Phase III Trial of Ursodeoxycholic Acid To Prevent Colorectal Adenoma Recurrence

David S. Alberts, María Elena Martínez, Lisa M. Hess, Janine G. Einspahr, Sylvan B. Green, A. K. Bhattacharyya, Jose Guillen, Mary Krutzsch, Ashok K. Batta, Gerald Salen, Liane Fales, Kris Koonce, Dianne Parish, Mary Clouser, Denise Roe, Peter Lance

For the Phoenix and Tucson Gastroenterologist Networks

Background: **Ursodeoxycholic acid (UDCA) treatment is associated with a reduced incidence of colonic neoplasia in preclinical models and in patients with conditions associated with an increased risk for colon cancer. We conducted a phase III, double-blind placebo-controlled trial of UDCA to evaluate its ability to prevent colorectal adenoma recurrence.** ***Methods:*** **We randomly assigned 1285 individuals who had undergone removal of a colorectal adenoma within the past 6 months to daily treatment with UDCA (8–10 mg/kg of body weight; 661 participants) or with placebo (624 participants) for 3 years or until follow-up colonoscopy. Recurrence rates (number of recurrent adenomas per unit time) were compared by use of a Huber–White variance estimator. Proportions of participants with one or more recurrent adenomas were compared with a Pearson chi-square statistic; adjusted odds ratios (ORs) were obtained by logistic regression. All statistical tests were two-sided.** ***Results:*** **We observed a non–statistically significant 12% reduction in the adenoma recurrence rate associated with UDCA treatment, compared with placebo treatment. However, UDCA treatment was associated with a statistically significant reduction ($P = .03$) in the recurrence of adenomas with high-grade dysplasia (adjusted OR = 0.61, 95% confidence interval = 0.39 to 0.96). We observed no statistically significant differences between UDCA and placebo groups in recurrence with regard to adenoma size, villous histology, or location.** ***Conclusions:*** **UDCA treatment was associated with a non–statistically significant reduction in total colorectal adenoma recurrence but with a statistically significant 39% reduction in recurrence of adenomas with high-grade dysplasia. Because severely dysplastic lesions have a high risk of progression to invasive colorectal carcinoma, this finding indicates that future chemoprevention trials of UDCA in individuals with such lesions should be considered. [J Natl Cancer Inst 2005;97:846–53]**

Colorectal cancer is the second leading cause of cancer death in the United States with more than 56 290 deaths anticipated in 2005 *(1)*. Secondary bile acids in stool, particularly deoxycholic acid (DCA), have been implicated in the pathogenesis of colorectal cancer *(2–7)* through their disruption of the balance between colorectal crypt cell proliferation, differentiation, and apoptosis. Secondary bile acids appear to act by modifying intracellular signaling and gene expression *(8–11)*. Specifically, DCA appears to stimulate signaling through at least two different pathways that regulate the activity of activator protein-1 *(9)*. DCA and other secondary bile acids are cytotoxic to colonic epithelial cells *(12–14)*, are mutagenically active in bacterial test systems *(15)*, are associated with dysplasia *(16)*, and have antiapoptotic properties *(8,17)*. However, the biological activity of ursodeoxycholic acid (UDCA), a tertiary bile acid, is diametrically opposed to that of DCA *(18,19)*. For instance, UDCA suppresses many of the same pathways, such as the mitogen-activated protein kinase pathway, that are activated by DCA *(18,19)*. Moreover, UDCA appears to inhibit cell proliferation *(8)*.

We *(20)* and others *(21,22)* have reported that UDCA can prevent colon carcinogenesis in preclinical models and that it inhibits vital cell proliferation signal transduction pathways *(19)*. Consequently, the chemopreventive properties of UDCA may result from its ability to inhibit mitogenic signaling and thus to suppress cell growth *(8,23)*. Three clinical studies of UDCA have strengthened interest in this agent as a chemopreventive agent for colorectal cancer *(24–26)*. UDCA treatment was associated with decreased recurrence rates of colorectal adenomas in participants with a history of primary biliary cirrhosis after a median intervention period of 45.6 months *(27)* and was associated with a lower prevalence of colonic neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis after median treatment durations of 50.4 and 42 months, respectively *(24,26)*. Recently, we reported *(28)* the results of a phase I dose-finding trial of UDCA in healthy volunteers that detected a decreased proportion of DCA in the aqueous-phase stool, with a peak effect observed with a daily UDCA dose of 600 mg (i.e., 8–10 mg/kg of body weight), compared with baseline values. The concentration of DCA and other bile acids in the aqueous phase of stool may be of greater importance to colon carcinogenesis than those in the solid phase because of the direct contact of the aqueous phase of stool with the colonic epithelium *(29)*.

Results of these preclinical and early-phase trial findings and the documented activity of UDCA in other gastrointestinal diseases prompted us to initiate a large, phase III, double-blind,

Affiliations of authors: Departments of Medicine (DSA, JGE, PL), Pathology (AKB), and the Arizona Cancer Center (DSA, MEM, LMH, JGE, SBG, AK Bhattacharyya, JG, MK, LF, KK, DP, MC, DR, PL), College of Medicine, Division of Biostatistics and Epidemiology, College of Public Health (DSA, MEM, SBG, DR), and the Department of Molecular and Cellular Biology, College of Science (PL), University of Arizona, Tucson; Department of Medicine (AK Batta, GS), University of Medicine and Dentistry of New Jersey, Newark.

