ORIGINAL ARTICLE

Calcium plus Vitamin D Supplementation and the Risk of Colorectal Cancer

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ABSTRACT

BACKGROUND

Higher intake of calcium and vitamin D has been associated with a reduced risk of colorectal cancer in epidemiologic studies and polyp recurrence in polyp-prevention trials. However, randomized-trial evidence that calcium with vitamin D supplementation is beneficial in the primary prevention of colorectal cancer is lacking.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial involving 36,282 postmenopausal women from 40 Women's Health Initiative centers: 18,176 women received 500 mg of elemental calcium as calcium carbonate with 200 IU of vitamin D_3 twice daily (1000 mg of elemental calcium and 400 IU of vitamin D_3) and 18,106 received a matching placebo for an average of 7.0 years. The incidence of pathologically confirmed colorectal cancer was the designated secondary outcome. Baseline levels of serum 25-hydroxyvitamin D were assessed in a nested case–control study.

RESULTS

The incidence of invasive colorectal cancer did not differ significantly between women assigned to calcium plus vitamin D supplementation and those assigned to placebo (168 and 154 cases; hazard ratio, 1.08; 95 percent confidence interval, 0.86 to 1.34; P=0.51), and the tumor characteristics were similar in the two groups. The frequency of colorectal-cancer screening and abdominal symptoms was similar in the two groups. There were no significant treatment interactions with baseline characteristics.

CONCLUSIONS

Daily supplementation of calcium with vitamin D for seven years had no effect on the incidence of colorectal cancer among postmenopausal women. The long latency associated with the development of colorectal cancer, along with the seven-year duration of the trial, may have contributed to this null finding. Ongoing follow-up will assess the longer-term effect of this intervention. (ClinicalTrials.gov number, NCT00000611.)

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N Engl J Med 2006;354:684-96.

As the second leading cause of death from cancer in the United States,[1] colorectal cancer is the focus of considerable preventive effort.[2] Most observational studies have associated increased calcium and vitamin D intake with a decreased risk of colorectal cancer[3-6] and recurrent polyps.[7,8] Although the results are somewhat mixed, one pooled analysis of 10 cohort studies that assessed dietary consumption and total calcium intake (diet plus supplements) reported a reduction in the incidence of colorectal cancer of 10 to 15 percent,[9] whereas an earlier pooled analysis found no effect.[10] The suggestion that increased calcium intake helped prevent colorectal cancer led to randomized clinical trials that found that calcium supplementation lowered the incidence of recurrent colorectal polyps to some degree,[11,12] with one report demonstrating that this protection was confined to subjects with higher endogenous vitamin D levels.[13] As part of the Women's Health Initiative (WHI), we conducted a randomized clinical trial to determine whether calcium plus vitamin D supplementation would help prevent colorectal cancer and to examine the effect of supplementation on bone mineral density and the risk of fractures. We report the results related to colorectal cancer; the results related to fracture and bone mineral density are reported elsewhere in this issue of the *Journal*.[14]

METHODS

STUDY POPULATION, ELIGIBILITY, AND CONSENT

Between 1993 and 1998, postmenopausal women 50 to 79 years of age were enrolled in the WHI randomized trials assessing the risks and benefits of hormone therapy and dietary modification.[15-18] Exclusion criteria were related to competing risks, safety, adherence, and retention. One year later, these participants were invited to enroll in the calcium plus vitamin D trial, designed to determine whether calcium plus vitamin D supplementation would prevent hip fracture (the primary outcome) and colorectal cancer (a designated secondary outcome), as described by Jackson et al.[14] Exclusion criteria for the calcium plus vitamin D supplementation trial included a predicted survival of less than three years, a history of renal calculi or hypercalcemia, current use of oral corticosteroids, and current daily use of at least 600 IU of supplemental vitamin D or calcitriol.[19] Ninety-one percent joined the calcium with vitamin D portion of the study during their first annual visit, and 9 percent the following year. Fifty-four percent of the participants had been enrolled in the trials assessing hormone therapy, 69 percent had been enrolled in the trial assessing dietary modification, and 14 percent had participated in both trials. The protocol and consent forms were approved by the institutional review board at each participating institution. All women provided written informed consent.

RANDOMIZATION, BLINDING, AND INTERVENTION

A permuted-block algorithm was used for randomization, with participants stratified according to clinical center and age. Among the 36,282 participants, 18,176 were randomly assigned to receive one tablet of 500 mg of elemental calcium as calcium carbonate combined with 200 IU of vitamin D_3 (GlaxoSmithKline) twice daily (total, 1000 mg of elemental calcium and 400 IU of vitamin D_3) and 18,106 to receive an identical-appearing placebo tablet twice daily. Blinding of the study was achieved by bottle labeling.[15] Participants were given chewable tablets until 1997, at which time tablets that could be swallowed were also offered. Initially, 61 percent of the women in both groups were given chewable tablets. By the end of the study, 70 percent chose the formulation that could be swallowed. Two years after randomization, a comparison of serum 25-hydroxyvitamin D levels in 227 women in the group given calcium with vitamin D and 221 women in the placebo group revealed that the levels were 28 percent higher in the supplement group.

Before enrollment, participants had blood drawn after a 12-hour fast. Samples were processed, frozen at –70°C, and stored according to standardized protocols. After a review of initial findings, a nested case–control study was proposed to determine whether the serum 25-hydroxyvitamin D level at baseline modified the outcome. As of April 8, 2005, 317 women with confirmed invasive colorectal cancer were matched according to age, center, race or ethnic group, and the date of blood sampling with 317 control women who were randomly selected from the group of participants who were free of colorectal cancer. Of these 317 pairs, 306 had adequate stored serum for analysis. Bruce Hollis, Ph.D. (Stillwater, Minn.), measured serum 25-hydroxyvitamin D levels using the DiaSorin Liaison 25(OH)D chemiluminescent radioimmunoassay

system, which has an interassay coefficient of variation of 11.8 percent.

FOLLOW-UP PROCEDURES AND ASCERTAINMENT OF OUTCOMES

Participants were telephoned four weeks after randomization to assess abdominal symptoms and reinforce the importance of adherence; they were contacted semiannually thereafter for self-reported updates on medical history. Any reported colorectal cancers were verified in a blinded fashion by local and central physician adjudicators and coded with the use of the Surveillance, Epidemiology, and End Results system[20,21]; 99.4 percent of reported cancers were centrally confirmed. Adherence was assessed by weighing returned pill bottles. Regardless of their level of adherence, participants were followed up until they died, were lost to follow-up, or requested no further contact or until the study ended.

