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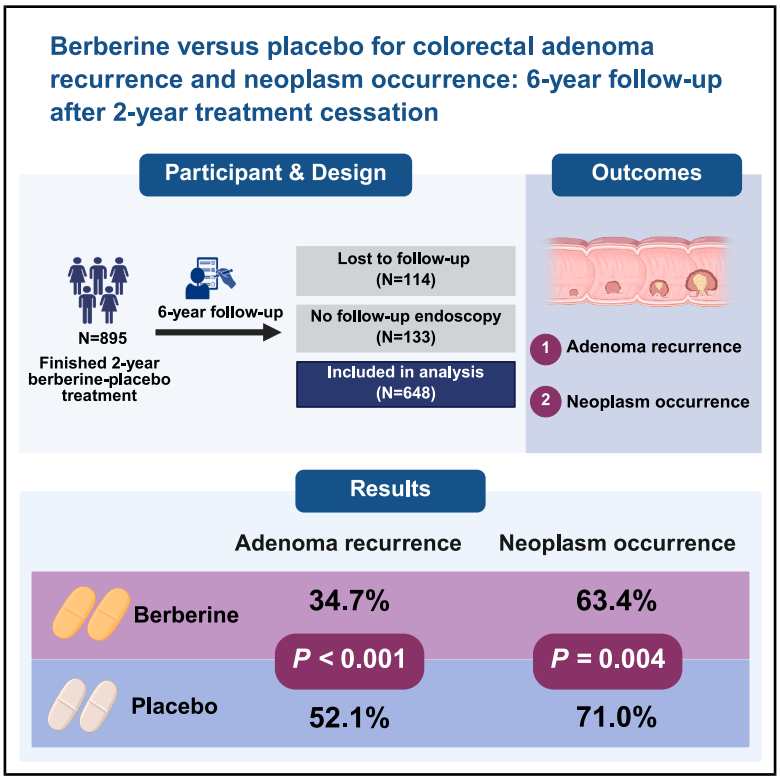
Berberine for preventing colorectal adenoma recurrence and neoplasm occurrence: 6-Year follow-up of a randomized clinical trial

Graphical abstract



Highlights

- Berberine prevents adenoma recurrence in the 6-year post-treatment follow-up period
- Berberine can also reduce colorectal neoplasm and non-advanced adenoma occurrence
- Berberine emerges as a promising candidate for chemoprevention after polypectomy

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In brief

Tan et al. demonstrate that berberine has the potential to serve as a long-term chemopreventive agent against colorectal adenoma recurrence and neoplasm occurrence after polypectomy. During the median 6-year follow-up period after treatment cessation, the adenoma recurrence rate in the berberine group is 34.7% versus 52.1% in the placebo group.

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Berberine for preventing colorectal adenoma recurrence and neoplasm occurrence: 6-Year follow-up of a randomized clinical trial

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SUMMARY

Berberine has been reported as a safe and effective pharmacological agent to reduce colorectal adenoma recurrence after polypectomy. This retrospective cohort study is an extended follow-up of a previous clinical trial (NCT02226185) during the post-treatment observational phase. We aim to evaluate the long-term protective effects of berberine on adenoma recurrence. Among 895 patients who finished the previous 2-year randomized trial, we recruited 781 patients at 7 clinical centers across 6 provinces in China. The primary outcome is adenoma recurrence. Between December 29, 2018, and October 10, 2024, 648 patients underwent at least one colonoscopy during the follow-up. The protective effects of berberine persist for at least 6 years after treatment cessation, with lower adenoma recurrence rate (34.7% vs. 52.1%) and lower neoplasm occurrence rate (63.4% vs. 71.0%). Berberine may serve as a potential long-term preventive agent against adenoma recurrence after polypectomy.

INTRODUCTION

As the precursor of colorectal cancer, colorectal adenoma demonstrates a high recurrence rate after endoscopic resection.[1,2] Recurrent colorectal adenomas can increase the incidence of colorectal cancer due to genetic alterations over at least 10 years.[3] Chemopreventive interventions have demonstrated efficacy in lowering colorectal adenoma recurrence, and several relevant pharmacological agents and nutritional supplements have been discovered: folic acid,[4] aspirin,[5] celecoxib,[6] calcium,[7,8] and vitamin D.[9,10] However, some of these agents and supplements lack long-term follow-up data, or their use has been restricted for potential side effects. Traditional medicine has been playing an increasingly crucial role in cancer chemoprevention.[11–13] Berberine (molecular formula: $C_{20}H_{18}NO_4$), isolated from the Chinese herb *Coptis chinensis*, has been used to treat diarrhea and enteritis for centuries in China.[14,15] Recent animal studies have reported that berberine can inhibit colorectal tumorigenesis pathways and affect the tumor microenvironment by altering microbiota composition, making it a potential chemopreventive agent for colorectal cancer.[16–18]

Our previous randomized clinical trial was named Chemoprevention of Berberine in Adenoma Recurrence (CBAR) (NCT 02226185)[19] for convenience in this study. The CBAR trial used a double-blind, randomized, placebo-controlled, and multicenter design to evaluate the chemopreventive effects of berberine against colorectal adenoma recurrence. Over the 2-year randomized trial, the recurrence rates of colorectal adenoma and any kind of polypoid lesion remained significantly lower without serious adverse events in the berberine group than in the placebo group (36% vs. 47%, respectively; relative risk [RR], 0.77; 95% confidence interval [CI]: 0.66–0.91; p = 0.001; and 43% vs. 55%, respectively; RR, 0.77; 95% CI: 0.67–0.89; p = 0.0002). These findings indicated the clinical applicability of berberine for preventing recurrent colorectal adenoma.