Correspondence to: David S. Alberts, MD, Arizona Cancer Center, 1515 N. Campbell Avenue, PO Box 245024, Tucson, AZ 85724–5024 (e-mail: dalberts@azcc.arizona.edu).

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placebo-controlled trial of UDCA to prevent the recurrence of colorectal adenoma.

Patients and Methods

Study Design

We conducted a randomized, double-blind, placebo-controlled trial designed to test the efficacy of UDCA to prevent recurrence of colorectal adenomas. The planned total number of participants was 1200. Eligibility criteria included the removal of one or more colorectal adenomas with a diameter of 3 mm or more during a colonoscopy examination within the 6-month period before study registration, age between 40 and 80 years, no clinical evidence of organic disease, resident of Maricopa or Pima Counties in Arizona, and no invasive cancer within the previous 5 years. All other colon neoplasms must have been completely removed, except for diminutive (<3 mm) sessile rectal polyps. It was estimated that the study would have 81% power to detect a 20% reduction in the adenomatous polyp recurrence rate, 95% power to detect a 25% reduction, and 99% power to detect a 30% reduction. Written consent forms, approved by the University of Arizona Human Subjects Committee and local hospital/clinic-based institutional review boards, were signed by all participants in this trial, allowing review, as required, of colonoscopy and colorectal adenoma histopathology data and use of paraffin-embedded histopathologic materials for pathology review and measurement of various biomarkers.

UDCA, supplied as 300-mg capsules, and placebo capsules that were identical in appearance were from Novartis (East Hanover, NJ). The drug was stored at room temperature in a locked storage facility. Drug stability was tested by high-performance liquid chromatography on an annual basis and was found to contain more than 90% pure UDCA over the course of 7 years of storage. The phase III trial was registered with the Food and Drug Administration under Investigational New Drug (IND) number 50236.

A preexisting network of more than 80 gastroenterologists from the Phoenix and Tucson metropolitan areas worked directly with research staff of the Arizona Cancer Center's Colon Cancer Prevention Team to identify eligible participants for the phase III trial. Letters were mailed from each of the gastroenterologists to their potentially eligible patients. Arizona Cancer Center colon cancer prevention research clinics were established near the referring gastroenterologists in Sun City, Central Phoenix, Mesa, and Tucson, Arizona, and staffed with experienced clinical trial personnel. Recruitment of study participants began on November 11, 1995, and was completed on December 17, 1999.

Of 6570 potential participants, 1537 were eligible for random assignment to treatment. These eligible participants, who signed the institutional review board–approved consent forms, began 4 weeks of placebo intake (i.e., the run-in assessment period) to determine adherence to study requirements (i.e., returning for clinic visits, intake of at least 75% of placebo). These participants were randomly assigned, by use of a simple random allocation, to a daily dose of UDCA capsules containing 8–10 mg/kg of body weight or to a daily dose of matched placebo capsules. Because only 300-mg UDCA capsules were available, the assigned dose was adjusted to the nearest 300 mg of UDCA. The 1285 participants who adhered to all the study requirements were eligible to begin their randomly assigned treatment—either daily UDCA treatment (8–10 mg/kg; 661 participants) or daily matched placebo (624 participants). Only the capsule manager and the study biostatisticians had access to the randomized assignment. Duration of treatment was approximately 3 years or until completion of the follow-up colonoscopy that was to be scheduled within 6 months of the 3-year anniversary date of the qualifying colonoscopy; this examination was the only follow-up colonoscopy required by the protocol.

Adenoma Recurrence

The primary outcome of this phase III trial was the recurrence of colorectal adenomas. Recurrence was defined as the occurrence of one or more colorectal adenomas or adenocarcinomas 6 months or more after the qualifying colonoscopy. Advanced adenomas were defined as those with any of the following characteristics: diameter of 10 mm or more, tubulovillous or villous histology, high-grade dysplasia, or adenocarcinoma. All other adenomas were considered nonadvanced. Outcome data were obtained from colonoscopy, sigmoidoscopy, or surgical resection procedure reports, plus corresponding histology reports, performed during the follow-up period. Data from these reports were reviewed by trained abstractors who coded the information to study forms by use of detailed specifications. Because the degree of dysplasia was incompletely documented in histology reports, determination of the presence of high-grade dysplasia was made primarily by central pathology review. When there was more than one adenomatous polyp in a participant, either at baseline or at follow-up colonoscopy, characterization of the histologic type and degree of dysplasia were based on polyps that had the most advanced histology and degree of dysplasia. An Endpoints Review Committee performed a blinded final review of any questions related to these report forms and was responsible for making final recommendations for analyses. As recommended by this committee, any procedure occurring within 6 months of the qualifying colonoscopy was considered part of the baseline examination. All colonoscopies performed more than 6 months after the qualifying colonoscopy were included in the endpoint analyses. In a few cases, although the colonoscopy procedure report noted that "multiple" polyps had been removed, all the tissue pieces were placed in the same container. Because a single resected polyp may yield more than one piece of tissue, when all specimens from an endoscopic examination are placed in the same container, it is impossible at subsequent histologic examination to determine the precise number of polyps removed. In this situation, the number of polyps was coded as 1.