The protocol did not include a requirement for colorectal-cancer screening; any such tests were ordered by each participant's personal physician. The frequency of rectal examination, fecal occult-blood testing, sigmoidoscopy or colonoscopy, and barium enema was ascertained during medical-history updates. The frequency of abdominal symptoms (bloating or gas, constipation, diarrhea, nausea, a change in appetite, heartburn, and stomach upset) was assessed by a self-administered questionnaire at the time of enrollment in the calcium with vitamin D study; in a random subsample at years 3, 6, and 9; and among all participants, at the completion of the study. Such symptoms were managed by temporary reduction in the number of pills taken. Study pills were discontinued if kidney stones, hypercalcemia, dialysis, or the use of calcitriol or of daily supplements of more than 1000 IU of vitamin D was reported.

STUDY MONITORING AND TERMINATION

An independent data and safety monitoring board reviewed the trial data semiannually.[15] By design, early stopping considerations were based on comparisons between groups of the incidence of hip fracture, colorectal cancer, breast cancer, and death from other causes. Closeout visits occurred as planned between October 1, 2004, and March 31, 2005, with outcomes assessed before the treatment assignment was revealed.

WHI investigators and National Institutes of Health sponsors all contributed to the study design and execution. All authors helped write or revise the manuscript. Statistical analyses and data management were conducted at the WHI Clinical Coordinating Center, whose members vouch for the completeness and veracity of the data and analyses.

STATISTICAL ANALYSIS

Primary analyses used time-to-event methods, according to the intention-to-treat principle. The incidence of colorectal cancer was compared in the two groups with the use of hazard ratios (with 95 percent confidence intervals) and Wald statistic P values from Cox proportional-hazards models,[22] stratified according to age, history of colorectal cancer, and treatment assignment in the Hormone Therapy and Dietary Modification trials. The use of a two-sided, weighted log-rank test was specified in the protocol, with weight increasing linearly from zero at randomization to a maximum of one at 10 years, to enhance the statistical power of the study according to the design assumptions. Both Bonferroni's adjusted and unadjusted tests of significance are given for the weighted log-rank test. The adjusted tests take into account the four end points indicated in the study monitoring plan. Kaplan–Meier estimates were used to describe event rates over time. Potential differential effects across subgroups of important risk factors for colorectal cancer were tested individually with the use of a likelihood ratio test for interaction between the risk factor and treatment assignment after including both as main effects. Thirty-seven subgroup comparisons were tested, with 19 reported (those not reported include the number of first-degree relatives with colorectal cancer; geographic location, tested with the use of two additional methods; any personal use of calcium supplements; the duration and recency of use of hormone therapy; the use of hormone therapy among participants in the dietary-modification trial; and 10 interactions evaluated in women with invasive colon, not rectal, cancer). Accordingly, the results of two tests would be expected to be significant at the 0.05 level by chance. Participants with missing values were excluded from analyses requiring that value.

In planning the study, we calculated that for the secondary end point of colorectal cancer, a trial involving 35,000 women who were followed for an average of eight years would have a statistical power of 83 percent to detect an absolute

reduction in the incidence of colorectal cancer of 22 percent with calcium with vitamin D supplementation, as compared with placebo (given an α value of 0.05). The interaction between serum 25-hydroxyvitamin D levels at baseline and randomized assignment to calcium with vitamin D supplementation or placebo was assessed with the use of conditional logistic regression. Tests for trend and interaction used the logarithm of serum 25-hydroxyvitamin D levels. All reported P values are two-sided and, along with the confidence intervals, were not adjusted for multiplicity, unless noted.

RESULTS

Between 1995 and 2000, 36,282 women underwent randomization. Age, self-reported race or ethnic group, level of education, body-mass index, presence or absence of a family history of colorectal cancer, presence or absence of a history of polyps, level of physical activity, caloric intake, saturated fat intake, multivitamin use, personal intake of elemental calcium, personal intake of vitamin D, level of ultraviolet exposure, cigarette-smoking status, history of hormone use, and randomized assignment in the Hormone Therapy and Dietary Modification trials were similar in the two groups (Fig. 1).[14] The mean (±SD) duration of follow-up was 7.0 ±1.4 years, with a maximum of 9.7 years. During year 1, 60 percent of the participants took at least 80 percent of their study medication, and this percentage remained stable through year 6, with small differences between groups (Fig. 2A). At least 70 percent took 50 percent or more of their study medication through year 6.

The frequency of bowel examination was similar in the two groups throughout follow-up (Fig. 2B). In each group, 60 percent of participants underwent sigmoidoscopy, flexible sigmoidoscopy, or colonoscopy at least once during the study, whereas 15 percent had no bowel assessment of any kind.

Data on events were available for 97 percent of living participants within 18 months before the end of the study. At the time the study ended, 352 women assigned to calcium with vitamin D supplements and 332 women assigned to placebo had withdrawn; 144 and 152, respectively, had been lost to follow-up; and 744 and 807, respectively, had died. A total of 339 colorectal cancers were reported. Of these, nine were in situ and eight were primary cancers of other sites.

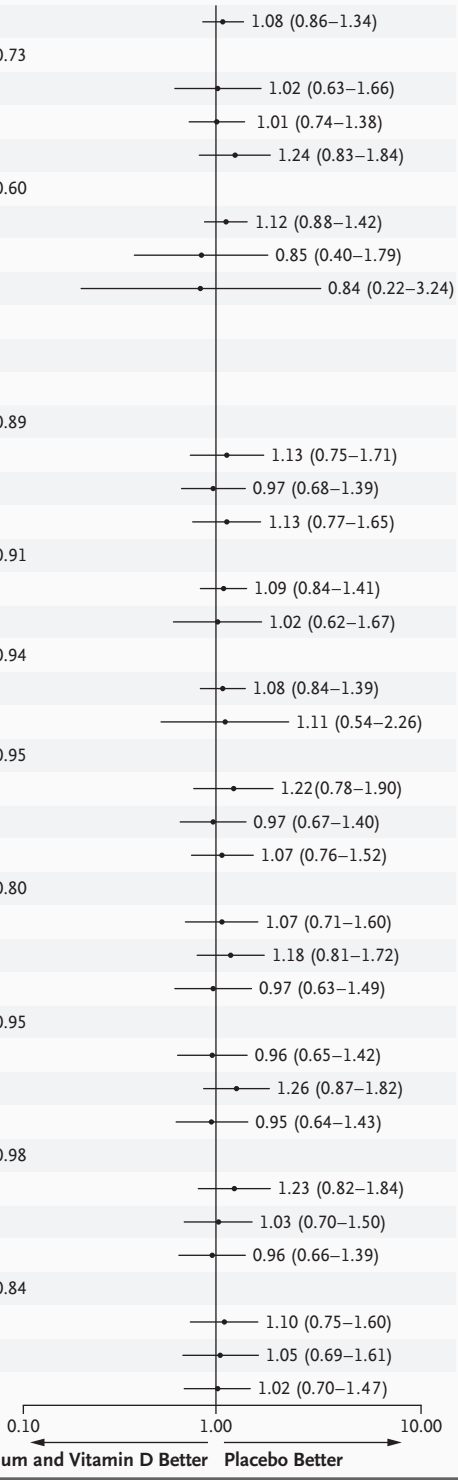
Figure 1 (next page). Estimated Effects of Supplemental Calcium with Vitamin D on the Risk of Colorectal Cancer, According to Selected Baseline Characteristics.

