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Efficacy and Safety of Curcumin in Treatment of Intestinal Adenomas in Patients With Familial Adenomatous Polyposis

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BACKGROUND & AIMS: Familial adenomatous polyposis is an autosomal dominant disorder characterized by the development of hundreds of colorectal adenomas and eventually colorectal cancer. Oral administration of the spice curcumin has been followed by regression of polyps in patients with this disorder. We performed a double-blinded randomized trial to determine the safety and efficacy of curcumin in patients with familial adenomatous polyposis. **METHODS:** This study included 44 patients with familial adenomatous polyposis (18–85 years old) who had not undergone colectomy or had undergone colectomy with ileorectal anastomosis or ileal anal pouches, had at least 5 intestinal adenomatous polyps, and had enrolled in Puerto Rico or the United States from September 2011 through November 2016. Patients were randomly assigned (1:1) to groups given 100% pure curcumin (1,500 mg orally, twice per day) or identical-appearing placebo capsules for 12 months. The number and size of lower gastrointestinal tract polyps were evaluated every 4 months for 1 year. The primary outcome was the number of polyps in the curcumin and placebo groups at 12 months or at the time of withdrawal from the study according to the intention-to-treat principle. **RESULTS:** After 1 year of treatment, the average rate of compliance was 83% in the curcumin group and 91% in the placebo group. After 12 weeks, there was no significant difference in the mean number of polyps between the placebo group (18.6; 95% CI, 9.3–27.8) and the curcumin group (22.6; 95% CI, 12.1–33.1; $P = .58$). We found no significant difference in mean polyp size between the curcumin group (2.3 mm; 95% CI, 1.8–2.8) and the placebo group (2.1 mm; 95% CI, 1.5–2.7; $P = .76$). Adverse events were few, with no significant differences between groups. **CONCLUSIONS:** In a double-blinded randomized trial of patients with familial adenomatous polyposis, we found no difference in the mean number or size of lower intestinal tract adenomas between patients given curcumin 3,000 mg/day and those given placebo for 12 weeks. Clinicaltrials.gov ID NCT00641147.

Keywords: Familial Adenomatous Polyposis; Herbal; Cancer Prevention; Turmeric.

Familial adenomatous polyposis (FAP) is an autosomal dominant condition characterized by the development of hundreds of colorectal adenomas in teenagers and young adults.[1,2] This condition is caused by a germline alteration in the *APC* gene on the long arm of chromosome 5.[3–6] Almost all patients with FAP will have colorectal cancer by the fifth decade of life if prophylactic colectomy is not performed.[1]

The regression of intestinal adenomas in patients with FAP occurs with the use of some nonsteroidal anti-inflammatory drugs (NSAIDs), including sulindac and celecoxib.[7] However, these compounds have different side effects that can limit their long- term use.[7]

Curcumin is the major yellow pigment extracted from turmeric, the powdered root of the herb *Curcuma longa*. This compound has long been used as a spice in Asia and is considered a safe food additive.[8] Curcumin is a naturally occurring polyphenol composite with antioxidant and anti-inflammatory biological effects and can regulate numerous intracellular targets that control tumor progression.[8] The regression of intestinal adenomas in 5 patients with FAP was reported with the use of curcumin in combination with homeopathic doses of quercetin.[9] However, no controlled trial of curcumin to decrease intestinal adenomas in patients has been reported.

Methods

Study Population

The study was conducted from September 2011 to November 2016 at the Johns Hopkins Hospital and the University of Puerto Rico Medical Sciences Campus. The trial is registered at clinicaltrials.gov (NCT00641147).

Abbreviations used in this paper: **FAP, familial adenomatous polyposis; NSAID, nonsteroidal anti-inflammatory drug.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Oral administration of curcumin in a pilot study caused regression of colorectal adenomas in familial adenomatous polyposis (FAP) patients.

NEW FINDINGS

Curcumin was well tolerated, but no difference was noted in the number and size of intestinal adenomas in patients taking curcumin compared to those on placebo at 1 year.

LIMITATIONS

This study used pure curcumin without additives which enhance absorption.

IMPACT

The results do not support the use of pure curcumin at a dose of 3000 mg/day for regression of intestinal polyps in FAP patients.