Bile Acid Concentrations in the Aqueous Phase of the Stool

A total of 552 of the study participants (261 in the placebo group and 291 in the UDCA group) consented to collect pooled 72-hour stool samples at baseline and just before their endpoint colorectal evaluation. The baseline 72-hour stool collection was completed during the last 3 days of the placebo run-in period. A second 72-hour stool collection was completed during the week before the planned endpoint colonoscopy. Stool samples were collected and stored in metal containers, frozen, and transported to the study center on dry ice. Once in the laboratory, the specimens were stored at –80 °C. For analysis, each 72-hour sample

was first homogenized for 15 minutes with equal weight of water, and an aliquot was ultracentrifuged at 4 °C. The stool aliquot volume was 10 mL (duplicate), and the ultracentrifuge conditions were 1 hour in a 70.1 Ti rotor at 38 500 revolutions per minute. The aqueous phase or supernate was removed, weighed, and stored at −80 °C. Gas chromatography of bile acids was carried out on a Hewlett-Packard model 6890 gas chromatograph equipped with a flame ionization detector and an injector with a split/splitless device for capillary columns *(30,31)*. The amounts of bile acids obtained were expressed as milligram per milliliter of aqueous-phase solution.

Evaluation for Adverse Effects or Toxicity

The evaluation for adverse events specifically captured information about nausea, vomiting, abdominal pain, diarrhea, and the occurrence of other adverse events at each study visit by a research nurse who inquired about all adverse events at every scheduled study visit, which took place every 3–4 months throughout the follow-up period, in addition to telephone call visits that took place between the clinic visits when additional follow-up was needed. Blood levels, to determine abnormalities in levels of serum creatinine or hemoglobin, in white blood cell count, and in liver enzyme profiles, were recorded at the start of the study, 2 months after starting the study medication, and each year thereafter throughout the follow-up period, as well as at the end of study participation.

Statistical Analysis

Adenoma recurrence in the UDCA group was compared with adenoma recurrence in the placebo group in two ways. First, as specified in the protocol as the primary analysis, we compared rates of recurrence (i.e., the mean number of recurrent adenomas per unit time). Because there was evidence of overdispersion (i.e., more variability in number of adenomas) relative to a Poisson distribution, a robust variance estimator (i.e., the Huber-White sandwich estimator in Stata, Version 8) was used to standardize this comparison. Second, we compared proportions of participants with one or more recurrent adenomas using a Pearson chi-square statistic for the 2 × 2 contingency table.

The UDCA group and the placebo group were also compared with regard to advanced adenomas found at follow-up (i.e., proportion of participants who had one or more adenomas meeting the definition of advanced, as specified above). When categorizing adenoma recurrence in three categories (none, nonadvanced, or advanced), a Cochran–Mantel–Haenszel 1-degree-of-freedom chi-square statistic was calculated for the ordered 2 × 3 contingency table. Because the protocol specified an interest in histologic type, size, and location, separate comparisons of the two intervention groups were performed for presence at follow-up of one or more large adenomas (defined as being ≥10 mm in diameter), any villous histology, any adenoma with high-grade dysplasia, and a proximal location; the first three characteristics are components of the definition of advanced adenoma.

Analyses of outcome were based on all patients who had outcome data. Participants were counted in the group to which they were originally randomized (i.e., intent-to-treat analysis). All statistical tests were two-sided; 95% confidence intervals (CIs) were calculated for rate ratios, risk ratios, and odds ratios.

The UDCA group and the placebo group were compared with regard to median levels of fecal bile acids by the Wilcoxon–Mann–Whitney rank sum test. When concentrations were undetectable, the value was set to zero.

Adherence to the assigned medication dose was calculated from returned capsule count at each clinic visit as follows: {[(number of pills dispensed – number of pills returned) / (daily prescribed dose)] / number of days in evaluation period × 100}.

External Data and Safety Monitoring

An External Data and Safety Monitoring Committee met semiannually in Tucson, Arizona, or by teleconference. This committee was responsible for reviewing protocol amendments and human consent form documents, participant accrual and retention rates, participant safety, drug toxic effects, and outcome analyses. At the end of each semiannual meeting, the committee took a mandatory vote to continue or not continue the trial and provided a detailed summary report to the study statisticians who had access to unblinded data. This report was summarized to remove any items that could potentially compromise blinding and was sent to the study investigators. This summary report, including the results of each vote taken by the committee, was included with each annual progress report to the National Cancer Institute.

Results

Enrollment and Randomization

Of the 6570 potential study participants identified, 4448 (67.7%) declined to participate, and 567 (8.6%) were found ineligible. The remaining 1555 (23.7%) signed a consent form. Of these, 18 (1.2%) were found ineligible before randomization and 1537 (98.8%) were assigned a randomization code for treatment and began a run-in period on placebo. Of these 1537 participants, 252 were excluded for various reasons (Fig. 1), and 1285 (83.6%) started the randomly allocated UDCA (661 participants) or placebo (624 participants) intervention. Of these, a total of 1192 (92.8%) underwent at least one colorectal evaluation 6 months or more after randomization and were thus evaluable for outcome: 579 in the placebo group and 613 in the UDCA group (Fig. 1). Table 1 shows the baseline characteristics of these participants. All baseline characteristics were similar across treatment groups, with the exception of carbohydrate intake, which was higher in the UDCA-treated group ($P = .02$) than in the placebo group.