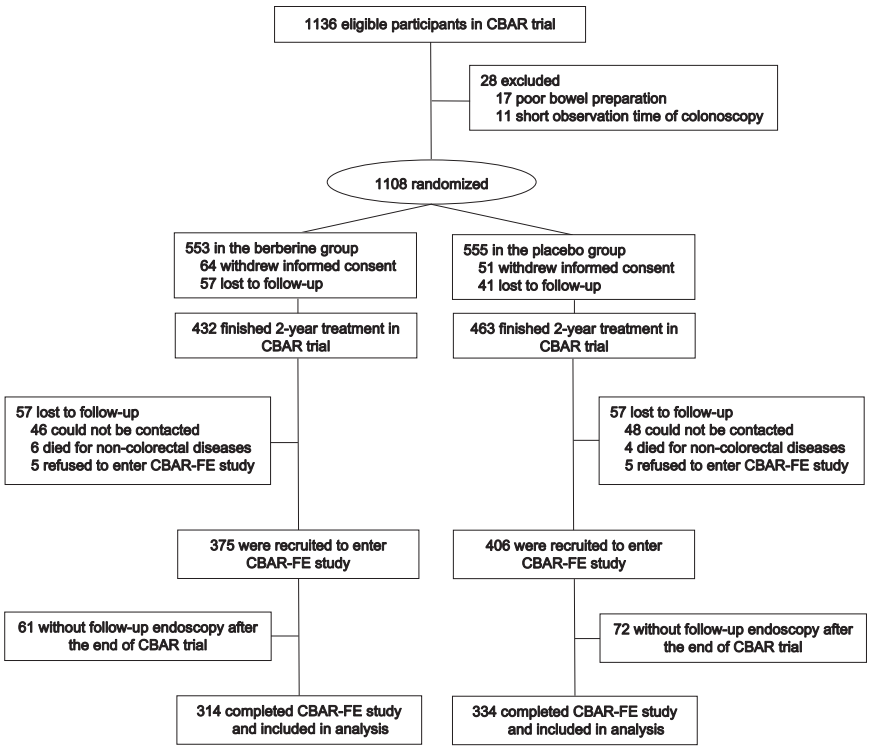


Figure 1. Flowchart of participants in the CBAR trial and CBAR-FE study

After the end of the 2-year randomized CBAR trial, we conducted the current retrospective study, named CBAR Follow-up Extension (CBAR-FE) study; here, we extended the CBAR trial by continuing to follow up with the trial participants over a median of 6 years. We aimed to assess the long-term prevention of berberine on colorectal adenoma recurrence after polypectomy without continued supplementation.

RESULTS

Baseline characteristics of participants

Of the 1,136 participants who entered the CBAR trial, 895 finally completed the 2-year randomized trial (432 in the berberine group and 463 in the placebo group) (Figure 1). In total, 5 (1.2%) patients in the berberine group and 5 (1.1%) in the placebo group refused to participate in the CBAR-FE study. Moreover, 6 (1.4%) patients in the berberine group and 4 (0.9%) in the placebo group died, whereas 46 (10.6%) in the berberine group and 48 (10.4%) in the placebo group could not be contacted. Of all 781 participants who entered the CBAR-FE study, 314 (83.7%) in the berberine group and 334 (82.3%) in the placebo group received at least one follow-up colonoscopy after the CBAR trial and therefore were included in the analysis. The baseline demographic characteristics and colorectal adenoma risk factors were well matched between the two groups (Table 1).

Primary outcome

After a median follow-up of 78.0 (interquartile range [IQR]: 73.0–85.0) months, 34.7% (109/314) of patients in the berberine group and 52.1% (174/334) of patients in the placebo group demonstrated colorectal adenoma recurrence in any follow-up colonoscopy (adjusted hazard ratio [HR], 0.58; 95% CI: 0.45–0.74; $p < 0.001$) (Table 2), indicating the long-term effect of berberine on the reduction of colorectal adenoma recurrence after endoscopic resection during the post-treatment period. Sensitivity analyses also demonstrated the same trend: patients in the berberine group had lower risk of colorectal adenoma recurrence (adjusted HR, 0.62; 95% CI: 0.49–0.79; $p < 0.001$) (Table S2).

The risks of cumulative colorectal adenoma recurrence per follow-up year were identical to those of overall adenoma recurrence (Figure 2). After the randomized trial termination, the protective effects of berberine reached statistical significance in the third year, with the increasing number of participants undergoing follow-up colonoscopies (odds ratio [OR], 0.63; 95% CI: 0.41–0.97; $p = 0.04$), and remained stable from the fifth year (OR, 0.50; 95% CI: 0.35–0.70; $p < 0.001$).

We also analyzed recurrence rates of colorectal adenoma according to different follow-up periods. With fewer than 60 colonoscopies conducted per treatment group during the first year of follow-up, no significant difference was observed in the adenoma recurrence rate between the groups (Table S4). However, the effects were significant during 1–3, 3–5, and >5 years of follow-up, as well as ≤5 years of follow-up (Table S4). In the subgroup analysis, we evaluated several subgroups based on predetermined baseline characteristics. None of the p values for interaction were statistically significant (all p values for interaction >0.05), indicating that the treatment effect of berberine was consistently protective across all the subgroups analyzed (Figure 3).

Secondary outcomes

During the 6–8 years of follow-up, 199 (63.4%) and 237 (71.0%) patients in the berberine and placebo group demonstrated any type of neoplasm, respectively (adjusted HR, 0.75; 95% CI: 0.62–0.91; $p = 0.004$) (Table 2). However, there was no statistically significant difference between the two groups in the sensitivity analyses of neoplasm occurrence (adjusted HR, 0.83; 95% CI: 0.69–1.01; $p = 0.06$) (Table S2). Moreover, berberine did not reduce neoplasm occurrence within 1, 1–3, and >5 years of follow-up; notably, it appeared to be effective in the 3- to 5-year and ≤5-year periods after the randomized trial (OR, 0.61; 95% CI: 0.38–0.98; $p = 0.04$; and OR, 0.48; 95% CI, 0.34–0.67; $p < 0.001$, respectively) (Table S4). The occurrence rate of serrated lesion was lower but not statistically significant in the berberine group

Table 1. Baseline characteristics of the participants

	Berberine (n = 314)	Placebo (n = 334)	p value
Age, years			
Median (IQR)	66.0 (60.0–71.0)	67.0 (59.0–72.0)	
No. (%)			
<60	73 (23.2)	93 (27.8)	0.18
≥60	241 (76.8)	241 (72.2)	
Gender, no. (%)			
Male	213 (67.8)	222 (66.5)	0.71
Female	101 (32.2)	112 (33.5)	
BMI, median (IQR), kg/m^2	24.1 (22.0–25.8)	24.1 (21.8–26.1)	0.70
Smoking, no. (%)			
Smoker	43 (13.7)	47 (14.1)	0.89
Non-smoker	271 (86.3)	287 (85.9)	
Family history of colorectal cancer, no. (%)			
Yes	11 (3.5)	14 (4.2)	0.65
No	303 (96.5)	320 (95.8)	
Colorectal adenoma recurrence in the CBAR trial, no. (%)			
Yes	129 (41.1)	162 (48.5)	0.06
No	185 (58.9)	172 (51.5)	
Total follow-up time, median (IQR), m	78.0 (74.0–85.0)	78.0 (73.0–85.0)	0.67
Time to the first colonoscopy after the CBAR trial, median (IQR), m	22.0 (12.0–42.3)	21.5 (12.0–39.0)	0.68
Time to the last colonoscopy after the CBAR trial, median (IQR), m	54.0 (36.0–74.0)	54.5 (33.0–69.0)	0.88
No. of follow-up colonoscopies, no. (%)			
1	131 (41.7)	144 (43.1)	0.93
2–4	171 (54.5)	178 (53.3)	
5–7	12 (3.8)	12 (3.6)	
Total no. of follow-up colonoscopies	627	652	
Berberine use after the CBAR trial, no. (%)			
No use	303 (96.5)	329 (98.5)	0.10
Any use	11 (3.5)	5 (1.5)	
No. of participants in the clinical center, no. (%)			
1	64 (20.4)	70 (21.0)	0.84
2	48 (15.3)	41 (12.3)	
3	43 (13.7)	43 (12.9)	
4	45 (14.3)	49 (14.7)	
5	27 (8.6)	26 (7.8)	
6	43 (13.7)	58 (17.4)	
7	44 (14.0)	47 (14.1)	

Data are presented as median (IQR) or no. (%). Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; IQR, interquartile range. Percentages in some categories may not add up to 100% due to rounding. See also Tables S1 and S8.

