints of the supplement categories (vitamin D: 0, 400, 600; calcium: 0, 200, 700).

Table S6. Adenoma Risk Ratios by Baseline Advanced/Multiple Adenoma Status

	0, 1 or 2 small (<1 cm) tubular adenoma at baseline		Advanced or > 2 adenomas at baseline		
Event	**Events/N (%)**	**Risk Ratio* (95% CI)**	**Events/N (%)**	**Risk Ratio* (95% CI)**	**p for interaction**
One or More Adenomas					
No Vitamin D	292/723 (40.4)	reference	132/275 (48.0)	reference	0.91
Vitamin D	287/702 (40.9)	1.01 (0.89-1.14)	139/284 (48.9)	1.00 (0.84-1.19)	
No Calcium	236/521 (45.3)	reference	115/211 (54.5)	reference	0.58
Calcium	214/511 (41.9)	0.91 (0.79-1.05)	116/220 (52.7)	0.98 (0.82-1.18)	
Calcium	169/452 (37.4)	reference	78/178 (43.8)	reference	0.98
Vitamin D + Calcium	174/452 (38.5)	1.02 (0.86-1.21)	78/170 (45.9)	1.02 (0.80-1.30)	
Neither Vitamin D nor Calcium	123/271 (45.4)	reference	54/97 (55.7)	reference	0.43
Vitamin D + Calcium	107/259 (41.3)	0.89 (0.73-1.09)	62/110 (56.4)	1.00 (0.77-1.30)	
One or More Advanced Adenomas†					
No Vitamin D	60/730 (8.2)	reference	33/275 (12.0)	reference	0.41
Vitamin D	55/706 (7.8)	0.95 (0.67-1.35)	43/283 (15.2)	1.20 (0.78-1.84)	
No Calcium	48/524 (9.2)	reference	28/208 (13.5)	reference	0.16
Calcium	38/517 (7.4)	0.81 (0.54-1.22)	39/223 (17.5)	1.25 (0.79-1.99)	
Calcium	38/458 (8.3)	reference	21/179 (11.7)	reference	0.14
Vitamin D + Calcium	29/454 (6.4)	0.77 (0.48-1.22)	27/171 (15.8)	1.29 (0.75-2.21)	
Neither Vitamin D nor Calcium	22/272 (8.1)	reference	12/96 (12.5)	reference	0.13
Vitamin D + Calcium	15/262 (5.7)	0.73 (0.38-1.41)	22/111 (19.8)	1.55 (0.77-3.10)	

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

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

†Denominators may differ between adenomas and advanced adenomas due to missing lesion size and an assumption that small lesions (<6mm) with missing pathology data are not advanced adenomas (see Pathology Procedures and Rules above).

Table S7. Per Protocol* Analysis

Event	Events/N (%)	Risk Ratio† (95% CI)
One or More Adenomas		
No Vitamin D	318/767 (41.5)	reference
Vitamin D	337/796 (42.4)	1.00 (0.89-1.13)
No Calcium	283/604 (46.9)	reference
Calcium	259/587 (44.1)	0.95 (0.83-1.07)
Calcium	182/478 (38.1)	reference
Vitamin D + Calcium	190/481 (39.5)	1.02 (0.87-1.20)
Neither Vitamin D nor Calcium	136/289 (47.1)	reference
Vitamin D + Calcium	134/300 (44.7)	0.95 (0.79-1.13)
One or More Advanced Adenomas‡		
No Vitamin D	74/775 (9.6)	reference
Vitamin D	77/802 (9.6)	0.96 (0.71-1.31)
No Calcium	64/605 (10.6)	reference
Calcium	64/598 (10.7)	0.99 (0.71-1.38)
Calcium	47/486 (9.7)	reference
Vitamin D + Calcium	40/486 (8.2)	0.82 (0.54-1.23)
Neither Vitamin D nor Calcium	27/289 (9.3)	reference
Vitamin D + Calcium	30/306 (9.8)	1.01 (0.61-1.69)

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

* Includes participants reporting ≥ 80% compliance with study tablets, and excluding those who ever took ≥1000IU of non-study vitamin D supplements or ≥400mg of non-study calcium.