Modeling for interaction testing used the continuous form of the following variables: age at screening, body-mass index, total energy intake, saturated fat intake, total calcium intake, and total vitamin D intake. The data set used to determine the P value for the interaction with race or ethnic group was restricted to black participants and white participants. Data on solar irradiance were adapted from Garland and Garland[23]; higher values indicate greater exposure. Data were missing for some variables. Body-mass index is the weight in kilograms divided by the square of the height in meters. The hormone-therapy status at the time of enrollment in the calcium plus vitamin D supplement trial (year 1 of the WHI Hormone Therapy studies) includes exposure related to the Hormone Therapy trials. Race and ethnic groups are listed as they appeared on the questionnaire. HS denotes high school, GED general equivalency diploma, MET metabolic equivalents, NSAID nonsteroidal antiinflammatory drugs, E estrogen, and P progestin.

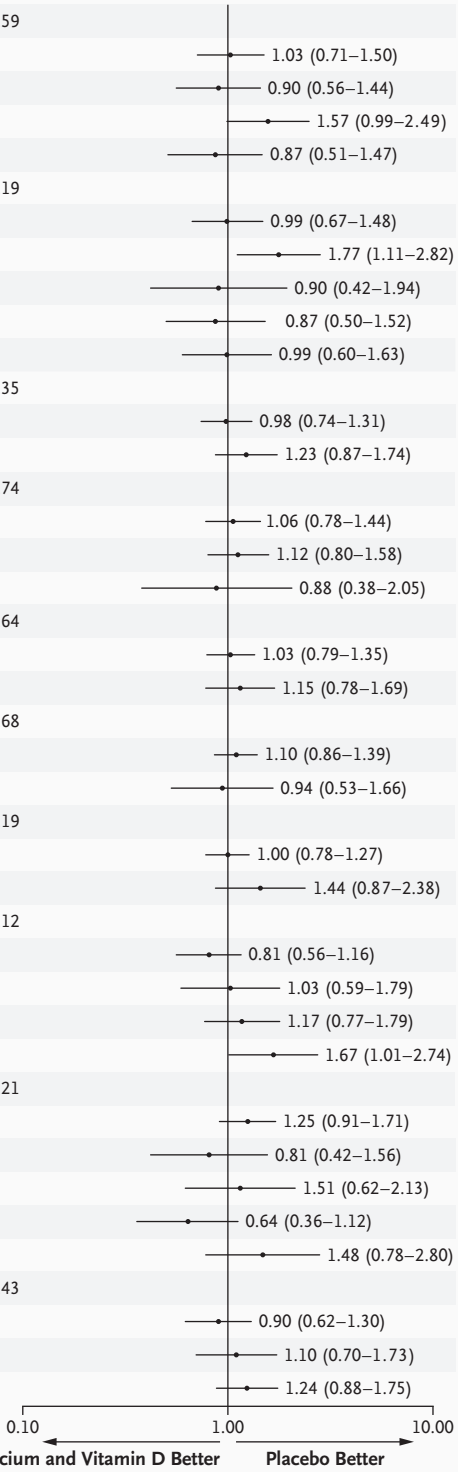
Analyses limited to the 322 invasive colorectal cancers revealed that calcium with vitamin D supplementation, as compared with placebo, had no effect on the risk of colorectal cancer (168 vs. 154 cases; hazard ratio, 1.08; nominal 95 percent confidence interval, 0.86 to 1.34; P=0.51) (Fig. 3). The protocol-specified, weighted log-rank test yielded an unadjusted P value of 0.26 and a P value of 0.32 after adjustment for multiple outcomes. Sensitivity analyses censoring follow-up on participants six months after their rate of adherence to the study medication dropped below 50 percent did not change the findings (hazard ratio in the supplement group as compared with the placebo group, 1.08; 95 percent confidence interval, 0.83 to 1.39), nor did censoring follow-up six months after adherence dropped below 80 percent (hazard ratio, 0.98; 95 percent confidence interval, 0.73 to 1.32). Analyses excluding the 36 women in the supplement group and the 38 women in the placebo group with prior colorectal cancer yielded similar results (hazard ratio for the comparison of the supplement group with the placebo group, 1.09; 95 percent confidence interval, 0.87 to 1.36; P=0.44). No significant interactions were found with any baseline characteristic examined (Fig. 1).

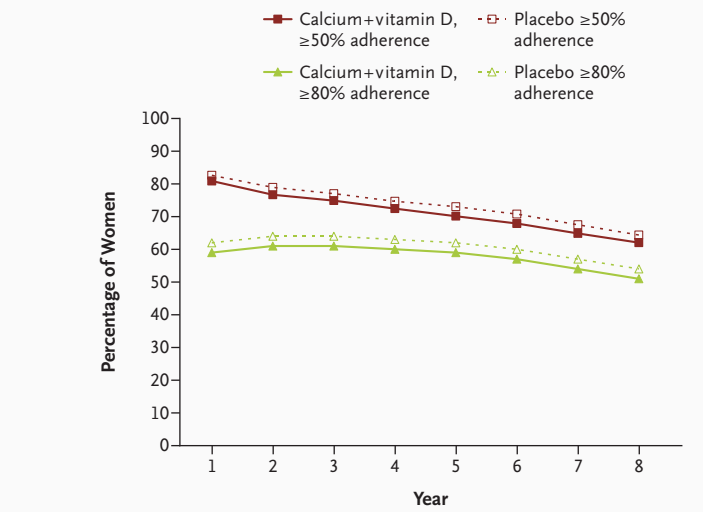
Personal use of any calcium supplementation was reported by 54 percent of the participants at