Table 2. Adenoma recurrence and neoplasm occurrence during follow-up

	Berberine (n = 314)	Placebo (n = 334)	Adjusted HR (95% CI)	p value
Adenomas	109 (34.7)	174 (52.1)	0.58 (0.45–0.74)	<0.001
Neoplasms	199 (63.4)	237 (71.0)	0.75 (0.62–0.91)	0.004

Data are presented as no. (%). An analysis of colorectal adenoma recurrence and neoplasm occurrence was conducted during the median 6-year follow-up. Adenomas only include traditional colorectal adenomas. Neoplasms include colorectal cancer and polypoid lesions (colorectal adenomas, serrated lesions [sessile serrated lesions, traditional serrated adenomas, and hyperplastic polyps], and inflammatory polyps). HRs, 95% CIs, and p values are calculated by adjusted multivariate Cox regression model. Covariates include age, gender, clinical center, body mass index (BMI), smoking, family history of colorectal cancer, hypertension and diabetes history, and medication use (e.g., calcium, statin, and aspirin). Abbreviations: HR, hazard ratio; CI, confidence interval. See also Tables S2, S5, and S6.

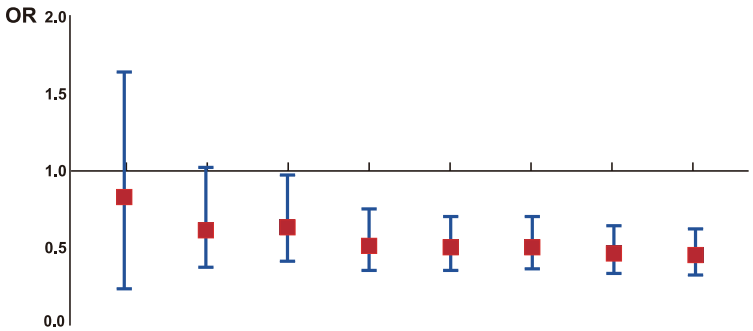
compared with the placebo group (adjusted HR, 0.72; 95% CI: 0.52–0.99; p = 0.05) (Table S5). However, the occurrence of hyperplastic polyps, sessile serrated lesions, and traditional serrated adenomas did not significantly differ between the berberine and placebo groups (18.8% vs. 24.0%, p = 0.11; 2.2% vs. 1.5%, p = 0.46; and 0.6% vs. 1.8%, p = 0.13, respectively) (Table S6). In each group, colorectal cancer occurred in only one participant (0.3% vs. 0.3%, p = 0.97) (Table S6).

Advanced colorectal adenomas occurred in 13 (4.1%) and 17 (5.1%) patients in the berberine and placebo groups, respectively (adjusted HR, 0.99; 95% CI: 0.96–1.02; p = 0.57) (Table S5). Moreover, non-advanced colorectal adenoma occurrence rate was lower in the berberine group than in the placebo group (adjusted HR, 0.56; 95% CI: 0.43–0.71; p < 0.001) (Table S5); however, high-risk colorectal adenoma occurrence rate did not significantly differ between the berberine and placebo groups (adjusted HR, 0.84; 95% CI: 0.56–1.25; p = 0.38).

We analyzed the number and size of colorectal adenomas and neoplasms in participants who had accurate recordings (167 in the berberine group and 169 in the placebo group) (Table S7). The total number and the average number of colorectal adenomas and neoplasms were much lower in the berberine group, with a statistically significant smaller size. Large serrated lesions (≥1 cm in size) were also much less in the berberine group (p < 0.001).

Event-free period analysis

We used Kaplan-Meier curves to analyze the event-free period in the berberine and placebo groups and compared outcome risks by using univariate and adjusted multivariate Cox regression models. The results suggested that berberine significantly improved the event-free period rate of colorectal adenoma recurrence compared with the placebo group (HR, 0.61; 95% CI: 0.48–0.77; adjusted HR, 0.58; 95% CI: 0.45–0.74; p < 0.001, log rank test) (Figure 4A). The time point with the largest risk ratio was 6.9 years after the randomized trial, with 43.0% and 18.5% of the berberine and placebo group patients remaining event-free, respectively. Moreover, the berberine group demonstrated a higher event-free period rate of neoplasm occurrence than the



Follow-up Year	1	2	3	4	5	6	7	8
Berberine	14/54	38/168	56/217	70/244	92/283	105/300	109/313	109/314
Placebo	19/57	58/187	84/238	116/271	147/309	161/325	172/333	174/334
OR	0.61	0.61	0.63	0.51	0.50	0.50	0.46	0.45
Lower limit 95% CI	0.23	0.37	0.41	0.35	0.35	0.36	0.33	0.32
Upper limit 95% CI	1.64	1.02	0.97	0.75	0.70	0.70	0.64	0.62
p value	0.33	0.06	0.04*	0.001**	<0.001***	<0.001***	<0.001***	<0.001***

*, $p<0.05$; **, $p<0.01$; ***, $p<0.001$

Figure 2. Cumulative adenoma recurrence by year

Cumulative colorectal adenoma recurrence per follow-up year after the 2-year randomized trial. ORs and 95% CIs are calculated by multivariable logistic regression and illustrated on the graph using points and lines, respectively. Covariates include age, gender, clinical center, body mass index (BMI), smoking, family history of colorectal cancer, hypertension and diabetes history, and medication use (e.g., calcium, statin, and aspirin). The ratios in the berberine and placebo lines are the ratio of cumulative number of recurrent adenoma participants to the cumulative number of participants who underwent colonoscopy in the two groups, respectively. ORs, lower and upper limits of 95% CIs, and *p* values of the two groups are presented under the graph. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Abbreviations: OR, odds ratio; CI, confidence interval.

See also Table S4.

placebo group (HR, 0.80; 95% CI: 0.66–0.96; adjusted HR, 0.75; 95% CI: 0.62–0.91; $p = 0.02$, log rank test) (Figure 4B). The time point with the largest risk ratio was 5.2 years after the randomized trial, with 35.5% and 24.0% of the berberine and placebo group patients remaining event-free, respectively. Similarly, the event-free period rate of non-advanced colorectal adenoma occurrence was also significantly higher in the berberine group (HR, 0.59; 95% CI: 0.46–0.75; adjusted HR, 0.56; 95% CI: 0.43–0.71; $p < 0.001$, log rank test) (Figure S1A); however, the serrated lesions and high-risk colorectal adenoma occurrence did not differ significantly between the two groups in terms of the event-free period (HR, 0.76; 95% CI: 0.55–1.05; adjusted HR, 0.72; 95% CI: 0.52–1.00; $p = 0.10$; and HR, 0.87; 95% CI: 0.59–1.29; adjusted HR, 0.84; 95% CI: 0.56–1.25; $p = 0.48$, log rank test, respectively) (Figures S1B and S1C).