Participants were identified and recruited from the Johns Hopkins Polyposis Registry or from the University of Puerto Rico Familial Colorectal Cancer Registry. Written informed consent was obtained from all participants. The protocol was approved by institutional review boards of the Johns Hopkins Hospital and the University of Puerto Rico Medical Sciences Campus.

Patients with FAP 18–85 years old who had not undergone colectomy or had undergone colectomy with ileorectal anastomosis or ileal anal pouches and had at least 5 intestinal adenomatous polyps were eligible for the study. The following were the reasons for exclusion from the study: absence of effective birth control (in women of childbearing age); pregnancy; a white blood cell count lower than 3,500/mL; platelet count lower than 100,000/mL; serum urea nitrogen level higher than 25 mg/dL (8.9 mmol/L) or serum creatinine concentration higher than 1.5 mg/dL (132.6 μmol/L); malignancy; unwillingness to discontinue NSAIDs; active gastroesophageal reflux; history of peptic ulcer; active bacterial infection; use of warfarin or antiplatelet agents; or allergy to curcumin. There was a 3-month washout period for individuals taking NSAIDs, curcumin, turmeric, aspirin, calcium supplements, vitamin D, green tea, or polyphenol E supplements.

Study Design

The participants were entered into a double-blinded placebo-controlled trial. Participants, care providers, and data analysists were blinded. Participants were randomly assigned to receive 100% pure curcumin in 3 500-mg capsules or identical-appearing placebo capsules orally 2 times a day for 12 months in consecutively numbered bottles. After the investigator had obtained consent from the participants, the research nurse contacted the independent study pharmacist. Then, the study pharmacist dispensed the curcumin or placebo capsules according to a computer-generated randomization list with a 1:1 allocation using randomization block sizes of 4.2.4. The curcumin and placebo were generously supplied by the National Cancer Institute. Compliance with treatment was assessed by pill counts and telephone calls.

Lower intestinal adenomatous polyps were assessed by flexible video sigmoidoscopy. Two investigators (MC-C and FMG), who did not review the records of previous examinations, performed all assessments. Evaluations were performed before treatment with curcumin or placebo was begun (month 0) and every 4 months after treatment was initiated for a total of 12 months. At each examination, the endoscopist counted the total number of polyps in the circumference of the colorectum from 20 cm to the anal verge or in the entirety of the ileal pouch, and the examination was recorded on videotape. The diameter of up to 5 polyps just distal to 20 cm was measured in millimeters with a graduated scale passed through the biopsy channel of the sigmoidoscope. These measurements were averaged to determine the mean polyp size of each participant. There were no changes to the methods after the trial commenced.

Evaluation of Safety

Adverse events were monitored by telephone every 2–4 weeks and at each 4-month visit. A complete blood cell count was obtained and levels of glucose, serum urea nitrogen, serum creatinine, serum electrolytes, and bilirubin were measured at 0, 4, and 12 months. Adverse events were graded in accordance with the Common Toxicity Criteria of the National Cancer Institute.[10] On this scale, a score of 0 indicates no adverse event and a score of 5 indicates a fatal event.

Statistical Analysis

The primary outcome variable was the number of polyps in the curcumin and placebo groups at 12 months or at the time of withdrawal from the study according to the intention-to-treat principle. The primary analysis was a 2-sample t test comparing the final mean polyp numbers in the 2 arms of the study. Analysis of covariance was used to confirm the primary treatment arm comparison by adjusting for baseline polyp number. Final polyp size was similarly analyzed with a 2-sample t test followed by analysis of covariance.

Adverse events and increases in polyp burden were compared between study arms with Fisher exact or χ^2 tests.

The correlation between pre- and post-treatment polyp number was assessed with the Pearson correlation coefficient. All P values reported are 2-sided. The sample size was calculated to provide the study with 80% power to detect a difference of 1 SD in the number of polyps between groups using a 2-sided α value of 0.05 level by t test. There were no changes to the trial outcomes after the trial commenced. All authors had access to the study data and reviewed and approved the final report.

Results

Demographic Characteristics

Sixty-two individuals were assessed for eligibility. Of these, 10 individuals did not meet the inclusion criteria and 8 declined to participate.