Adherence, Dose Reduction, and Time on Treatment

Mean primary adherence (based on returned pill count) was 94.4% in the placebo group and 94.7% in the UDCA group. Nineteen (3.3%) of the 624 participants in the placebo group and 19 (3.1%) of the 661 participants in the UDCA group required a dose reduction at some point during the trial. Of these participants, 15 and 18, respectively, in the placebo and UDCA groups required a reduction in dosage because of toxicity. The most common toxicity was diarrhea (five in the placebo group and eight in the UDCA group). The other reasons for reduced dosage included medical conditions unrelated to the study (four participants in the placebo group) and vacation or personal reason (one in the

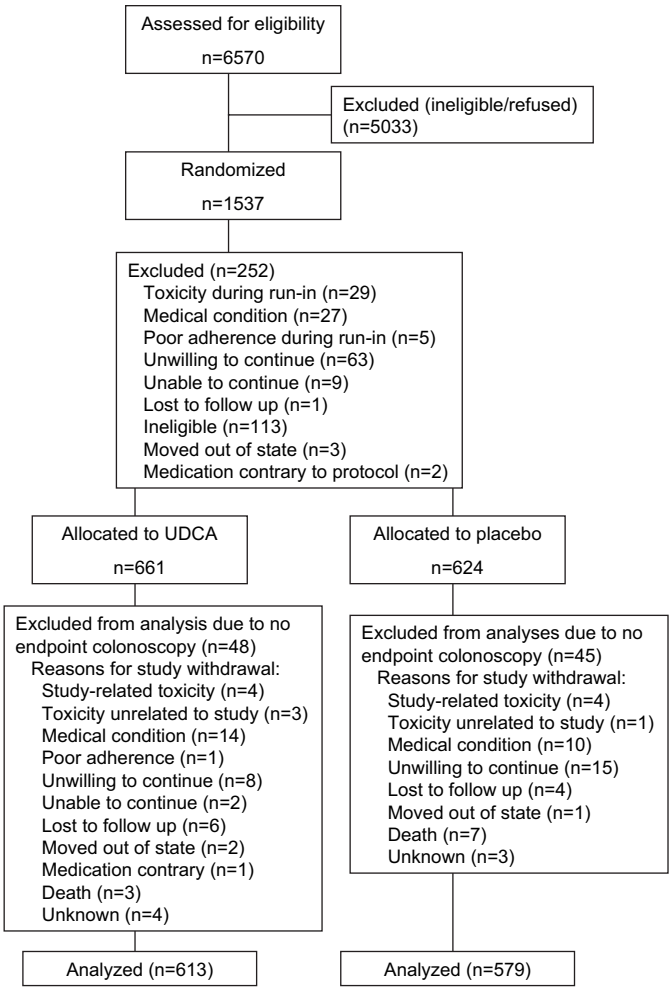

Fig. 1. CONSORT trial flow diagram.

UDCA group). The median time on the UDCA treatment was 31.8 months; median time on the placebo treatment was 32.0 months ($P = .19$).

Colorectal Evaluation

Evaluable colorectal examinations for the primary analysis included 1694 colonoscopies (97.7%), 30 sigmoidoscopies (1.7%), and nine surgical resections (0.5%). The median time from randomization to follow-up colorectal examination on both study arms was 34 months. A total of 579 participants (92.8%) randomly assigned to the placebo arm and 613 participants (92.7%) randomly assigned to the UDCA treatment arm had at least one follow-up colorectal evaluation 6 months or more after randomization. After the baseline colorectal examination, 64.5% (769 participants) had one follow-up procedure, 28.1% (335 participants) had two procedures, 5.5% (66 participants) had three procedures, 1.2% (14 participants) had four procedures, and less than 1% (eight participants) had more than four follow-up colorectal evaluation procedures that were included in the final analysis of recurrence. Of all participants with at least one follow-up examination, 1179 (98.9%) had at least one procedure in which the cecum was reported to have been reached. There were no statistically significant differences between the two study arms with regard to completion of study procedures.

Polyp Characteristics

Of the 913 recurrent adenomatous polyps, 87.5% were tubular, 10.5% were tubulovillous, and 1.0% were villous. The histologic category was unknown for 1.0% of recurrent polyps. The median polyp size at recurrence was 4.9 mm (mean = 5.4 mm; range = 0.9–50 mm; two unknown). Ten percent were 1 cm or greater in diameter. Approximately 26% of all of the colorectal adenoma recurrences occurred solely in the distal colon (i.e., polyps located in the rectum, sigmoid, descending, or left transverse colon); when location was unknown, polyp distance was 30 cm or less from the anal verge. In contrast, approximately 74% of all adenoma recurrences occurred in the proximal or both proximal and distal colorectum.

Adenoma Recurrence

Analysis of recurrent adenomas per unit time revealed a yearly rate of adenoma recurrence in the placebo group of 0.26 polyp per year and in the UDCA group of 0.23 polyp per year. The UDCA to placebo adenoma recurrence rate ratio was 0.88 (95% CI = 0.73 to 1.05; $P = .15$, based on a robust [Huber–White] variance estimator). Thus, UDCA treatment was associated with a non–statistically significant 12% reduction in the adenoma recurrence rate, compared with placebo treatment.