Multiple outcome events during follow-up

There were cases of multiple colorectal adenoma recurrence and multiple neoplasm occurrence. To evaluate these multi-events, we used the Anderson and Gill model to analyze with adjustment for similar cofounding factors as aforementioned. We found that multi-recurrence of colorectal adenoma and multi-occurrence of non-advanced adenoma remained significantly lower in the berberine group (adjusted HR, 0.67; 95% CI: 0.54–0.83; $p < 0.001$; and adjusted HR, 0.66; 95% CI: 0.53–0.82; $p < 0.001$, respectively) (Figure S2); however, the between-group difference in neoplasm occurrence became nonsignificant with regard to multiple occurrence (adjusted HR, 0.88; 95% CI: 0.76–1.02; $p = 0.10$).

DISCUSSION

In this post-treatment follow-up study of the CBAR trial, we found that a 2-year berberine treatment had prolonged chemoprevention effects against colorectal adenoma recurrence and neoplasm occurrence in polypectomy patients over a median observation time of 78.0 months (6 years). Compared with that during the CBAR trial, the chemopreventive effects of berberine were more evident in the post-treatment period, whereby the recurrence rate of colorectal adenoma decreased further.

Many *in vivo* and *in vitro* studies have reported that berberine can inhibit harmful microbiota related to colorectal tumorigenesis pathways and modulate the tumor microenvironment.[16,17] In addition to inhibiting colorectal cancer through gut microbiota, berberine has been widely demonstrated to resolve hyperlipidemia,[20] diabetes,[21] and other metabolic disorders through gut microbiota interactions.[22–24] Considering the prolonged effects of berberine, intermittent dosing might maximize the chemopreventive effects of berberine on colorectal adenoma recurrence while minimizing side effects. The intermittent period and related mechanisms warrant further analysis.

Our subgroup analysis did not reveal significant differences in certain groups. There may be other potential modifiers not considered, such as socioeconomic status, race, and ethnicity. Only one participant in each of the berberine and placebo groups eventually developed colorectal cancer during the 6-year follow-up period. According to the eighth edition of the *AJCC Cancer Staging Manual*,[25] the placebo group patient had stage IIA colorectal cancer, whereas the berberine group patient had *in situ* colorectal cancer. This may be due to our total follow-up duration being 6–8 years—shorter than the average duration of 10 years during which adenoma-to-carcinoma alterations occur.[3] Moreover, advanced colorectal adenoma and high-risk colorectal adenoma detection rates were lower in our study compared with others[26]; this result might be attributable to the frequent endoscopic surveillance of our participants. Any polyp detected during colonoscopy was promptly removed, preventing its progression to advanced and high-risk colorectal adenoma. Restricted by the lack of endoscopic examinations on the number and size of colorectal adenomas or neoplasms, we

	Events/N		HR (95% CI)	p value	p value for interaction
	Berberine (n=314)	Placebo (n=334)			
Age					
<60	23/73	40/93	0.61 (0.36-1.02)	0.06	1.00
≥60	86/241	134/241	0.61 (0.46-0.80)	<0.001	
Gender					
Male	76/213	121/222	0.60 (0.45-0.80)	0.001	0.92
Female	33/101	53/112	0.64 (0.41-0.98)	0.04	
BMI, kg/m^2					
<24	54/155	85/163	0.64 (0.46-0.90)	0.01	0.69
≥24	55/159	89/171	0.58 (0.41-0.81)	0.002	
Smoking					
Smoker	14/43	24/47	0.61 (0.31-1.17)	0.14	0.92
Non-smoker	95/271	150/287	0.60 (0.47-0.78)	<0.001	
Family history of colorectal cancer					
Yes	7/11	7/14	1.57 (0.52-4.72)	0.43	0.14
No	102/303	167/320	0.58 (0.46-0.75)	<0.001	
Hypertension					
Yes	24/77	50/87	0.51 (0.31-0.83)	0.007	0.42
No	85/237	124/247	0.65 (0.49-0.85)	0.002	
Diabetes					
Yes	10/27	17/33	0.63 (0.29-1.39)	0.25	0.97
No	99/287	157/301	0.61 (0.47-0.78)	<0.001	
Calcium use					
Yes	3/7	4/5	0.38 (0.07-1.97)	0.25	0.63
No	106/307	170/329	0.61 (0.48-0.78)	<0.001	
Statin use					
Yes	13/32	20/33	0.41 (0.20-0.85)	0.02	0.25
No	96/282	154/301	0.63 (0.49-0.81)	<0.001	
Aspirin use					
Yes	13/38	22/36	0.35 (0.17-0.70)	0.003	0.09
No	96/276	152/298	0.65 (0.50-0.84)	0.001	
Recurrence of adenomas in the CBAR trial					
Yes	59/129	96/162	0.75 (0.54-1.03)	0.08	0.17
No	50/185	78/172	0.53 (0.37-0.75)	<0.001	
Recurrence of advanced adenomas in the CBAR trial					
Yes	8/13	10/19	1.22 (0.48-3.10)	0.68	0.08
No	101/301	164/315	0.58 (0.45-0.75)	<0.001	

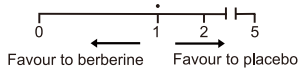


Figure 3. Subgroup analysis

Subgroup analysis of colorectal adenoma recurrence include age, gender, body mass index (BMI), smoking, family history of colorectal cancer, hypertension and diabetes history, medication use (e.g., calcium, statin, and aspirin use), as well as previous recurrence status of colorectal adenoma and advanced colorectal adenoma in the CBAR trial, calculated by univariate Cox regression model. *p* values for interaction <0.05, significant. Abbreviations: HR, hazard ratio; CI, confidence interval.

only analyzed 336 participants with accurate records. However, we still found that patients in the berberine group tended to have adenomas and neoplasms less in number and smaller in size. Large serrated lesions, as increasing risk factors of colorectal carcinogenesis, showed the same trend.

Many clinical trials have reported on chemoprevention of post-resection adenoma recurrence. For instance, low-dose aspirin has been noted to prevent colorectal adenoma recurrence after 1 year[5,27] or 2 years[28] of treatment but not 4 years of treatment.[29] Folic acid (1 mg, daily) reduced adenoma recurrence risk 5 years after treatment.[4] At 3–5 years after treatment, supplementation of calcium (1,200 mg) plus vitamin D (1,000 IU) daily could not prevent adenoma recurrence.[9] There were other clinical trials on the secondary prevention of colorectal adenoma, almost all of which were observational analysis of continued supplementation of certain agents and mostly in follow-up of 1–5 years.