Variable	Calcium+Vitamin D (N=18,176) no./total no. (annualized %)	Placebo (N=18,106) no./total no. (annualized %)	P Value	Hazard Ratio (95% CI)
Invasive colorectal cancer	168/18,176 (0.13)	154/18,106 (0.12)		1.08 (0.86–1.34)
Age at screening			0.73	
50–59 yr	33/6728 (0.07)	32/6694 (0.07)		1.02 (0.63–1.66)
60–69 yr	81/8275 (0.14)	78/8245 (0.14)		1.01 (0.74–1.38)
70–79 yr	54/3173 (0.25)	44/3167 (0.21)		1.24 (0.83–1.84)
Race or ethnic group			0.60	
White	145/15,047 (0.14)	129/15,106 (0.12)		1.12 (0.88–1.42)
Black	13/1682 (0.11)	16/1635 (0.14)		0.85 (0.40–1.79)
Hispanic	5/789 (0.09)	4/718 (0.08)		0.84 (0.22–3.24)
Indian/Alaskan Native	2/77 (0.37)	0/72 (0.00)		
Asian or Pacific Islander	2/369 (0.08)	3/353 (0.13)		
Unknown	1/212 (0.07)	2/222 (0.13)		
Education			0.89	
None–HS diploma or GED	49/4286 (0.16)	44/4289 (0.15)		1.13 (0.75–1.71)
School after high school	60/7216 (0.12)	60/7156 (0.12)		0.97 (0.68–1.39)
College degree or higher	57/6555 (0.12)	50/6543 (0.11)		1.13 (0.77–1.65)
First-degree relative with colorectal cancer			0.91	
No	121/13,916 (0.12)	111/13,890 (0.11)		1.09 (0.84–1.41)
Yes	33/2684 (0.18)	31/2704 (0.16)		1.02 (0.62–1.67)
History of polyp removal			0.94	
No	129/14,854 (0.13)	118/14,740 (0.12)		1.08 (0.84–1.39)
Yes	18/1409 (0.19)	16/1459 (0.16)		1.11 (0.54–2.26)
Body-mass index			0.95	
<25	44/4745 (0.13)	35/4833 (0.10)		1.22(0.78–1.90)
25–<30	56/6472 (0.12)	58/6483 (0.13)		0.97 (0.67–1.40)
≥30	68/6867 (0.14)	61/6695 (0.13)		1.07 (0.76–1.52)
Physical activity			0.80	
0–3.00 MET/wk	50/5517 (0.13)	46/5478 (0.12)		1.07 (0.71–1.60)
>3.00–<11.75 MET/wk	59/5463 (0.16)	50/5477 (0.13)		1.18 (0.81–1.72)
≥11.75 MET/wk	41/5566 (0.11)	42/5493 (0.11)		0.97 (0.63–1.49)
Total energy intake			0.95	
<1382.11 kcal/day	49/5905 (0.12)	52/5897 (0.13)		0.96 (0.65–1.42)
1382.11–1909.48 kcal/day	65/5958 (0.15)	51/5888 (0.12)		1.26 (0.87–1.82)
>1909.48 kcal/day	48/5958 (0.11)	48/5968 (0.11)		0.95 (0.64–1.43)
Energy from saturated fat			0.98	
<10.895%	53/6044 (0.12)	43/5937 (0.10)		1.23 (0.82–1.84)
10.895–<13.088%	54/5810 (0.13)	54/5927 (0.13)		1.03 (0.70–1.50)
≥13.088%	55/5967 (0.13)	54/5889 (0.13)		0.96 (0.66–1.39)
Total calcium intake (supplements+diet)			0.84	
<800 mg/day	59/6104 (0.14)	52/6003 (0.12)		1.10 (0.75–1.60)
800–<1200 mg/day	45/4715 (0.14)	42/4655 (0.13)		1.05 (0.69–1.61)
≥1200 mg/day	58/7002 (0.12)	57/7095 (0.11)		1.02 (0.70–1.47)



Variable	Calcium+Vitamin D (N=18,176) no./total no. (annualized %)	Placebo (N=18,106) no./total no. (annualized %)	P Value	Hazard Ratio (95% CI)
Total vitamin D intake (supplements+diet)			0.59	
<200 IU/day	56/6827 (0.11)	53/6671 (0.11)		1.03 (0.71–1.50)
200–<400 IU/day	33/3379 (0.14)	38/3423 (0.16)		0.90 (0.56–1.44)
400–<600 IU/day	46/4188 (0.16)	30/4295 (0.10)		1.57 (0.99–2.49)
≥600 IU/day	27/3427 (0.11)	30/3364 (0.13)		0.87 (0.51–1.47)
Region according to solar irradiance			0.19	
300–325 Langleys	49/5366 (0.13)	49/5351 (0.13)		0.99 (0.67–1.48)
350 Langleys	51/3920 (0.19)	28/3880 (0.10)		1.77 (1.11–2.82)
375–380 Langleys	13/2012 (0.09)	15/2009 (0.11)		0.90 (0.42–1.94)
400–430 Langleys	24/3018 (0.11)	28/3015 (0.13)		0.87 (0.50–1.52)
475–500 Langleys	31/3860 (0.12)	34/3851 (0.13)		0.99 (0.60–1.63)
Multivitamin use (with or without minerals)			0.35	
No	96/11,562 (0.12)	95/11,388 (0.12)		0.98 (0.74–1.31)
Yes	72/6613 (0.16)	59/6718 (0.13)		1.23 (0.87–1.74)
Smoking status			0.74	
Never smoked	84/9325 (0.13)	80/9428 (0.12)		1.06 (0.78–1.44)
Former smoker	73/7255 (0.14)	62/7133 (0.12)		1.12 (0.80–1.58)
Current smoker	10/1405 (0.10)	12/1356 (0.13)		0.88 (0.38–2.05)
NSAID use			0.64	
No	111 /12,193 (0.13)	106/12,215 (0.12)		1.03 (0.79–1.35)
Yes	57/5983 (0.14)	48/5891 (0.12)		1.15 (0.78–1.69)
Nonaspirin NSAID use			0.68	
No	144/15,126 (0.14)	130/15,182 (0.12)		1.10 (0.86–1.39)
Yes	24/3050 (0.11)	24/2924 (0.12)		0.94 (0.53–1.66)
Aspirin (≥80 mg/day)			0.19	
No	128/14,624 (0.12)	127/14,589 (0.12)		1.00 (0.78–1.27)
Yes	40/3552 (0.16)	27/3517 (0.11)		1.44 (0.87–2.38)
Hormone-therapy use			0.12	
Never used	53/5814 (0.13)	65/5690 (0.16)		0.81 (0.56–1.16)
Former use	26/3004 (0.12)	24/2932 (0.12)		1.03 (0.59–1.79)
Current use, E alone	47/4515 (0.15)	40/4609 (0.12)		1.17 (0.77–1.79)
Current use, E+P	42/4843 (0.12)	25/4875 (0.07)		1.67 (1.01–2.74)
Enrollment in WHI Hormone Therapy trials			0.21	
No	87/10,122 (0.12)	68/10,071 (0.10)		1.25 (0.91–1.71)
E-alone placebo group	16/1540 (0.15)	20/1562 (0.18)		0.81 (0.42–1.56)
E-alone active group	22/1531 (0.21)	19/1543 (0.18)		1.51 (0.62–2.13)
E+P placebo group	20/2475 (0.12)	31/2395 (0.19)		0.64 (0.36–1.12)
E+P active group	23/2508 (0.13)	16/2535 (0.09)		1.48 (0.78–2.80)
Enrollment in WHI Dietary Modification trial			0.43	
No	55/5582 (0.14)	60/5490 (0.16)		0.90 (0.62–1.30)
Dietary-modification group	40/4767 (0.12)	37/4878 (0.11)		1.10 (0.70–1.73)
Control group	73/7827 (0.13)	57/7738 (0.10)		1.24 (0.88–1.75)