Analysis of the proportion of participants who had any recurrent adenoma from 6 months after randomization through the final follow-up colonoscopy showed that 43.9% of the participants in the placebo group experienced at least one recurrent adenoma, compared with 41.0% in the UDCA group ($P = .31$, Pearson chi-square test; OR = 0.89. 95% CI = 0.71 to 1.12, when the UDCA group was compared with the placebo group) (Table 2). Adjustment by age and sex produced similar results (adjusted OR = 0.89. 95% CI = 0.70 to 1.12). The risk ratio for adenoma recurrence comparing the UDCA group with the placebo group was 0.93 (95% CI = 0.82 to 1.07). Thus, UDCA treatment was associated with a non–statistically significant reduction in risk of adenoma recurrence, compared with placebo treatment.

Nineteen percent of participants in the placebo group and 16.2% in the UDCA group had a recurrent adenoma that met the definition of advanced (adjusted OR = 0.83, 95% CI = 0.61 to 1.11; Table 2). The risk ratio for advanced adenoma was 0.85 (95% CI = 0.66 to 1.09), when the UDCA group was compared with the placebo group, representing a non–statistically significant risk reduction. Furthermore, the Cochran–Mantel–Haenszel test comparing the UDCA group and the placebo group across the three ordered categories (no recurrence, nonadvanced recurrent adenoma, and advanced adenoma) gave a P value of .20 (Table 3).

A planned secondary endpoint analysis documented a statistically significant 39% reduction ($P = .03$) in the incidence of high-grade dysplasia comparing the placebo group (8.7%) with the UDCA treatment group (5.5%) (adjusted OR = 0.61, 95% CI = 0.39 to 0.96; Table 2). Outcomes for size, villous histology, and location of recurrent adenomas were not statistically significantly different between the UDCA group and the placebo group (Table 2). Colorectal adenocarcinomas were diagnosed in three participants in the placebo group and four in the UDCA group during the study ($P = 1.0$) by Fisher's exact test.

Table 1. Baseline characteristics by treatment group*

Variable	All randomized participants who started intervention (n = 1285)		Participants with one or more follow-up procedure(s) (n = 1192)	
	Placebo (n = 624)	UDCA (n = 661)	Placebo (n = 579)	UDCA (n = 613)
Demographics				
Mean age, y (SD)	66.4 (8.3)	66.1 (8.7)	66.5 (8.3)	66.0 (8.6)
Male, No. (%)	413 (66.2)	457 (69.1)	381 (65.8)	423 (69.0)
White, No. (%)	576 (92.3)	615 (93.0)	535 (92.4)	573 (93.5)
Married, No. (%)	510 (81.7)	547 (82.8)	471 (81.3)	509 (83.0)
Mean education, y (SD)	14.0 (2.3)	13.9 (2.2)	14 (2.3)	13.9 (2.3)
Clinic				
Phoenix, No. (%)	94 (15.1)	86 (13.0)	82 (14.2)	80 (13.1)
Mesa, No. (%)	170 (27.2)	183 (27.7)	161 (27.8)	174 (28.4)
Sun City, No. (%)	237 (38.0)	278 (42.1)	225 (38.9)	259 (42.3)
Tucson, No. (%)	123 (19.7)	114 (17.2)	111 (19.2)	100 (16.3)
Mean dietary intake (SD)				
Energy, kcal/day	1944.3 (775.6)	2039.7 (859.6)	1940.1 (761.4)	2043 (857.0)
Protein, g/day	72.4 (30.0)	74.3 (31.4)	72.0 (29.2)	74.4 (31.3)
Carbohydrates, g/day	269.1 (112.1)	287.4 (128.4)†	268.6 (111.7)	287.8 (128.3)†
Fiber [total dietary], g/day	21.3 (10.3)	22.4 (11.4)	21.2 (10.1)	22.4 (11.2)
Total lipid fat, g/day	64.2 (31.9)	66.7 (34.4)	64.0 (30.7)	66.8 (34.4)
Calcium, mg/day	962.1 (461.3)	980.0 (460.1)	959.2 (454.6)	982.8 (463.0)
Total calcium, mg/day	1207.2 (591.7)	1221.0 (578.5)	1206.4 (584.5)	1227.9 (581.6)
Alcohol, g/day	8.3 (14.2)	7.6 (13.4)	8.3 (14.3)	7.8 (13.6)
Nondietary factors				
Ever smoker, No. (%)	427 (68.4)	439 (66.4)	398 (68.7)	404 (65.9)
Current smoker, No. (%)	78 (12.5)	79 (12.0)	71 (12.3)	69 (11.3)
Mean BMI (SD)	27.5 (4.7)	27.3 (4.5)	27.5 (4.7)	27.3 (4.5)
Aspirin use,‡ No. (%)	166 (26.6)	188 (28.4)	161 (27.8)	170 (27.7)
Previous polyp,§ No. (%)	266/581 (45.8)	303/628 (48.2)	247/543 (45.5)	286/584 (49.0)
History of cancer,|| No. (%)	35 (5.6)	26 (3.9)	33 (5.7)	26 (4.2)
Family history of colorectal cancer,¶ No. (%)	181 (29.0)	168 (25.4)	171 (29.5)	156 (25.4)
Size of largest adenoma, mm [mean (SD); median]	8.8 (5.7); 8	8.8 (5.4); 8	8.9 (5.8); 8	8.8 (5.5); 8
No. of adenomas, mean (SD)	1.5 (0.8)	1.6 (1.0)	1.5 (0.8)	1.6 (1.0)
Proximal adenomas, No. (%)	219/622 (35.2)	221/660 (33.5)	201/578 (34.8)	203/612 (33.2)
Villous component to adenoma, No. (%)	124/624 (19.9)	139/659 (21.1)	115/579 (19.9)	132/611 (21.6)
High-grade dysplasia, No. (%)	56/528 (10.6)	57/567 (10.1)	52/493 (10.6)	53/525 (10.1)