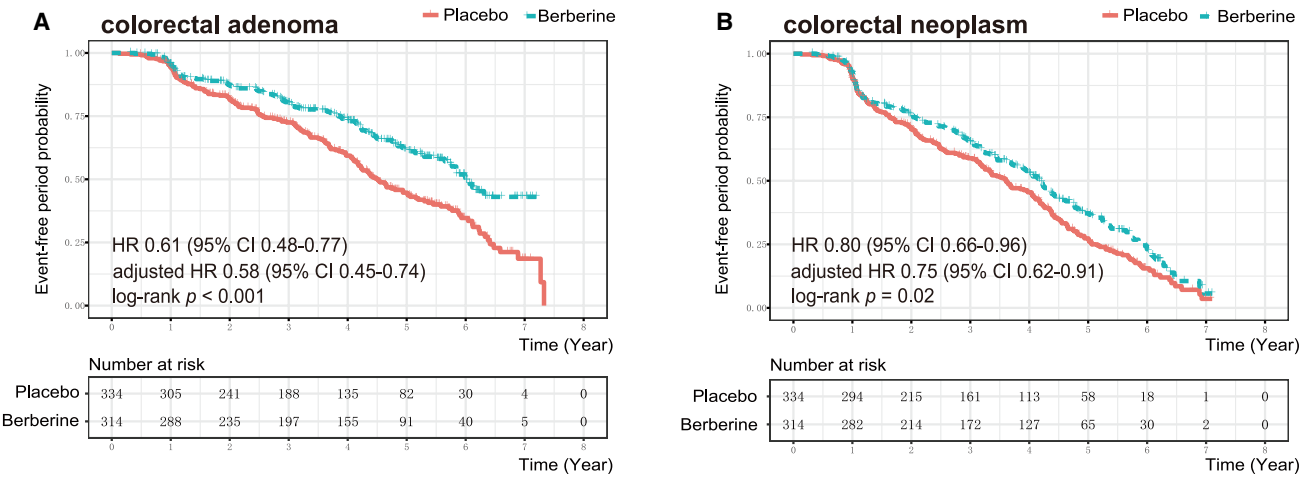


Figure 4. Event-free period of colorectal adenoma and neoplasm

(A) Colorectal adenoma and (B) colorectal neoplasm. HRs and 95% CIs are calculated by univariate and adjusted multivariate Cox regression models. *p* values are calculated by log rank test. Abbreviations: HR, hazard ratio; CI, confidence interval.
See also Figure S1.

However, our CBAR trial demonstrated the chemopreventive effects of berberine during the treatment period. The current study further indicated that the preventive effect of berberine improved and lasted at least 6 years without supplementation. Berberine, a traditional Chinese medicine drug, may thus be a relatively safe, cheap drug with worldwide applicability.

In the present study, the median colonoscopy follow-up interval was 3 years—more frequent than that in some studies in Western countries. Surveillance intervals tend to differ by country according to their adenoma incidence and local conditions. For instance, in the United States, the current guidelines suggest that low-risk patients (1–2 adenomas or sessile serrated adenoma, <10 mm) should be followed up every 5–10 years, those with advanced adenomas or traditional serrated adenomas should be surveilled every 3–5 years, and patients with more than 10 adenomas should be followed up every 1 year.[30–32] In contrast, the Chinese consensus guidelines recommend that all patients should be followed up every 1–3 years after polypectomy and that, for patients with advanced colorectal adenomas, this follow-up interval should be shortened to 3–6 months.[33] The Chinese consensus guidelines are based on features of Chinese patients and their medical conditions, summarizing outcomes in recent clinical trials, meta-analyses, systematic reviews, and expert opinions.[34–36]

Limitations of the study

The current study has some limitations. First, the numbers of participants undergoing colonoscopy varied from 1 to 7 at different follow-up intervals; thus, those with adenoma at last colonoscopy were more likely to have more frequent surveillance colonoscopy. Nevertheless, the number of colonoscopies, time to the first/last follow-up colonoscopy after the CBAR trial, and median follow-up intervals did not significantly differ between the berberine and placebo groups. Second, some patients refused to participate, and some were lost to follow-up, which may have impacted the generalizability of our findings. Nevertheless, baseline characteristics did not differ between the two groups. Third, given the low frequency of some outcome events, the power of the analysis of the individual outcomes might have been low. Fourth, given that statistical methods for right-censored data are more mature and versatile, we based our primary analysis on right-censored statistical methods and supplemented it with an interval-censoring analysis to assess the potential impact of these methodological limitations on our results. Importantly, the interval-censored results were consistent with the findings of our primary right-censored analysis. Fifth, the treatment efficacy of berberine might be mediated by long-term gut microbiota changes, but we did not further investigate the potential mechanisms. Sixth, there might be other potential confounding factors, such as genetic variants, diet, and lifestyle, which may also influence adenoma recurrence. We have endeavored to include a comprehensive range of relevant covariates to minimize bias as much as possible. Nonetheless, some confounding factors remain unavoidable and warrant further investigation. Finally, we only got part of the number and size of recurrent colorectal adenomas, and we did not analyze their locations, all of which warrant further assessment.

In conclusion, at 6–8 years after treatment, berberine can prevent colorectal adenoma recurrence and colorectal neoplasm occurrence without continual supplementation. Thus, it might be a crucial secondary chemopreventive agent for colorectal adenoma and a potential candidate for colorectal cancer.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Jing-Yuan Fang (jingyuanfang@sjtu.edu.cn).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- De-identified individual participant-level data required to reanalyze the data are available from the lead contact upon request. Any additional details about individual participants that could compromise patient confidentiality will not be disclosed.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

Conceptualization, Y.-J.T., T.-H.Z., Y.-X.C., and J.-Y.F.; methodology, K.Y. and Y.-J.T.; investigation, Y.-J.T., T.-H.Z., P.J., M.-J.Z., X.-T.D., S.-H.H., X.-N.Y., X.-M.S., H.-L.C., Y.-X.Z., Q.-Y.G., H.-M.C., and Y.C.; writing – original draft, Y.-J.T.; writing – review and editing, Y.-J.T. and T.-H.Z.; funding acquisition, J.-Y.F., Y.-X.C., and H.-M.C.; supervision, J.-Q.S., X.-P.Z., S.-D.L., J.-L.R., Z.-J.L., and B.-M.W. All authors agreed to submit the manuscript, read and approved the final draft, and take full responsibility of its content, including the accuracy of the data and the fidelity of the trial to the registered protocol and its statistical analysis.