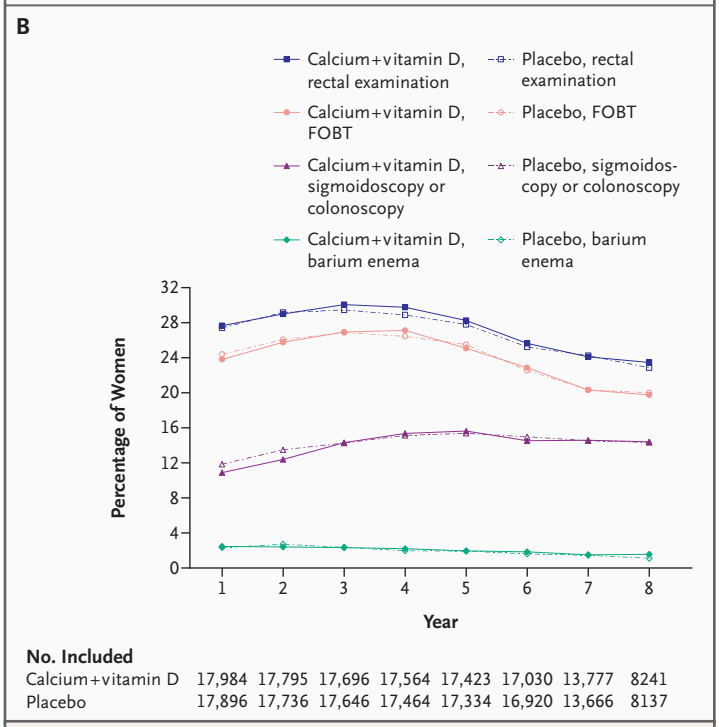


Figure 2. Rates of Adherence (Panel A) and Bowel Examination (Panel B) in the Two Groups during the Study.

FOBT denotes fecal occult-blood test. The category of sigmoidoscopy or colonoscopy included flexible sigmoidoscopy. The category of barium enema included radiographic examination.

baseline, rising to 69 percent at annual visit 9. The mean dose increased by less than 100 mg per day (from 325 mg per day at enrollment) during this interval and was similar across treatment groups. Modeling personal use of calcium supplements as a time-dependent covariate left the hazard ratio essentially unchanged (hazard ratio, 1.06; 95 percent confidence interval, 0.85 to 1.32). The interaction between personal use of calcium supplementation over time and treatment group was not significant (P=0.25).

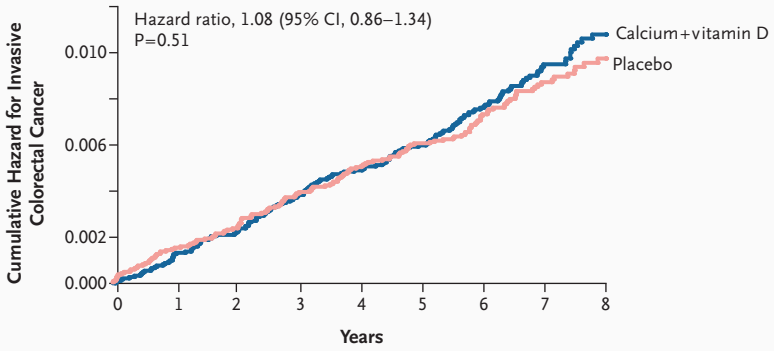
The location, histologic characteristics, grade, stage, and size of colorectal cancers were similar in the two groups (Table 1). In the supplement group, as compared with the placebo group, hazard ratios for invasive colon cancer (hazard ratio, 1.00; 95 percent confidence interval, 0.78 to 1.28; P=0.99), invasive rectal cancer (hazard ratio, 1.46; 95 percent confidence interval, 0.92 to 2.32; P=0.11), proximal-colon cancer (hazard ratio, 0.95; 95 percent confidence interval, 0.69 to 1.30; P=0.74), and distal-colon cancer (hazard ratio, 1.08; 95 percent confidence interval, 0.69 to 1.69; P=0.73) did not differ from unity. The hazard ratio for death from colorectal cancer was 0.82 in the supplement group as compared with the placebo group (95 percent confidence interval, 0.52 to 1.29; P=0.39); however, too few events had occurred (34 vs. 41) to make the comparison meaningful.

SAFETY AND TOLERABILITY

As of March 31, 2005, 744 women in the supplement group had died, as compared with 807 women in the placebo group (hazard ratio, 0.91; 95 percent confidence interval, 0.83 to 1.01; P=0.07). Supplementation with calcium plus vitamin D was not associated with any significant risk or benefit with respect to any major disease outcomes, including cardiovascular diseases and cancer. The effects of calcium plus vitamin D supplementation, as compared with placebo, on the total risk of cancer (hazard ratio, 0.98; 95 percent confidence interval, 0.91 to 1.05; P=0.53) and the risk of death from cancer (hazard ratio, 0.89; 95 percent confidence interval, 0.77 to 1.03; P=0.12) were not significant.

The self-reported occurrence of polyps (all types combined) was similar in the supplement group and the placebo group (hazard ratio, 0.99; 95 percent confidence, 0.94 to 1.04; P=0.71). Kidney stones were reported by 449 women in the supplement group, as compared with 381 women in the placebo group (hazard ratio, 1.17; 95 percent confidence interval, 1.02 to 1.34; P=0.02).

Overall, the supplements were well tolerated. There was no significant difference between groups in the frequency of reported symptoms at any time.



Calcium+vitamin D									
No. of events	0	23	17	28	20	19	27	23	9
No. at risk	18,176	18,048	17,936	17,780	17,605	17,248	14,680	9138	4403
Placebo									
No. of events	0	27	16	27	20	18	20	17	7
No. at risk	18,106	17,967	17,832	17,663	17,471	17,093	14,530	9041	4351

Figure 3. Kaplan–Meier Estimates of the Cumulative Hazard for Invasive Colorectal Cancer with Supplemental Calcium plus Vitamin D, as Compared with Placebo.

CI denotes confidence interval. Two events in each group that occurred after year 8 are not shown.

The frequency of any moderate or severe abdominal symptom in the four weeks preceding enrollment was 34 percent in both groups, increasing to 39 percent in the group assigned to calcium with vitamin D supplementation and to 37 percent in the placebo group at annual visit 3 (P=0.29).

SERUM VITAMIN D LEVELS

Findings from the nested case–control study revealed no significant interaction between serum 25-hydroxyvitamin D levels at baseline and treatment assignment (P=0.54). However, analyses adjusting only for case–control matching demonstrated a significant inverse trend with lower baseline levels of serum 25-hydroxyvitamin D associated with an increased risk of colorectal cancer (P for trend=0.02) (Table 2).

DISCUSSION

In this randomized clinical trial, daily supplementation with 1000 mg of elemental calcium as calcium carbonate combined with 400 IU of vitamin D_3 for an average of seven years had no detectable effect on the incidence of colorectal cancer among postmenopausal women. This absence of an effect was consistent across subgroups, including personal calcium and vitamin D intake and serum vitamin D levels at baseline. Thus, our findings fail to validate previous observational studies and polyp-prevention trials associating calcium and vitamin D intake with reduced risk.