*UDCA = ursodeoxycholic acid; SD = standard deviation; BMI = body mass index.

†$P = .02$, compared with placebo (two-sided Wilcoxon test).

‡Regular aspirin use (current or within last 30 days) at time of randomization.

§History of polyps before qualifying colonoscopy.

||History of any cancer more than 5 years before study entry.

¶History of colorectal cancer in a parent or sibling.

Bile Acid Concentrations in the Aqueous Phase of the Stool

Data were available on the concentration of bile acids in the aqueous phase of the stool from pooled 72-hour stool samples from the 552 study participants, 261 in the placebo group and 291 in the UDCA group. We found no statistically significant differences at baseline between the placebo and UDCA groups with respect to the concentrations of either DCA (placebo median DCA concentration = 114. 9 μg/mL; UDCA group median DCA concentration = 102.2 μg/mL, Wilcoxon–Mann–Whitney $P = .08$) or UDCA (placebo group median UDCA concentration = 0.0 μg/mL; UDCA group median UDCA concentration = 0.0 μg/mL; Mann–Whitney $P = .09$) in the aqueous phase of the stool. This absence of a difference at baseline is consistent with the balance expected as a result of randomization.

We observed a large increase in the median concentration of UDCA in the aqueous phase of the stool between the baseline and endpoint 72-hour stool samples obtained from the UDCA group (median increase = 17.6 μg/mL) but not from the placebo group. This expected increase in the median concentration of UDCA in the aqueous phase of the stool during the study in the UDCA group was statistically significantly different from that in the placebo group (Wilcoxon–Mann–Whitney $P<.001$). The median ratio of DCA to total bile acids in the endpoint stool samples was statistically significantly lower in the UDCA group (median ratio = 0.33) than in the placebo group (median ratio = 0.51) (Wilcoxon–Mann–Whitney $P<.001$), and the median ratio of UDCA to total bile acids in the endpoint stool samples was statistically significantly higher in the UDCA group (median ratio = 0.10) than in the placebo group (median ratio = 0.0) (Wilcoxon–Mann–Whitney $P<.001$). These results indicate that treatment with UDCA decreased the relative concentration of DCA in the colon, compared with treatment with placebo.

Adverse Events

The rates of death and other adverse events experienced by the 1285 randomly assigned participants who received any

Table 2. Risk of adenoma recurrence*

	No. with recurrence/total No. (%)	OR (95% CI)	Adjusted† OR (95% CI)
Any adenoma			
Placebo	254/579 (43.9)	1.00 (referent)	1.00 (referent)
UDCA	251/613 (41.0)	0.89 (0.71 to 1.12)	0.89 (0.70 to 1.12)
High-grade dysplasia			
Placebo	50/574 (8.7)	1.00 (referent)	1.00 (referent)
UDCA	33/603 (5.5)‡	0.61 (0.38 to 0.96)	0.61 (0.39 to 0.96)
Any large adenoma§			
Placebo	60/579 (10.4)	1.00 (referent)	1.00 (referent)
UDCA	54/613 (8.8)	0.84 (0.57 to 1.23)	0.84 (0.57 to 1.23)
Any villous histology‖			
Placebo	42/574 (7.3)	1.00 (referent)	1.00 (referent)
UDCA	46/607 (7.6)	1.04 (0.67 to 1.60)	1.05 (0.68 to 1.62)
Advanced lesion¶			
Placebo	110/579 (19.0)	1.00 (referent)	1.00 (referent)
UDCA	99/613 (16.2)	0.82 (0.61 to 1.11)	0.83 (0.61 to 1.11)
Proximal location of adenoma#			
Placebo	121/578 (20.9)	1.00 (referent)	1.00 (referent)
UDCA	110/610 (18.0)	0.83 (0.62 to 1.11)	0.83 (0.63 to 1.11)

*OR = odds ratio; CI = confidence interval; UDCA = ursodeoxycholic acid.
†Adjusted for age and sex.
‡P = .03, compared with placebo (two-sided Pearson chi-square statistic).
§Large adenoma denotes lesions of 10 mm or more in diameter.
‖Any villous denotes presence of tubulovillous or villous lesions.
¶Advanced adenoma includes diameter of 10 mm or more, high-grade dysplasia, tubulovillous or villous histology, or carcinoma.
#Denotes the presence of only proximal adenoma(s).