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

‡ Denominators may differ between adenomas and advanced adenomas due to missing lesion size and an assumption that small lesions (<6mm) with missing pathology data are not advanced

adenomas (see Pathology Procedures and Rules above).

Table S8. Observational Adenoma risk ratios for change in serum 25-OH-vitamin D and calcium Intake

	Change in Serum 25-OH-vitamin†			Change in Calcium Intake‡		
Quartile*	**Events/N (%)**	**Risk Ratio (95% CI)**	**Risk Ratio per 10 ng/ml (95% CI)**	**Events/N (%)**	**Risk Ratio (95% CI)**	**Risk Ratio per 200mg (95% CI)**
One or More Adenomas			0.98 (0.94-1.04)			0.99 (0.98-1.01)
Quartile 1	227/500 (45.4)	reference		220/510 (43.1)	reference	
Quartile 2	209/496 (42.1)	0.90 (0.78-1.04)		245/508 (48.2)	1.16 (1.01-1.34)	
Quartile 3	203/496 (40.9)	0.88 (0.77-1.02)		200/505 (39.6)	1.02 (0.88-1.18)	
Quartile 4	211/496 (42.5)	0.92 (0.80-1.07)		201/508 (39.6)	0.95 (0.82-1.10)	
P for trend§		0.28			0.16	
One or More Advanced Adenomas			1.06 (0.93-1.21)			1.02 (0.98-1.06)
Quartile 1	54/507 (10.7)	reference		38/509 (7.5)	reference	
Quartile 2	39/496 (7.9)	0.70 (0.47-1.04)		59/511 (11.6)	1.62 (1.09-2.39)	
Quartile 3	47/504 (9.3)	0.84 (0.58-1.22)		48/510 (9.4)	1.43 (0.95-2.16)	
Quartile 4	50/496 (10.1)	0.91 (0.63-1.32)		46/516 (8.9)	1.26 (0.84-1.91)	
P for trend§		0.84			0.56	

*Change in Serum 25-OH-vitamin D is measured as the difference between seasonally adjusted serum vitamin D at baseline and seasonally adjusted vitamin D at end of treatment blood draw. Quartile 1: ≤ -1.95 ng/ml; Quartile 2: -1.949 to 3.72 ng/ml; Quartile 3: 3.721-10.29 ng/ml; Quartile 4: 10.291+ ng/ml. Change in calcium intake is measured as the difference between baseline intake (dietary + supplements) and intake at the questionnaire closest in time to the last treatment exam (dietary + supplements + study calcium (either 0 or 1200 mg x overall compliance),
Quartile 1: ≤ -48 mg; Quartile 2: -47.9 to 460 mg; Quartile 3: 460.1-1026 mg; Quartile 4: 1026.1+ mg.

†Risk Ratio adjusted for age, clinical center, anticipated surveillance interval (3 or 5 years), 3 level variable for sex and arm of randomization (male, 2-arm female, full factorial female), number of baseline adenomas (1, 2, 3+) and calcium treatment assignment (2-arm participants are grouped with full factorial participants receiving calcium).

‡Risk Ratio adjusted for age, clinical center, anticipated surveillance interval (3 or 5 years), 3 level variable for sex and arm of randomization (male, 2-arm female, full factorial female), number of baseline adenomas (1, 2, 3+) and vitamin D treatment assignment.

§P for trend calculated using midpoints of the quartiles.