Adherence was relatively good throughout the trial among the more than 36,000 women enrolled; thus, we had sufficient power to detect a 20 percent difference in risk. How should our findings be interpreted in the context of the body of published literature and a growing public perception that calcium and vitamin D supplementation can prevent colorectal cancer? Previous observational studies have often interpreted the protection afforded by calcium and vitamin D supplementation only in the context of comparisons of extreme quintiles of intake. Findings from observational studies should be reviewed cautiously, since they are more prone to confounding and bias than are randomized clinical trials,[24] especially with respect to the assessment of preventive behaviors that may be difficult to detect, measure, and control for. The randomized trial design we used has greater potential to limit bias.

Previous trials demonstrating beneficial effects of calcium and vitamin D supplementation, such as polyp prevention, have led to the use of these agents in risk-reduction strategies. However, there has been no demonstration that secondary prevention of polyps with calcium and vitamin D supplementation translates into a reduction in colorectal cancer. We found no evidence that calcium with vitamin D supplementation prevented

Table 1. Incidence of and Annualized Percentage of Women with Invasive Colorectal Cancer and Other Outcomes.*

Variable	Calcium + Vitamin D (N = 18,176)	Placebo (N = 18,106)	Hazard Ratio (95% CI)†	P Value†
Duration of follow-up — yr	7.0±1.4	7.0±1.4		
Invasive colorectal cancer — no. of cases (annualized %)	168 (0.13)	154 (0.12)	1.08 (0.86–1.34)	0.51
Invasive colon cancer	128 (0.10)	126 (0.10)	1.00 (0.78–1.28)	0.99
Proximal‡	77 (0.06)	80 (0.06)	0.95 (0.69–1.30)	0.74
Distal§	41 (0.03)	37 (0.03)	1.08 (0.69–1.69)	0.73
Invasive rectal cancer¶	44 (0.03)	30 (0.02)	1.46 (0.92–2.32)	0.11
Histologic subtype of invasive colorectal cancer‖				
Carcinoma, not otherwise specified	3 (<0.01)	0	—	—
Adenocarcinoma	135 (0.11)	134 (0.11)	1.00 (0.78–1.26)	0.97
Mucinous	22 (0.02)	15 (0.01)	1.43 (0.74–2.75)	0.29
Signet-ring cell	0	2 (<0.01)	—	—
Data missing	8 (0.01)	3 (<0.01)	—	—
Tumor grade of invasive colorectal cancer‖				
Well differentiated	17 (0.01)	15 (0.01)	1.11 (0.55–2.22)	0.77
Moderately differentiated	95 (0.07)	91 (0.07)	1.04 (0.78–1.39)	0.79
Poorly differentiated or anaplastic	38 (0.03)	32 (0.03)	1.14 (0.71–1.83)	0.58
Data missing	18 (0.01)	16 (0.01)	—	—
SEER stage of invasive colorectal cancer‖				
Localized	71 (0.06)	63 (0.05)	1.11 (0.79–1.56)	0.54
Regional	68 (0.05)	62 (0.05)	1.09 (0.77–1.54)	0.63
Distant	21 (0.02)	21 (0.02)	0.97 (0.53–1.78)	0.93
Data missing	8 (0.01)	8 (0.01)	—	—
Tumor size of invasive colorectal cancer‖				
<3.9 cm	47 (0.04)	50 (0.04)	0.92 (0.62–1.38)	0.70
≥3.9 cm	65 (0.05)	51 (0.04)	1.27 (0.88–1.84)	0.20
Data missing	56 (0.04)	53 (0.04)	—	—
Total cases of cancer — no. (annualized %)	1634 (1.28)	1655 (1.30)	0.98 (0.91–1.05)	0.53
Death from colorectal cancer — no. (annualized %)	34 (0.03)	41 (0.03)	0.82 (0.52–1.29)	0.39
Death from cancer — no. (annualized %)	344 (0.27)	382 (0.30)	0.89 (0.77–1.03)	0.12
Death from any cause — no. (annualized %)	744 (0.58)	807 (0.63)	0.91 (0.83–1.01)	0.07
Intestinal polyps — no. (annualized %)**	2983 (2.33)	2997 (2.36)	0.99 (0.94–1.04)	0.71
Kidney stones — no. (annualized %)**	449 (0.35)	381 (0.30)	1.17 (1.02–1.34)	0.02

* Plus–minus values are means ±SD. SEER denotes Surveillance, Epidemiology, and End Results.
† Hazard ratios, 95 percent confidence intervals (CIs), and P values were derived from Cox proportional-hazards analyses stratified according to age, randomized assignment in the Hormone Therapy and Dietary Modification trials, and presence or absence of corresponding prevalent condition.
‡ This category includes the cecum, the ascending colon, the hepatic flexure, and the transverse colon.
§ This category includes the splenic flexure, the descending colon, and the sigmoid colon.
¶ This category includes cancers of both the rectum and the rectosigmoid junction.
‖ Data were available only for centrally adjudicated cases.
** Information on intestinal polyps and kidney stones is from self-reported data and was not centrally confirmed.

Table 2. Odds Ratios for Invasive Colorectal Cancer According to the Quartile of Serum 25-Hydroxyvitamin D Level at Baseline and Treatment Groups in a Nested Case–Control Study.*

Baseline Serum 25-Hydroxyvitamin D	Main-Effect Odds Ratio (95% CI)†	Calcium + Vitamin D	Placebo	Intervention Odds Ratio (95% CI)‡
		No. with Colorectal Cancer/ No. of Controls		
≥58.4 nmol/liter	1.00	33/48	27/45	1.15 (0.58–2.27)
42.4–58.3 nmol/liter	1.96 (1.18–3.24)	44/41	34/32	1.12 (0.59–2.12)
31.0–42.3 nmol/liter	1.95 (1.18–3.24)	35/32	45/41	0.99 (0.51–1.91)
<31.0 nmol/liter	2.53 (1.49–4.32)	46/39	42/28	0.75 (0.39–1.48)

* To convert values for 25-hydroxyvitamin D to nanograms per milliliter, multiply by 0.401. CI denotes confidence interval.
† Odds ratios were derived from a logistic-regression model, conditioned on case–control pairs, estimating the main effect of the serum 25-hydroxyvitamin D level on the risk of invasive colorectal cancer (P for trend=0.02).
‡ P for interaction=0.54. The odds ratios were obtained from a logistic-regression model, conditioned on case–control pairs, and estimate the calcium with vitamin D intervention effect on the risk of colorectal cancer, according to serum 25-hydroxyvitamin D levels.

colorectal cancer. Although self-reported, the incidence of polyps was also similar in the supplement and placebo groups. As such, our results raise questions regarding the widely held concept that calcium and vitamin D supplementation will prevent colorectal cancer.