intervention during the phase III trial are shown in Table 4. Ten deaths (1.60%) were reported in the placebo group, and six deaths (0.9%) were reported in the UDCA group. Forty-five (7.21%) cancers, excluding colorectal cancer, were reported in the placebo group, and 40 (6.05%) cancers were reported in the UDCA group. Similar numbers of participants in both groups had cardiovascular disease, cerebrovascular accidents, or other severe adverse events. A borderline statistically significant difference in the rate of hospitalizations related to gastrointestinal events, however, was found between the placebo group (3.85%) and the UDCA group (6.20%) (P = .06, Fisher's exact test) (Table 4). The incidence of all grades of diarrhea was statistically significantly greater in the UDCA group (69 participants, 10.44%) than in the placebo group (40 participants, 6.41%) (P = .01, Fisher's exact test). No difference in the incidence of nausea, vomiting, or abdominal pain was observed between the two groups.

Discussion

In this randomized, double-blind, placebo-controlled phase III trial, we did not detect a statistically significant difference in the overall rate of recurrence of sporadic colorectal adenomas associated with the oral treatment with UDCA, compared with placebo. Analysis of the 1192 participants who had at least one follow-up colonoscopy after baseline revealed a non–statistically significant (P = .15) 12% reduction in the adenoma recurrence rate associated with UDCA intervention (rate ratio = 0.88, 95% CI = 0.73 to 1.05). There was, however, a statistically significant (P = .03) UDCA-related reduction in recurrence of adenomas with high-grade dysplasia (adjusted OR = 0.61, 95% CI = 0.39 to 0.96). Because severely dysplastic lesions have a greater potential for progression to invasive colorectal carcinoma than lesions with less dysplasia, this finding warrants further investigation in future chemoprevention trials of UDCA in this population.

Table 3. Presence of advanced colorectal adenoma by treatment group*

Treatment Group	No recurrence	Nonadvanced adenoma only	Advanced adenoma
Placebo, No. (%)	325 (56.1)	144 (24.9)	110 (19.0)
UDCA, No. (%)	362 (59.1)	152 (24.8)	99 (16.2)

*Cochran–Mantel–Haenszel test (two-sided) across ordered categories: chi square = 1.68; P = .20. UDCA = ursodeoxycholic acid.

Table 4. Serious adverse events and gastrointestinal toxicity for all randomly assigned participants that started treatment by treatment group*

	Placebo (n = 624)	Ursodeoxycholic acid (n = 661)
Deaths, No. (%)	10 (1.60)	6 (0.91)
Serious adverse events*, No. (%)		
All cancers (except colon), No. (%)	45 (7.21)	40 (6.05)
Cardiovascular disease, No. (%)	65 (10.42)	62 (9.38)
Stroke, No. (%)	8 (1.28)	8 (1.21)
GI hospitalization,† No. (%)	24 (3.85)	41 (6.20)
Other serious adverse events, No. (%)	162 (25.96)	181 (27.38)
Gastrointestinal toxicities considered study related*		
Diarrhea,‡ No. (%)	40 (6.41)	69 (10.44)
Lower abdominal pain, No. (%)	25 (4.01)	36 (5.45)
Nausea, No. (%)	15 (2.4)	21 (3.18)
Upper abdominal pain, No. (%)	17 (2.72)	14 (2.12)
Vomiting, No. (%)	2 (0.32)	7 (1.06)

*Some subjects had more than one adverse event. GI = gastrointestinal.
†P = .06 (two-sided Fisher's exact test).
‡P = .01 (two-sided Fisher's exact test).

The observation that UDCA appears to suppress colonic mucosal dysplasia in individuals with a history of adenomatous polyps also warrants further investigation because it may provide a link with reports of chemopreventive benefits from UDCA in patients with ulcerative colitis *(24,26)*, which is an established risk factor for colorectal cancer *(32,33)*. Although a consensus has not been reached as to a uniform approach to management of patients with ulcerative colitis who are at risk for developing colorectal cancer, the diagnosis and grade of dysplasia are key to the assessment of this risk *(34)*. Both studies *(24,26)* in patients with ulcerative colitis reported that UDCA treatment was statistically significantly associated with a reduced risk for developing colonic mucosal dysplasia, compared with nontreatment. Potential mechanisms for this effect include modulations of the changes in protein kinase C isoforms induced by carcinogens *(23,35)* and changes in arachidonic acid metabolism *(36)*.

A recent study of the APC-mutant Min mouse model for familial polyposis coli found that UDCA treatment decreased tumors throughout the entire intestine in a dose-dependent fashion, compared with control treatment *(37)*. Combined treatment with UDCA plus sulindac, an inhibitor of cyclooxygenase 1 and -2 that is active in the treatment of familial polyposis coli, was more effective than either agent alone for the prevention of tumors throughout the entire intestine *(37)*. Thus, UDCA may be a useful agent to manage patients with this rare genetic disorder familial polyposis coli.

The non–statistically significant results of this large phase III trial related to overall recurrence were unexpected, because a preclinical study in rats demonstrated that UDCA inhibits the formation of azoxymethane-induced colorectal tumors and cancers *(21)* and because UDCA treatment appeared to be associated with a decrease in the incidence of colorectal neoplasia in patients with primary biliary cirrhosis *(25)*, a reduced prevalence of colorectal neoplasia in patients with primary sclerosing cholangitis *(24)*, and the eradication of severe colonic mucosal dysplasia in patients with ulcerative colitis *(24,26)*.