Forty-four eligible participants were randomly assigned to 1 of the 2 treatment groups. Twenty-one patients received curcumin and 23 received placebo. There were no

Table 1. Demographic Characteristics of Study Participants According to Treatment Group

Characteristic	Curcumin (n = 21)	Placebo (n = 23)
Age (*y*)	44.5 ± 15.4	38.7 ± 15.0
Sex, n (%)		
Male	7 (33)	9 (39)
Female	14 (67)	14 (61)
Race, n (%)		
White	10 (48)	11 (48)
Hispanic	11 (52)	11 (48)
Black	0 (0)	1 (4)
Institution, n (%)		
Site 1 (JHH)	11 (52)	12 (52)
Site 2 (PR)	10 (48)	11 (48)
Surgical status, n (%)		
Intact	3 (14)	4 (17)
Rectum (IRA)	6 (29)	12 (52)
Pouch (IAP)	12 (57)	7 (31)
Baseline number of polyps	23.3 ± 19.7	18.7 ± 13.1
Baseline size of polyps (*mm*)	3.1 ± 1.7	2.3 ± 0.6

IAP, procto-colectomy with ileoanal pull through; IRA, colectomy with ileorectal anastomosis; JHH, Johns Hopkins Hospital; PR, University of Puerto Rico Medical Sciences Campus.

significant differences in demographic characteristics between the 2 groups (Table 1). At 12 months (end of intervention trial), 6 participants in the curcumin group and 4 in the placebo group had been withdrawn. In the curcumin arm, 1 participant apiece was withdrawn for development of pruritus, desmoid tumor, diagnosis of thyroid cancer, noncompliance, having their colon removed prophylactically, and increasing polyp number and size. In the placebo arm, 1 participant apiece was withdrawn for increasing polyp number and referral to surgery, inability to make visits, thyroid cancer, and personal reasons.

Compliance and Adverse Events

The median rate of compliance (proportion of total prescribed doses taken by a given participant) with treatment was 83% (lower quartile, 70; upper quartile, 94) among participants in the curcumin group and 91% (lower quartile, 78; upper quartile, 96) among those in the placebo group.

Treatment with curcumin for 12 months was well tolerated (Table 2). Few adverse events were reported, and the incidence of adverse events did not differ significantly between the curcumin and placebo groups. No perturbations of laboratory tests (complete blood cell count, glucose, serum urea nitrogen, serum creatinine, serum electrolytes, and bilirubin) were assessed to be related to the study agent. Six grade 2 or greater adverse events occurred in 4 participants taking curcumin and all were assessed as unrelated to the study agent. One participant developed grade 1 pruritus with curcumin; this was the only adverse event evaluated as likely related to curcumin, and the participant was promptly withdrawn from the protocol.

Table 2. Incidence and Severity of Adverse Events[a]

Event	Curcumin (n = 21), n (%)	Placebo (n = 23), n (%)
Abdominal pain	3 (14)[b]	3 (13)
Diarrhea	2 (10)	2 (9)
Pruritus	1 (5)[c]	0
Thyroid cancer	1 (5)	1 (4)
Nausea	0	2 (8)
Headache	0	1 (4)
Sinusitis	0	1 (4)
Cellulitis	0	1 (4)
Herpes zoster	0	1 (4)
Facial abscess	1 (5)[d]	0
Upper respiratory infection	1 (5)	0
Influenza	0	1 (4)
Urinary tract infection	1 (5)	0
Chikungunya virus	0	1 (4)[d]
Back strain	1 (5)[d]	0
Plantar fasciitis	0	1 (4)
Torn ligament	0	1 (4)
Gout	1 (5)	0
Depression	0	1 (4)[d]
Back spasms	0	1 (4)
Earache	1 (5)	0
Vomiting	0	1 (4)

[a]Adverse events were grade 1 (mild) unless specified otherwise.
[b]One participant had 3 separate episodes of abdominal pain from appendicitis (grade 3), cholecystitis (grade 2), and ovarian cyst (grade 2) and 1 participant had grade 3 abdominal pain from desmoid tumor. All events were assessed as unrelated to curcumin.
[c]Grade 1 pruritus in 1 participant was assessed as likely related to curcumin.
[d]Grade 3 events were assessed as unrelated to curcumin.

Efficacy

At the end of treatment, there was no significant difference in the mean number of polyps between the placebo group (18.6; 95% CI, 9.3–27.8) and the curcumin group (22.6; 95% CI, 12.1–33.1; $P = .58$; Figure 1). Adjusting for baseline polyp number with analysis of covariance provided a similar result. Also, the change in polyp number and percentage of change of polyp number from baseline were not significantly different between the treatment arms ($P = .85$ and $P = .61$, respectively; Table 3).