Our randomized clinical trial had the potential to limit biases inherent in observational studies and moved beyond trials of secondary prevention of colon polyps. However, issues regarding the design and study population may have limited our ability to demonstrate a protective effect of calcium with vitamin D supplementation on the risk of colorectal cancer, if one does exist. Participants were healthy postmenopausal women selected to be generally free of disability and clinically dominant chronic illness. By design, participants were not restricted from taking calcium or vitamin D supplements on their own. At enrollment, participants had mean total calcium (1151 mg) and vitamin D (367 IU) intakes that were twice the national average[25] and nearly met current recommendations.[26] Intakes rose during the trial, while national averages remained relatively stable.[27] These high intakes may have limited our ability to affect the rates of colorectal cancer further. One prospective study found no additional protective effect of calcium intakes beyond 700 mg per day, and significant associations were limited to cancers of the distal colon.[28] In our study, calcium with vitamin D supplementation was not protective among women with baseline intakes below 800 mg per day, tempering enthusiasm for this explanation. Although our initial analyses of nested case–control studies found lower baseline serum 25-hydroxyvitamin D levels to be associated with an increased risk of colorectal cancer, in contrast to the findings of a previous study,[13] we did not find that serum levels modified the effect of the intervention on the outcome.

Our study has several other potential limitations. The calcium doses as well as vitamin D doses we used may have been insufficient to demonstrate a protective effect, particularly given the fraction of participants who were not fully adherent throughout the study. When we began the study, a daily supplement of 400 IU of vitamin D was considered relatively high. Studies published since that time have led some to recommend daily intakes of vitamin D higher than the one we used.[29] We evaluated a single regimen and cannot assess whether other formulations or doses would have changed the results.

Since the protocol did not require participants to undergo bowel examinations, some cancers may have been missed. However, the frequency of bowel examinations was very similar in the two groups throughout follow-up. Abdominal pain and a change in bowel habits are common initial manifestations of colorectal cancer that may lead to more aggressive screening[30,31]; however, the types and frequency of symptoms were similar in the two groups. Annualized rates of invasive colon cancer (0.10 percent) and rectal cancer (0.03 percent) in our study were similar to Surveillance, Epidemiology, and End Results rates for women of corresponding age during the years 1992 through 2002 (0.09 percent and 0.03 percent, respectively).[32]

Nonetheless, regular or end-of-study colonoscopies may have enabled us to make a more accurate assessment of the effect of calcium with vitamin D supplementation on these tumors.

Two other limitations are the timing of administration of the intervention and the length of follow-up. If the benefit of calcium with vitamin D supplementation is to prevent or slow the progression of colorectal cancer in its early stages and if colorectal cancer has a latency of 10 to 20 years, the average intervention and follow-up of 7 years in our study may have been insufficient to demonstrate an effect. The duration of follow-up was shorter in our trial than in some observational studies that have found a link between calcium and vitamin D intake and the risk of colorectal cancer. Although we did not find a trend toward protection in the later years of follow-up, the ongoing five-year WHI extension study, without intervention, will continue to assess incident colorectal cancers and allow us to identify later effects of this intervention, if they exist.

The strengths of our study include its randomized, double-blind, placebo-controlled design; the large racially and ethnically diverse study population; the comprehensive assessment of risk factors for colorectal cancer at baseline; and the standardized assessment of colorectal-cancer events in a blinded fashion.

In summary, we found that seven years of calcium carbonate plus vitamin D_3 supplementation had no effect on the incidence of colorectal cancer in a randomized trial. Although calcium plus vitamin D supplementation may provide some protection against fracture,[23] it did not protect against colorectal cancer. The long latency associated with the development of colorectal cancer, in concert with the seven-year duration of the trial, may have contributed to this null finding. However, these results do not provide support for the general use of calcium plus vitamin D supplementation to prevent colorectal cancer.

Supported by the National Heart, Lung, and Blood Institute, Department of Health and Human Services. Many clinical centers received assistance from the General Clinical Research Center program of the National Center for Research Resources. The active study drug and placebo were supplied by GlaxoSmithKline Consumer Healthcare (Pittsburgh).

Dr. Assaf reports being an employee of Pfizer since December 2002 and reports owning stock and having stock options in Pfizer. Dr. Brunner reports being principal investigator of a study funded by the National Cancer Institute of Canada and Pfizer. Dr. O'Sullivan reports receiving grant support from Pfizer-Viracept PK. Dr. Robbins reports having received grants with industry support but without salary support. Dr. Sharma reports having received grant support from Merck and GlaxoSmithKline for an HPV vaccine study. Dr. Hays reports having received lecture fees for a conference sponsored by Procter & Gamble. Dr. Howard reports having received lecture fees from Schering-Plough and serving as a consultant for Merck, the Egg Nutrition Council, and General Mills. Dr. Jackson reports having received consulting fees from Procter & Gamble, lecture fees from Aventis/Procter & Gamble, and grant support from Novartis. Dr. LaCroix reports having received consulting fees from Pfizer, Procter & Gamble, and the Alliance for Better Bone Health and a lecture fee from Schering Plough. Dr. Lewis reports receiving grant support from Pfizer and Novartis. No other potential conflict of interest relevant to this article was reported.

We are indebted to the investigators and staff of the WHI clinical centers, the WHI Clinical Coordinating Center, and the National Heart, Lung, and Blood Institute program office for their dedication and effort; to Rebecca J. Rodabough for her invaluable assistance and expertise in completing the statistical analyses for this article; and to the WHI participants for their extraordinary commitment to the study.

APPENDIX 1

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APPENDIX 2

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diet, supplements, or both. But one message is clear: calcium with vitamin D supplementation by itself is not enough to ensure optimal bone health. Clinicians and patients should be aware that even if a woman is receiving adequate calcium with vitamin D supplementation, she may still be at risk for fracture, particularly if she has low bone mineral density or other clinical risk factors. Additional therapy with agents that have been proved to reduce the risk of fracture in women with osteoporosis, such as antiresorptive medications or teriparatide, may be indicated. Calcium with vitamin D supplementation is akin to the ante for a poker game: it is where everyone starts. If the clinical data suggest that the risk of fracture is significant, however, a woman probably needs something more.

Supported by a grant (K24 DK02759) from the National Institutes of Health.

No potential conflict of interest relevant to this article was reported.