DECLARATION OF INTERESTS

The authors declare no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS
  - Patient characteristics
- METHOD DETAILS
  - Study design
  - Outcomes
- QUANTIFICATION AND STATISTICAL ANALYSIS
- ADDITIONAL RESOURCES

SUPPLEMENTAL INFORMATION

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REFERENCES

1. Weitz, J., Koch, M., Debus, J., Höhler, T., Galle, P.R., and Büchler, M.W. (2005). Colorectal cancer. Lancet *365*, 153–165. https://doi.org/10.1016/s0140-6736(05)17706-x.
2. Zauber, A.G., Winawer, S.J., O'Brien, M.J., Lansdorp-Vogelaar, I., van Ballegooijen, M., Hankey, B.F., Shi, W., Bond, J.H., Schapiro, M., Panish, J.F., et al. (2012). Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N. Engl. J. Med. *366*, 687–696. https://doi.org/10.1056/NEJMoa1100370.
3. Corley, D.A., Jensen, C.D., Marks, A.R., Zhao, W.K., Lee, J.K., Doubeni, C.A., Zauber, A.G., de Boer, J., Fireman, B.H., Schottinger, J.E., et al. (2014). Adenoma detection rate and risk of colorectal cancer and death. N. Engl. J. Med. *370*, 1298–1306. https://doi.org/10.1056/NEJMoa1309086.
4. Cole, B.F., Baron, J.A., Sandler, R.S., Haile, R.W., Ahnen, D.J., Bresalier, R.S., McKeown-Eyssen, G., Summers, R.W., Rothstein, R.I., Burke, C.A., et al. (2007). Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. JAMA *297*, 2351–2359. https://doi.org/10.1001/jama.297.21.2351.
5. Baron, J.A., Cole, B.F., Sandler, R.S., Haile, R.W., Ahnen, D., Bresalier, R., McKeown-Eyssen, G., Summers, R.W., Rothstein, R., Burke, C.A., et al. (2003). A randomized trial of aspirin to prevent colorectal adenomas. N. Engl. J. Med. *348*, 891–899. https://doi.org/10.1056/NEJMoa021735.
6. Arber, N., Eagle, C.J., Spicak J Fau - Rácz, I., Rácz, I., Dite, P., Hajer, J., Zavoral, M., Lechuga, M.J., Gerletti, P., Tang, J., et al. (2006). Celecoxib for the prevention of colorectal adenomatous polyps. N. Engl. J. Med. *355*, 885–895. https://doi.org/10.1056/NEJMoa061652.
7. Bonithon-Kopp, C., Kronborg, O., Giacosa A Fau - Räth, U., Räth, U., and Faivre, J. (2000). Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. European Cancer Prevention Organisation Study Group. Lancet *356*, 1300–1306. https://doi.org/10.1016/s0140-6736(00)02813-0.
8. Baron, J.A., Beach, M., Mandel, J.S., van Stolk, R.U., Haile, R.W., Sandler, R.S., Rothstein, R., Summers, R.W., Snover, D.C., Beck, G.J., et al. (1999). Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. N. Engl. J. Med. *340*, 101–107. https://doi.org/10.1056/NEJM199901143400204.
9. Baron, J.A., Barry, E.L., Mott, L.A., Rees, J.R., Sandler, R.S., Snover, D.C., Bostick, R.M., Ivanova, A., Cole, B.F., Ahnen, D.J., et al. (2015). A Trial of Calcium and Vitamin D for the Prevention of Colorectal Adenomas. N. Engl. J. Med. *373*, 1519–1530. https://doi.org/10.1056/NEJMoa1500409.
10. Wactawski-Wende, J., Kotchen, J.M., Anderson, G.L., Assaf, A.R., Brunner, R.L., O'Sullivan, M.J., Margolis, K.L., Ockene, J.K., Phillips, L., Pottern, L., et al. (2006). Calcium plus vitamin D supplementation and the risk of colorectal cancer. N. Engl. J. Med. *354*, 684–696. https://doi.org/10.1056/NEJMoa055222.
11. Gou, H., Su, H., Liu, D., Wong, C.C., Shang, H., Fang, Y., Zeng, X., Chen, H., Li, Y., Huang, Z., et al. (2023). Traditional Medicine Pien Tze Huang Suppresses Colorectal Tumorigenesis Through Restoring Gut Microbiota and Metabolites. Gastroenterology *165*, 1404–1419. https://doi.org/10.1053/j.gastro.2023.08.052.
12. Yin, S., Jin, W., Qiu, Y., Fu, L., Wang, T., and Yu, H. (2022). Solamargine induces hepatocellular carcinoma cell apoptosis and autophagy via inhibiting LIF/miR-192-5p/CYR61/Akt signaling pathways and eliciting immunostimulatory tumor microenvironment. J. Hematol. Oncol. *15*, 32. https://doi.org/10.1186/s13045-022-01248-w.
13. Qian, C., Zhou, Y., Zhang, T., Dong, G., Song, M., Tang, Y., Wei, Z., Yu, S., Shen, Q., Chen, W., et al. (2024). Targeting PKM2 signaling cascade with salvianic acid A normalizes tumor blood vessels to facilitate chemotherapeutic drug delivery. Acta Pharm. Sin. B *14*, 2077–2096. https://doi.org/10.1016/j.apsb.2024.02.003.
14. Wang, K., Feng, X., Chai, L., Cao, S., and Qiu, F. (2017). The metabolism of berberine and its contribution to the pharmacological effects. Drug Metab. Rev. *49*, 139–157. https://doi.org/10.1080/03602532.2017.1306544.
15. Imanshahidi, M., and Hosseinzadeh, H. (2008). Pharmacological and therapeutic effects of Berberis vulgaris and its active constituent, berberine. Phytother Res. *22*, 999–1012. https://doi.org/10.1002/ptr.2399.
16. Qian, Y., Kang, Z., Zhao, L., Chen, H., Zhou, C., Gao, Q., Wang, Z., Liu, Q., Cui, Y., Li, X., et al. (2023). Berberine might block colorectal carcinogenesis

by inhibiting the regulation of B-cell function by Veillonella parvula. Chin. Med. J. *136*, 2722–2731. https://doi.org/10.1097/CM9.0000000000002752.