This study had several limitations. Possible explanations for the overall relatively low level of chemopreventive activity against sporadic colorectal adenoma recurrence shown by UDCA in this study may be related to inherent limitations of adenoma recurrence studies, which include inadequate dose or treatment duration *(38)*. For example, Pardi et al. *(26)* reported that consumption of a daily UDCA dose of 13–15 mg/kg of body weight for as long as 12 years was associated with a statistically significant reduction in colorectal neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis and that the chemopreventive effects of UDCA began to emerge only after 6 years of the intervention. Consequently, colorectal adenoma phase III trials may require new design considerations, including substantially longer interventions, possibly 6–10 years. Such studies will be extremely difficult to accomplish because of their large size, difficulties with long-term participant adherence, and extremely high expense. In addition to the increased duration of UDCA exposure that may be required to obtain a chemopreventive benefit, the secondary endpoints from our phase III trial indicate that future clinical studies of UDCA should focus on the recurrence of adenomas in participants with resected, highly dysplastic adenomas.

The fact that treatment with UDCA caused an overall reduction in the recurrence of highly dysplastic colorectal adenomas but did not affect the recurrence of lower-risk adenomas indicates that UDCA may work at a later point in colorectal carcinogenesis (i.e., at the point of high-grade dysplastic change in colorectal mucosa) than calcium carbonate or acetylsalicylic acid, both of which have proven effective in lowering the risk of adenoma recurrence in patients with a history of sporadic colorectal adenomas *(39,40)*.

The results of multiple smaller trials have documented UDCA's activity against markers of colonic neoplasia in patients with ulcerative colitis and its activity against severe dysplasia in patients with primary sclerosing cholangitis and patients with primary biliary cirrhosis. From previous findings and the results of this phase III trial evaluating the effects of UDCA treatment for 3 years on development of high-grade dysplastic, recurrent, sporadic adenomas, we propose that longer-term use of UDCA (e.g., >5 years) should continue to be evaluated for its role in the prevention of high-grade dysplasia in patients who are at high risk of experiencing the recurrence of highly dysplastic adenomas.

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Notes

Members of the Phoenix and Tucson Gastroenterologist Networks are Howard Abrams, MD, Michael Altman, MD, Robert Armbruster, MD, Karen Bader, MD, Sharad Bellapravalu, MD, Paul Berggreen, MD, Lawrence Bettinger, MD, Mike Bischof, MD, Scott Blinkoff, MD, Stephen Brown, MD, George Burdick, MD, Marc Caminker, MD, D.S. Cho, MD, Andrew Collins, MD, Edward Cooper, MD, James Dinning, MD, David Drewitz, MD, David Earnest, MD, Ronnie Fass, MD, Jeffrey Fein, MD, P. Gregory Foutch, DO, Denis Frank, MD, Jay Frankel, MD, Mitchell Giangobbe, MD, Stephen Glouberman, MD, Marc Goldblatt, MD,Gary Goldstein, MD, Andrew Grade, MD, Mark Gulinson, MD, John Hanigsberg, MD, John Harlan, MD, James Herde, MD, Mark Hoefer, MD, Vincent Honan, MD, P. Bryan Hudson, MD, Jose Hurtado, MD, Philip Jaffe, MD, David Johnson, MD, Richard Jonas, MD, Vance Julian, MD, Steven Kanner, MD, Carl Kanun, MD, Fredrick Kenny, MD, George Kerrihard, MD, James Klein, MD, Frederick Kogan, MD, Edmund Krasinski, MD, Robert E . Kravetz, MD, Prem Kumar, MD, David Larson, MD, Paul Laven, MD, David Leff, MD, Edmund Leff, MD, Brendan Levy, MD, Gregory Lewis, MD, Franklin Lewkowitz, MD, Barbara MacCollum, MD, Steven McIntosh, MD, Daniel McIntosh, MD, John McNernery, Jr., MD, Daniel Meline, MD, Jay Mellen, MD, Arnold Merin, MD, Joan Mitrius, MD, Raymond Moldow, MD, Gary Monash, MD, Thomas G. Morales, MD, Thomas Morales, MD, Sam Moussa, MD, Rebecca Natrajan, MD, Jagdish Patel, MD, Doug Peterson, MD, John Phelps, MD, Debra Polson, MD, Paravastha Ramanujam, MD, Francisco Ramirez, MD, Rawel Randhawa, MD, Steven Reeder, MD, Leon Rigberg, MD, Michael Rock, MD, David Saltzman, MD, Richard Sampliner, MD, Charles Sanner, MD, Victor E. Sartor, MD, Robert Sawyer, MD, Michael Schwimmer, MD, Prateek Sharma, MD, Masud Shaukat, MD, James Shaver, MD, Arthur Shiff, MD, Roger Siddoway, MD, Sylvain Sidi, MD, James Singer, MD, Craig Stein, MD, K.S. Venkatesh, MD, Darrell Wadas, MD, George Walker, MD, David Winston, MD, Michael Yanish, MD, Michele Young, MD, and J. Alan Ziegler, MD.

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