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Calcium plus Vitamin D_3 Supplementation and Colorectal Cancer in Women

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The effect of vitamin and mineral supplementation and diet on the risk of colorectal cancer is an active area of research. In this issue of the *Journal*, Wactawski-Wende et al.[1] report the results of a Women's Health Initiative (WHI) trial to test the hypothesis that postmenopausal women randomly assigned to receive 1000 mg of elemental calcium as calcium carbonate with 400 IU of vitamin D_3 daily would have a lower risk of hip fracture and, secondarily, a lower risk of any type of fracture and colorectal cancer than women receiving placebo. The calcium plus vitamin D study involved 36,282 women from 40 WHI centers across the United States. Only women who had already been enrolled for one year in another component of a WHI trial — dietary modification involving a low-fat diet high in fruits and vegetables, postmenopausal hormone therapy, both interventions, or placebo or usual diet — were eligible if they also met other eligibility criteria. The one-year delay was intended to avoid placing an undue burden on the participants.[2,3] An intention-to-treat analysis showed that after an average of seven years of follow-up, the rates of invasive colorectal cancer and the tumor characteristics were similar among the 18,176 women assigned to receive calcium with vitamin D supplementation and the 18,106 women assigned to the placebo group.[1] How do these

results fit into the contextual puzzle of the relation between total calcium and vitamin D intakes and the risk of colorectal cancer?

The WHI trial had three overlapping components: a dietary-modification group, a hormone-therapy group, and a calcium with vitamin D component added a year after the first two elements. By design, participants in one group were members of another; for example, in the calcium with vitamin D trial, 69 percent of the women had been enrolled in the Dietary Modification trial, 54 percent had been enrolled in the Hormone Therapy trial, and 14 percent had been enrolled in both trials.[1] Since the mean age of the women was 62 years at entry into the calcium with vitamin D trial, the women were just reaching the high-risk age for colorectal cancer when the trial ended. Thus, the study may have been stopped too early to detect the effects of calcium plus vitamin D supplementation on incident colorectal cancer, with its estimated latency period of 10 to 20 years.

The enrollment of women in three overlapping trials maximized the participation and size of the WHI trial but created a complex approach with potential confounders for biologic interpretation. For example, bone density is improved by increased intakes of dairy foods, fruit, and vegetables rich in vitamin C, vitamin K, and potassium and other minerals that enhance calcium absorption.[4] After the occurrence of additional cases of colorectal cancer among the participants, future analyses could examine whether dietary patterns in combination with supplementation modified the risk of colorectal cancer.

As compared with age-matched peers in the Third National Health and Nutrition Examination Survey, women in the calcium with vitamin D trial were better educated, were less likely to smoke cigarettes, were more likely to drink alcohol weekly, had higher average calcium intakes (by 130 mg per day), and had higher body-mass indexes.[2] The characteristics of the participants reflect those of healthy volunteers in some trials. However, the participants were at lower risk for colorectal cancer than men and women who received a diagnosis of an adenomatous polyp before enrollment in trials reporting that calcium supplementation reduced the risk of recurrent polyps.[5-7] More men than women were enrolled in the polyp-recurrence trials, and the supplement dose used was higher than the dose in the calcium with vitamin D trial.[5-7] The rates of colorectal cancer increase with age, but the age trajectory is later for women than for men.[8] Thus, the lower-risk profile of the WHI participants, their later age trajectory for colorectal cancer, and their earlier age at enrollment may have reduced the incidence of colorectal cancer and the study's power to detect any effects of calcium plus vitamin D supplementation on the risk of colorectal cancer.

Observational epidemiologic research on the effect of dietary intakes of calcium on the risk of colorectal cancer reveal inconsistent, weak inverse associations: there was a significant inverse relation with distal-colon cancer alone in the Nurses' Health Study, but no association in the Women's Health Study.[9,10] Few epidemiologic studies have been published on the association of vitamin D supplementation with the risk of colorectal cancer, with most findings not reaching significance.[10] In contrast, studies in animals indicate that supplementation with calcium and vitamin D reduces the risk of colorectal cancer.[11]

Given that colorectal cancer was a secondary end point in the WHI calcium with vitamin D trial and that the dose of calcium plus vitamin D was lower than the dose in polyp-recurrence trials, there is a need for a study in which colorectal cancer is the primary outcome among women who receive calcium with vitamin D supplements. Yet, before we consider initiating another trial, we should avail ourselves of several other opportunities. One is to examine the association between total calcium with vitamin D intake and the risk of colorectal cancer in the observational cohort from the WHI trial.[12] In a nested case–control study in the calcium with vitamin D trial population, there was a significant inverse association between lower serum 25-hydroxyvitamin D levels and a higher risk of colorectal cancer,[1] similar to the findings in the Nurses' Health Study,[13] another study involving women. Another opportunity is to compare changes in plasma levels of 25-hydroxyvitamin D and osteocalcin in postmenopausal women with osteopenia (stratified according to the severity of osteopenia, treatment such as alendronate or risedronate, and the use of supplements) with those in women without osteopenia who are eligible to receive calcium with vitamin D supplements.

A controlled feeding study could be designed to provide and keep track of all foods eaten by participants and to monitor their weight, physi-

cal activity, and exposure to ultraviolet light. Another study might examine the effects of various doses of calcium with vitamin D supplements in healthy postmenopausal women who follow a low-fat diet high in fruits and vegetables as compared with women who follow their usual diet. These studies could contribute data on the kinetics and the optimal doses of calcium plus vitamin D supplements in postmenopausal women with and in those without osteopenia. Such data could provide information to bridge the knowledge gap from the current study to the next step, a pooled study evaluating the sex-specific risk of colorectal cancer or, perhaps, a colorectal-cancer trial. Thus, the conclusion of Wactawski-Wende et al. about the role of calcium plus vitamin D supplementation in the prevention of colorectal cancer needs to be interpreted in the light of the complexities of the WHI study and the probability that the doses of these substances may have been too low to achieve the desired effect.

No potential conflict of interest relevant to this article was reported.

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Inhibition of Tumor Necrosis Factor α for Refractory Asthma

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Tumor necrosis factor (TNF), originally discovered and named on the basis of its tumor regression activity, is an important cytokine that regulates the pathogenetic mechanisms of chronic inflammatory diseases.[1,2] The translation of research findings to patient care resulted in the first successful cytokine-specific targeted therapies, the TNF inhibitors. Currently available inhibitors include the monoclonal antibodies against TNF-α, infliximab and adalimumab, and the soluble TNF receptor fused to human IgG, etanercept.[1,2] Agents that block TNF-α suppress inflammation, slow disease progression, and in some cases, induce remission in patients with rheumatoid arthritis, ankylosing spondylitis, psoriasis, and Crohn's disease.[2] In this issue of the *Journal*, Berry and colleagues provide evidence that the soluble TNF inhibitor etanercept may be of benefit in the treatment of another severe chronic inflammatory disease, refractory asthma.[3]

Although commonly diagnosed with the use of physiological measures of airflow limitation and bronchial hyperreactivity, asthma is a chronic inflammatory disorder of the airways, and management guidelines advocate the use of therapies that decrease inflammation.[4] In the majority of cases, therapy with inhaled or oral corticosteroids prevents symptoms and results in normal or near-normal lung function. However, approximately 10 percent of patients have asthma that is refractory to such therapies, with frequent exacerbations and continual symptoms limiting their activity and reducing their quality of life.[5-7] These patients account for a substantial proportion of