MINI REVIEW

Ursodeoxycholic acid and chemoprevention of colorectal cancer

L. Serfaty, M. Bissonnette, R. Poupon

Service d’hépatologie, hôpital Saint-Antoine, Assistance publique—Hôpitaux de Paris, université Pierre-et-Marie-Curie, 184, rue du Faubourg-Saint-Antoine, 75571 Paris cedex 12, France

Department of Medicine, University of Chicago, Medical Center 5891, S. Maryland Avenue, 60637 Chicago, IL, USA

Available online 6 July 2010

Summary  Colorectal cancer is respectively the third and second most common cancer among men and women in France. Interest in chemoprevention for colorectal cancer has increased over the last two decades. Beside non-steroidal anti-inflammatory drugs, ursodeoxycholic acid (UDCA) may have chemopreventive action in colorectal cancer with a likely better tolerance. In high-risk populations such as patients with inflammatory bowel disease or prior colorectal adenoma or carcinoma, retrospective and prospective studies have suggested a beneficial effect of UDCA. In azoxymethane model, UDCA inhibits tumor development by countering the tumor-promoting effects of secondary bile acids, such as deoxycholic acid (DCA). The opposing effects of UDCA and DCA on lipid raft composition may be central to their effects on colonic tumorigenesis. Differential effects of DCA and UDCA on growth factor and inflammatory signals involved in colorectal carcinogenesis, such as epidermal growth factor receptors (EGFR) signaling and Cox-2 expression, likely mediate their opposing effects on colonic tumor promotion and tumor inhibition, respectively.

© 2010 Elsevier Masson SAS. All rights reserved.

With an estimated 36,257 new cases and 15,973 deaths in 2000, colorectal cancer is the third most common cancer among men and the second most common cancer among women in France [1]. The number of new cases increased approximately by 50% between 1980 and 2000, and colorectal cancer is now the second leading cause of cancer-related mortality [1]. Epidemiological and observational data indicate that colorectal cancer develops over years and arises from premalignant polyps known as adenomas that are capable of progressing to invasive carcinoma [2]. A multistep process of colon carcinogenesis has been described that involves the transition from normal mucosa to the adenoma and then to carcinoma mutations in oncogenes and loss of tumor suppressor gene function [2]. This sequence provides opportunities for therapeutic intervention to prevent colorectal cancer development. Both primary and secondary prevention strategies have been developed and include dietary interventions as well as the use of specific nutrients or chemicals to suppress or reverse the process of carcinogenesis (i.e., chemoprevention).

Candidates for chemoprevention include those at high-risk of disease, such as inflammatory bowel disease, and individuals with inherited syndromes such as familial ade-
nomatous polyposis as well as subjects with prior colorectal adenomas and carcinomas. Interest in chemoprevention for colorectal cancer has increased over the last two decades, following evidence from epidemiological studies that have shown significantly lower rates of colorectal cancer in individuals reporting the regular consumption of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) [3–7]. A number of retrospective and prospective studies have reported 30 to 50% reductions in the rates of colorectal cancer in humans with a regular intake of aspirin or NSAIDs [8]. More recently, results of randomised controlled trials have suggested that aspirin could reduce the risk of adenoma development in patients with history of colorectal adenoma or cancer [9–11]. Nevertheless, digestive toxicity of NSAID could limit their large-scale use. Several data suggest that ursodeoxycholic acid (UDCA) may have chemopreventive action in colorectal cancer with a likely better tolerance.

### Bile acids and colorectal carcinogenesis

Fecal secondary bile acids, and particularly deoxycholic acid (DCA) are considered to promote the formation of colon adenoma and cancer. In animal models, feeding with cholic acid (CA) and DCA produces an increase in epithelial cell proliferation and promotes the formation of colonic tumors by chemical carcinogens [12–14]. In humans, epidemiological studies have provided data linking high serum or fecal bile acid concentrations with an increased risk of colorectal cancer. Serum levels of DCA, which in a steady state are assumed to reflect the amount of DCA absorbed from the colon, have been found to be significantly elevated in patients with colon adenomas and colon cancer compared with controls [15–17]. Fecal bile acid output in patients with colon cancer, with familial adenomatous polyposis and sporadic colonic adenomas, were reported to be increased in some studies, but most reported only a change in the composition of fecal bile acids [18–21]. Several reports showed an increase in secondary bile acids in the feces of patients with colon cancer and colonic adenomas [19–21]. In patients with ulcerative colitis (UC), colonic dysplasia or carcinoma are associated with high fecal bile acid concentrations [22]. Consistent with these observations, colonic mucosal proliferation has been shown to be related to serum DCA levels [23,24]. All of these findings are consistent with the concept that DCA promotes colorectal carcinogenesis.

**Ursodeoxycholic acid and chemoprevention of colorectal cancer: from animal to human**

UDCA is the first-line therapy for primary biliary cirrhosis (PBC) as well as for other chronic cholestatic liver diseases [25]. UDCA partially blocks the ileal absorption of endogenous bile acids, thus promoting high concentrations of both UDCA and endogenous bile acids in the colon [26]. For this reason, a challenging issue regarding the safety of long-term bile acid therapy is whether it may constitute a causal factor for an increased risk of colorectal adenoma and cancer. However, simultaneous studies conducted at the Universities of Arizona and Chicago using the azoxymethane (AOM) model of experimental colon cancer showed that dietary supplementation with UDCA significantly reduced the numbers of tumor-bearing rats and abolished the development of carcinoma [27]. Moreover, dietary supplementation with 0.2% UDCA together with a promoting dose of CA prevented tumor promotion by CA [27]. Based on these seminal observations, the idea of using UDCA as a chemopreventive agent for colon carcinogenesis has emerged [28].