Table S9. Adenoma Risk Ratios by Anticipated Colonoscopic Surveillance Interval

	3 Year Surveillance Interval		5 Year Surveillance Interval		
Event	**Events/N (%)**	**Risk Ratio* (95% CI)**	**Events/N (%)**	**Risk Ratio* (95% CI)**	**P for interaction**
One or More Adenomas					
No Vitamin D	225/529 (42.5)	reference	217/506 (42.9)	reference	
Vitamin D	232/527 (44.0)	1.04 (0.90-1.19)	206/497 (41.5)	0.93 (0.80-1.08)	0.28
No Calcium	181/385 (47.0)	reference	181/376 (48.1)	reference	
Calcium	187/403 (46.4)	0.98 (0.84-1.14)	158/359 (44.0)	0.90 (0.77-1.05)	0.47
Calcium	136/336 (40.5)	reference	123/319 (38.6)	reference	
Vitamin D + Calcium	140/335 (41.8)	1.05 (0.87-1.26)	119/308 (38.6)	0.96 (0.78-1.17)	0.50
Neither Vitamin D nor Calcium	89/193 (46.1)	Reference	94/187 (50.3)	Reference	
Vitamin D + Calcium	96/203 (47.3)	1.01 (0.81-1.25)	78/178 (43.8)	0.83 (0.66-1.03)	0.20
One or More Advanced Adenomas†					
No Vitamin D	51/529 (9.6)	reference	47/513 (9.2)	reference	
Vitamin D	60/532 (11.3)	1.16 (0.81-1.66)	38/500 (7.6)	0.80 (0.53-1.21)	0.17
No Calcium	41/386 (10.6)	reference	36/378 (9.5)	reference	
Calcium	49/407 (12.0)	1.11 (0.75-1.65)	32/366 (8.7)	0.91 (0.57-1.44)	0.50
Calcium	35/338 (10.4)	Reference	28/324 (8.6)	reference	
Vitamin D + Calcium	35/337 (10.4)	1.03 (0.66-1.61)	21/311 (6.8)	0.76 (0.44-1.31)	0.33
Neither Vitamin D nor Calcium	16/191 (8.4)	Reference	19/189 (10.1)	reference	
Vitamin D + Calcium	23/205 (11.2)	1.27 (0.67-2.42)	14/182 (7.7)	0.70 (0.34-1.43)	0.21

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

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

†Denominators may differ between adenomas and advanced adenomas due to missing lesion size and an assumption that small lesions (<6mm) with missing pathology data are not advanced adenomas (see Pathology Procedures and Rules above).

Table S10. Sensitivity analysis for missing data

	Assuming all participants with missing outcome data had NO adenomas		Assuming all participants with missing outcome data HAD adenomas	
Event	**Events/N (%)**	**Risk Ratio* (95% CI)**	**Events/N (%)**	**Risk Ratio* (95% CI)**
One or More Adenomas				
No Vitamin D	442/1129 (39.2)	reference	536/1129 (47.5)	reference
Vitamin D	438/1130 (38.8)	0.98 (0.88-1.08)	544/1130 (48.1)	1.00 (0.92-1.09)
No Calcium	362/835 (43.4)	reference	436/835 (52.2)	reference
Calcium	345/840 (41.1)	0.94 (0.84-1.05)	423/840 (50.4)	0.96 (0.87-1.05)
Calcium	259/714 (36.3)	reference	318/714 (44.5)	reference
Vitamin D + Calcium	259/710 (36.5)	1.00 (0.87-1.14)	326/710 (45.9)	1.02 (0.91-1.15)
Neither Vitamin D nor Calcium	183/415 (44.1)	reference	218/415 (52.5)	reference
Vitamin D + Calcium	174/421 (41.3)	0.92 (0.78-1.07)	214/421 (50.8)	0.95 (0.83-1.09)
One or More Advanced Adenomas†				
No Vitamin D	98/1129 (8.7)	reference	185/1129 (16.4)	reference
Vitamin D	98/1130 (8.7)	0.98 (0.75-1.28)	196/1130 (17.4)	1.05 (0.87-1.26)
No Calcium	77/835 (9.2)	reference	148/835 (17.7)	reference
Calcium	81/840 (9.6)	1.03 (0.76-1.39)	148/840 (17.6)	0.98 (0.80-1.21)
Calcium	63/714 (8.8)	reference	115/714 (16.1)	reference
Vitamin D + Calcium	56/710 (7.9)	0.89 (0.63-1.25)	118/710 (16.6)	1.02 (0.81-1.30)
Neither Vitamin D nor Calcium	35/415 (8.4)	reference	70/415 (16.9)	reference
Vitamin D + Calcium	37/421 (8.8)	0.99 (0.63-1.56)	71/421 (16.9)	0.98 (0.72-1.33)

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

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

† Denominators may differ between adenomas and advanced adenomas due to missing lesion size and an assumption that small lesions (<6mm) with missing pathology data are not advanced adenomas (see Pathology Procedures and Rules above)