17. Yu, Y.N., Yu, T.C., Zhao, H.J., Sun, T.T., Chen, H.M., Chen, H.Y., An, H.F., Weng, Y.R., Yu, J., Li, M., et al. (2015). Berberine may rescue Fusobacterium nucleatum-induced colorectal tumorigenesis by modulating the tumor microenvironment. Oncotarget *6*, 32013–32026. https://doi.org/10.18632/oncotarget.5166.
18. Wang, H., Guan, L., Li, J., Lai, M., and Wen, X. (2018). The Effects of Berberine on the Gut Microbiota in Apc (min/+) Mice Fed with a High Fat Diet. Molecules *23*, 2298, LID - 10.3390/molecules23092298 [doi] LID - 2298. https://doi.org/10.3390/molecules23092298.
19. Chen, Y.X., Gao, Q.Y., Zou, T.H., Wang, B.M., Liu, S.D., Sheng, J.Q., Ren, J.L., Zou, X.P., Liu, Z.J., Song, Y.Y., et al. (2020). Berberine versus placebo for the prevention of recurrence of colorectal adenoma: a multicentre, double-blinded, randomised controlled study. Lancet Gastroenterol. Hepatol. *5*, 267–275. https://doi.org/10.1016/S2468-1253(19)30409-1.
20. Kong, W., Wei, J., Abidi, P., Lin, M., Inaba, S., Li, C., Wang, Y., Wang, Z., Si, S., Pan, H., et al. (2004). Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. Nat. Med. *10*, 1344–1351. https://doi.org/10.1038/nm1135.
21. Wang, S., Ren, H., Zhong, H., Zhao, X., Li, C., Ma, J., Gu, X., Xue, Y., Huang, S., Yang, J., et al. (2022). Combined berberine and probiotic treatment as an effective regimen for improving postprandial hyperlipidemia in type 2 diabetes patients: a double blinded placebo controlled randomized study. Gut Microbes *14*, 2003176. https://doi.org/10.1080/19490976.2021.2003176.
22. Zhao, M.M., Lu, J., Li, S., Wang, H., Cao, X., Li, Q., Shi, T.T., Matsunaga, K., Chen, C., Huang, H., et al. (2021). Berberine is an insulin secretagogue targeting the KCNH6 potassium channel. Nat. Commun. *12*, 5616. https://doi.org/10.1038/s41467-021-25952-2.
23. Xu, X., Yi, H., Wu, J., Kuang, T., Zhang, J., Li, Q., Du, H., Xu, T., Jiang, G., and Fan, G. (2021). Therapeutic effect of berberine on metabolic diseases: Both pharmacological data and clinical evidence. Biomed. Pharmacother. *133*, 110984. https://doi.org/10.1016/j.biopha.2020.110984.
24. Harrison, S.A., Gunn, N., Neff, G.W., Kohli, A., Liu, L., Flyer, A., Goldkind, L., and Di Bisceglie, A.M. (2021). A phase 2, proof of concept, randomised controlled trial of berberine ursodeoxycholate in patients with presumed non-alcoholic steatohepatitis and type 2 diabetes. Nat. Commun. *12*, 5503. https://doi.org/10.1038/s41467-021-25701-5.
25. Amin, M.B., Greene, F.L., Edge, S.B., Compton, C.C., Gershenwald, J.E., Brookland, R.K., Meyer, L., Gress, D.M., Byrd, D.R., and Winchester, D.P. (2017). The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J. Clin. *67*, 93–99. https://doi.org/10.3322/caac.21388.
26. Pawlak, K.M. (2023). Can a high-quality screening colonoscopy decrease the need for subsequent surveillance colonoscopies? Endoscopy *55*, 754–755. https://doi.org/10.1055/a-2082-8002.
27. Benamouzig, R., Deyra, J., Martin, A., Girard, B., Jullian, E., Piednoir, B., Couturier, D., Coste, T., Little, J., and Chaussade, S. (2003). Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial. Gastroenterology *125*, 328–336. https://doi.org/10.1016/s0016-5085(03)00887-4.
28. Ishikawa, H., Mutoh, M., Suzuki, S., Tokudome, S., Saida, Y., Abe, T., Okamura, S., Tajika, M., Joh, T., Tanaka, S., et al. (2014). The preventive effects of low-dose enteric-coated aspirin tablets on the development of colorectal tumours in Asian patients: a randomised trial. Gut *63*, 1755–1759. https://doi.org/10.1136/gutjnl-2013-305827.
29. Benamouzig, R., Uzzan, B., Deyra, J., Martin, A., Girard, B., Little, J., and Chaussade, S.; Association pour la Prévention par l'Aspirine du Cancer Colorectal Study Group APACC (2012). Prevention by daily soluble aspirin of colorectal adenoma recurrence: 4-year results of the APACC randomised trial. Gut *61*, 255–261. https://doi.org/10.1136/gutjnl-2011-300113.
30. Ladabaum, U., and Schoen, R.E. (2016). Post-Polypectomy Surveillance That Would Please Goldilocks–Not Too Much, Not Too Little, but Just Right. Gastroenterology *150*, 791–796. https://doi.org/10.1053/j.gastro.2016.01.033.
31. Lieberman, D.A., Rex, D.K., Winawer, S.J., Giardiello, F.M., Johnson, D.A., and Levin, T.R. (2012). Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology *143*, 844–857. https://doi.org/10.1053/j.gastro.2012.06.001.
32. Winawer, S.J., Zauber, A.G., O'Brien, M.J., Ho, M.N., Gottlieb, L., Sternberg, S.S., Waye, J.D., Bond, J., Schapiro, M., Stewart, E.T., et al. (1993). Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Workgroup. N. Engl. J. Med. *328*, 901–906. https://doi.org/10.1056/NEJM199304013281301.
33. Fang, J.Y., Zheng, S., Jiang, B., Lai, M.D., Fang, D.C., Han, Y., Sheng, Q.J., Li, J.N., Chen, Y.X., and Gao, Q.Y. (2014). Consensus on the Prevention, Screening, Early Diagnosis and Treatment of Colorectal Tumors in China: Chinese Society of Gastroenterology, October 14-15, 2011, Shanghai, China. Gastrointest. Tumors *1*, 53–75. https://doi.org/10.1159/000362585.
34. Wong, M.C.S., Rerknimitr, R., Lee Goh, K., Matsuda, T., Kim, H.S., Wu, D.C., Wu, K.C., Yeoh, K.G., Chong, V.H., Ahmed, F., et al. (2021). Development and Validation of the Asia-Pacific Proximal Colon Neoplasia Risk Score. Clin. Gastroenterol. Hepatol. *19*, 119–127.e1. https://doi.org/10.1016/j.cgh.2019.12.031.
35. Chen, H., Shi, J., Lu, M., Li, Y., Du, L., Liao, X., Wei, D., Dong, D., Gao, Y., Zhu, C., et al. (2023). Comparison of Colonoscopy, Fecal Immunochemical Test, and Risk-Adapted Approach in a Colorectal Cancer Screening Trial (TARGET-C). Clin. Gastroenterol. Hepatol. *21*, 808–818. https://doi.org/10.1016/j.cgh.2022.08.003.
36. Chen, H., Lu, M., Liu, C., Zou, S., Du, L., Liao, X., Dong, D., Wei, D., Gao, Y., Zhu, C., et al. (2020). Comparative Evaluation of Participation and Diagnostic Yield of Colonoscopy vs Fecal Immunochemical Test vs Risk-Adapted Screening in Colorectal Cancer Screening: Interim Analysis of a Multicenter Randomized Controlled Trial (TARGET-C). Am. J. Gastroenterol. *115*, 1264–1274. https://doi.org/10.14309/ajg.0000000000000624.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
GraphPad Prism version 10.1.2	GraphPad Prism	https://www.graphpad.com/scientificsoftware/prism/
R version 4.4.2	R-Project	https://www.r-project.org/
IBM SPSS Statistics version 26.0	IBM	https://www.ibm.com/products/spss
Biorender	Biorender	Biorender.com