At the end of treatment, there was no significant difference in polyp size between the curcumin group (2.3 mm; 95% CI, 1.8–2.8) and the placebo group (2.1 mm; 95% CI, 1.5–2.7; $P = .76$; Figure 1). A videotaped evaluation at 12 months showed no significant difference in decrease in polyp burden between the treatment arms ($P = .85$).

No significance difference was noted between the treatment arms for the primary and secondary outcome variables when a per-protocol analysis was conducted, with adjustment for study site, compliance, or surgical type, or when nonparametric analysis was performed using Wilcoxon tests.

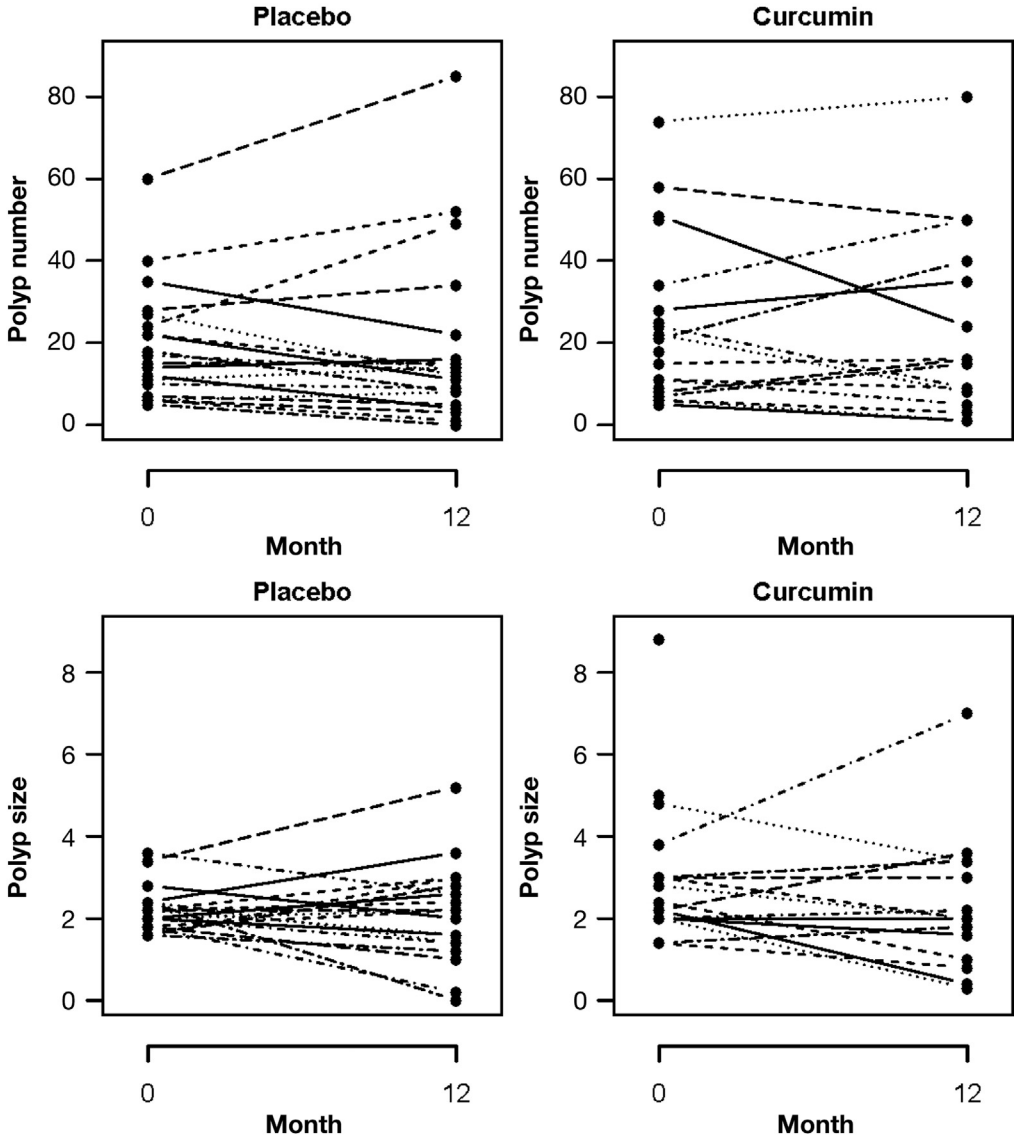

Figure 1. Polyp number and size at 0 and 12 months in the placebo and curcumin groups.