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

The Chemoprevention of Berberine in Adenoma Recurrence (CBAR) (NCT02226185)[19] trial was a prospective, double-blind, randomized, multicenter, and placebo-controlled study, investigating the chemopreventive effects of berberine on colorectal adenoma recurrence in patients aged 18–75 years who had undergone endoscopic polypectomy six months before recruitment at seven clinical centers across six provinces in China. The seven clinical centers included Renji Hospital, Shanghai Jiao Tong University School of Medicine; The Seventh Medical Center of PLA General Hospital; The Affiliated Drum Tower Hospital of Nanjing University Medical School; Nanfang Hospital, Southern Medical University; Zhongshan Hospital, Xiamen University; Shanghai Tenth People's Hospital, Tongji University; General Hospital, Tianjin Medical University. The design, inclusion and exclusion criteria were described elsewhere.[19] In total, 1136 eligible participants were recruited over November 14, 2014 to December 30, 2016, and 1:1 randomized to receive either berberine (0.3 g twice daily) or placebo tablets for 2 years until the last involved participant finished the 2-year treatment on December 29, 2018. At 1 year after recruitment (IQR: 11.3–13.7 months), 895 participants underwent the first follow-up colonoscopy. Those who had recurrent colorectal adenomas no longer followed up colonoscopy (116/432 in the berberine group and 168/463 in the placebo group), but they still continued to receive treatment accompanied with the rest 611 participants till 2 years. The unblinding was performed after the end of the CBAR trial.

The CBAR-FE study (NCT06629051) recruited all participants who completed the 2-year randomized treatment in the CBAR trial (432 in the berberine group and 463 in the placebo group). This study was conducted during the post-treatment observational phase of the CBAR trial. On October 10, 2024, 6–8 years after the completion of the 2-year treatment, we lost 114 CBAR trial participants to follow up. We obtained informed consent from the remaining 781 participants and obtained follow-up information. Among the 781 participants, 133 did not undergo follow-up colonoscopies after the CBAR trial, so we included 648 participants into analysis (314 from the berberine group and 334 from the placebo group). All participants had provided written informed consent for participation. This study was based on the Declaration of Helsinki and Guidelines for Good Clinical Practice. This study was approved by the Ethics Committee of Renji Hospital, Shanghai Jiao-Tong University School of Medicine; study approval was also obtained from the ethics committees in the other six participating clinical centers.

Patient characteristics

The median (IQR) age of 648 participants in the berberine and the placebo groups was 66.0 (60.0–71.0) years and 67.0 (59.0–72.0) years, respectively. The proportion of males was 67.8% in the berberine group and 66.5% in the placebo group (Tables 1 and S1).

METHOD DETAILS

Study design

We obtained follow-up information through the Hospital Information System query, face-to-face talk, or telephone call (Table S8). We tracked endoscopic examinations, major medical events, colorectal surgical procedures, family history of colorectal cancer, chronic disease history, and medication and other supplement use (e.g., aspirin, statin, calcium and berberine use). We recorded every endoscopy of 648 participants, including the number, size, and pathological classification of polypoid lesions (if available) (Table S7). All endoscopic examinations and polypectomies were performed by experienced endoscopists who were blinded to the grouping of participants. All endoscopies reached the caecum with Boston bowel preparation scores (BBPS) $\geq$ 6 and withdrawal time $\geq$6 min. Pathological diagnosis was based on the 5th WHO classification of colorectal tumors.

Outcomes

The primary outcome was colorectal adenoma recurrence in terms of the overall recurrence rate, cumulative recurrence rates per follow-up year, and recurrence rates during different periods (within 1 year and after 1–3, 3–5, and >5 years). Only traditional

colorectal adenomas (excluding traditional serrated adenomas and sessile serrated lesions) were considered as colorectal adenomas in this study.

Secondary outcomes were all neoplasms occurrence rates, including colorectal cancer and polypoid lesions (colorectal adenomas, serrated lesions [sessile serrated lesions, traditional serrated adenomas, and hyperplastic polyps], and inflammatory polyps), as well as those of advanced, non-advanced, high-risk colorectal adenomas at any colonoscopy during the follow-up duration. Here, an advanced colorectal adenoma was defined by the presence of a $\geq$10 mm adenoma, or with features of high-grade dysplasia, or villous histology ($\geq$25% villous), whereas a high-risk colorectal adenoma was defined by the presence of $\geq$1 advanced colorectal adenomas or $\geq$3 colorectal adenomas.

QUANTIFICATION AND STATISTICAL ANALYSIS

In the analysis of baseline characteristics, continuous variables with a normal distribution were presented as means with standard deviations (SDs) and differences in means were assessed with the Student's t test; continuous variables with a nonnormal distribution were presented as medians with interquartile ranges (IQRs) and differences in medians were assessed with Wilcoxon rank-sum test for pairwise comparisons or the Kruskal-Wallis test for multiple comparisons; and categorical variables presented as counts and percentages were assessed with the χ^2 or Fisher test (Tables 1, S1, and S7).

We calculated the risk of colorectal adenoma recurrence and neoplasm occurrence by adjusted multivariate Cox regression model, with covariates including age, gender, clinical center, body mass index (BMI), smoking, family history of colorectal cancer, hypertension and diabetes history, and medication use (e.g., calcium, statin, aspirin) (Tables 2 and S5). Categorical variables were presented as counts and percentages. Although participants who did not undergo follow-up colonoscopies were censored at their last colonoscopy, we conducted sensitivity analysis by repeating adjusted multivariate Cox regression model assuming that the 133 patients without follow-up colonoscopy had no recurrence of adenoma/neoplasm, regardless of group assignment (Table S2). Given that the exact time of adenoma recurrence or neoplasm occurrence is only known to lie between two successive colonoscopies, we also applied a Case II interval-censoring statistical analysis to validate the results (Table S3).

We employed multivariate logistic regression model to evaluate the risk of colorectal adenoma recurrence and neoplasm occurrence in different follow-up periods (within 1 year and after 1–3, 3–5, and >5 years), the cumulative adenoma recurrence per follow-up year, and the detection of CRC and serrated lesions (Table S4; Figure 2; Table S6). The covariates were the same as above.

Subgroup analyses of colorectal adenoma recurrence included age, gender, BMI, smoking, family history of colorectal cancer, hypertension and diabetes history, medication use (e.g., calcium, statin, and aspirin use), as well as previous recurrence status of colorectal adenoma and advanced colorectal adenoma in the CBAR trial by univariate Cox regression model. p values for interaction in these subgroup analyses were calculated to evaluate whether the protective effect of berberine varied significantly across different subgroups (Figure 3).

We used Kaplan-Meier survival curves to analyze the event-free period. HRs and 95% CIs were calculated by univariate and adjusted multivariate Cox regression models, and the significance was analyzed using the log rank test (Figures 4 and S1). We also evaluated multiple recurrence and occurrence in one participant at different follow-up time by using the Andersen and Gill (AG) model to compare the berberine and placebo groups with adjustments for the aforementioned covariates (Figure S2).

All p values were two-sided, and $p < 0.05$ was considered to indicate statistical significance.

ADDITIONAL RESOURCES

The study was registered at clinicaltrials.gov (NCT06629051).