Discussion

Prevention or delay in the development of lower and upper tract adenomas with long-term administration of a chemopreventive agent would be a significant therapeutic advance in the management of patients with FAP. Such a discovery could be extrapolated to chemoprevention of sporadic and other hereditary forms of colorectal cancer. Regression of intestinal adenomas in patients with FAP has been demonstrated with several NSAIDs and in combination with erlotinib,[11] but the side effects of these agents limit prolonged use.[7] Curcumin, a naturally occurring polyphenol compound used as a food spice, is viewed as a potential cancer chemopreventive agent because of its effect on multiple tumor progression pathways. Moreover, the limited oral bioavailability of curcumin results in only case reports of side effects,

Table 3. Polyp number: Final, Mean Change From Baseline, and Percentage of Change From Baseline Between the Placebo and Curcumin Treatment Groups

Polyp number	Placebo	Curcumin	Mean difference	95% CI	*P* value[a]
Final polyp number	18.57	22.62	−4.05	−18.76 to 10.66	.58
Change in polyp number from baseline	−0.48	−1.19	0.71	−6.98 to 8.40	.85
Percentage of change in polyp number from baseline	−15.46	−5.46	−10.00	−49.98 to 29.98	.61

[a]By *t* test.

and yet this agent could be efficacious through luminal activity.

In this randomized, double-blinded, placebo-controlled study using oral pure curcumin 3 g/day, few adverse events occurred. Only 1 participant with pruritus had an adverse event attributable to the study agent. However, patients with FAP in this protocol did not have regression of lower intestinal adenomas. No difference was seen in adenoma regression between the treatment arms with intention-to-treat analyses or per-protocol analyses adjusting for institution, compliance, or surgical status. Of note, there were no significant differences in baseline characteristics between the curcumin and placebo groups.

There are several potential reasons for the lack of efficacy of curcumin in this trial. First, compliance with the study agent could have limited efficacy. However, the curcumin group took 83% of the scheduled doses and the analysis was adjusted for compliance. Second, participants in the curcumin group had statistically nonsignificant differences in surgical status and ethnic background, but analysis showed no benefit of curcumin to any subgroup. Third, there was a small sample at the 12-month time point and the negative results could be explained in light of the power with which the study could identify a positive result. However, there were no statistically significant differences in the primary outcome variable at earlier study time points.

Fourth, a lack of sufficient curcumin dosing in this trial could be a principal factor resulting in the lack of regression of adenomas. The participants in this study were deliberately administered 100% pure curcumin. The intention of the protocol was to test the ability of this agent alone to regress adenomas. In the previous pilot investigation that showed polyp regression, patients took half the dose of curcumin but in a formulation that contained piperine. Piperine, a component of black pepper, is a known inhibitor of hepatic glucuronidation that increases the absorption of curcumin in humans by 2,000% and is reported to promote detectable serum concentrations at curcumin doses of 2 g/day.[12]

Of note, a recent study reported that patients with FAP harbor colonic biofilms containing tumorigenic bacteria.[13] In a murine model, bacteria from these biofilms increased DNA damage in colonic epithelium and promoted faster tumor onset. One potential mechanism of curcumin chemoprevention could be directly altering the colonic microbiome. In mice, curcumin can increase bacterial richness, expand native lactobacilli, and decrease members of the order Coriobacteriales. Similarly, bifidobacteria are increased and appear to decrease aberrant crypt foci in models of murine colorectal carcinogenesis.[14] Curcumin also might affect colonic bile acids, compounds associated with tumor-promoting activity as evidenced in experimental studies in rodents and human epidemiologic data. Turmeric, of which curcumin is a component, can alter bile acid secretion and de-conjugation through interplay with the microbiome.[15] The interaction of chemopreventive agents with the microbiome is likely an important area of future research.

In summary, our results do not provide support for the use of pure curcumin at an oral dose of 3,000 mg/day for regression of intestinal adenomas in patients with FAP.

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