### Clinical data

In human, potential chemopreventive action of UDCA has been suggested in three retrospective studies and one randomised trial [29–32]. Because of lack of data on patients criteria for selection and treatment assignment, results of retrospective studies should be considered with caution. In one study at Saint-Antoine Hospital, we conducted a screening program for colorectal adenoma in 114 PBC patients with long-term UDCA treatment (13–15 mg/kg per day) [29]. In the first part of the study, we compared prevalence of adenoma in patients already treated with UDCA (median duration: 46 mo) and in patients not treated at the time of colonoscopy. The percentage of patients with adenoma was not higher but lower in the treated group than in the untreated group, although the difference was not significant (13% vs. 24%, respectively; P = 0.16). UDCA treatment was significantly associated with smaller size polyps. In the second part of the study, we assessed the effect of UDCA on colorectal adenoma recurrence following removal. Cumulative probability of recurrence at 3 years was significantly lower in UDCA-treated patients than in age and sex matched-untreated controls (7% vs. 28%; P = 0.04) (Fig. 1). The relative risk of recurrence at 3 years in treated patients compared with controls was 0.25 (CI = 0.09–0.92; P = 0.04). These results were strengthened by the significant reduction in colonic epithelial cell proliferation seen in patients treated with UDCA, compared with untreated controls (Fig. 2). In the same time, two US teams have assessed the effect of long-term UDCA treatment on colonic...

![Figure 1](image-url) Cumulative probability of the recurrence of adenoma after polypectomy in primary biliary cirrhosis patients treated with ursodeoxycholic acid (unbroken line) and controls (dotted line).

With the permission of *Hepatology* [29].
dysplasia in patients with UC-associated with primary sclerosing cholangitis (PSC) [30,31]. The first study was the retrospective analysis of a subgroup of 52/85 patients participating to a randomised controlled trial, which evaluated efficacy of UDCA versus placebo in PSC [30]. It is of note that during endoscopic follow-up, 70% of initially assigned placebo patients were switched to UDCA treatment. In intention to treat, the relative risk for dysplasia or cancer occurrence between UDCA versus placebo groups was 0.26 (CI = 0.06–0.92; \( P = 0.03 \)). Cumulative probability of survival without dysplasia was significantly higher in UDCA group than in placebo group (Fig. 3). These results were not modified when adjusting on cofactors such as age at the time of diagnosis, disease duration, long-term use of NSAID or aminosalicylate. In the second study, authors have retrospectively analyzed risk factors for dysplasia occurrence in 59 patients with UC associated with PSC [31]. In multivariate analysis, UDCA use was negatively associated with the risk of colonic dysplasia (OR = 0.14; CI 0.03–0.64; \( P = 0.01 \)). Beneficial effect of UDCA was also demonstrated in patients with high-grade of dysplasia. In this study, there was no significant dose-effect of UDCA treatment on the risk of dysplasia. In a randomised, double blind, placebo-controlled trial, the potential preventive effect of UDCA on colorectal adenoma recurrence was assessed in 1285 individuals who had undergone adenoma removal [32]. UDCA was given at the dosage of 8–10 mg/kg per day versus placebo for a duration of 3 years. Although there was no significant difference in the overall rate of recurrence, there was a significant UDCA-related reduction in recurrence of adenomas with high-grade dysplasia (adjusted OR = 0.61; 95% CI = 0.39–0.96; \( P = 0.03 \)). Adenoma size, villous histology or location were similar between both groups. Given these results, longer term use of UDCA (e.g., >5 years) should be evaluated in the sub-population of patients who are at risk of experiencing the recurrence of highly dysplastic adenomas. However, a secondary analysis of the trial showed that gender of patients might modify UDCA effect, preventing advanced colorectal adenoma in men while the odds was increased among women with high fat intake [33].

**Mechanisms of action**

The pathways by which UDCA inhibits colonic carcinogenesis remain incompletely defined, but several molecular mech-
UDCA and colorectal cancer

Anchors have been proposed to explain the chemopreventive effects of this bile acid [28]. The AOM model has been widely employed to study colonic carcinogenesis and to investigate potential chemopreventive agents, including UDCA. This model recapitulates many of the clinical, histological, and molecular features of human colon cancer. UDCA inhibited tumor development in the AOM model when administered during tumor initiation, or when given only during tumor promotion [34]. Experimental data in this and other animal models of carcinogenesis have suggested that UDCA may prevent colonic neoplastic transformation by countering the tumor-promoting effects of secondary bile acids, such as DCA. DCA is the major colonic metabolite of CA and is known to damage cell membranes and increase free radical generation [35,36]. This leads to cell death and results in secondary colonic hyperproliferation that predisposes to tumorigenesis [27,37]. In contrast, UDCA, a more hydrophilic bile acid, exerts cytoprotective effects [35,36,38]. In this regard UDCA has been shown to antagonize DCA-induced cell death of transformed colonocytes [39].

In the AOM model dietary supplementation with UDCA enriched UDCA in the fecal water-soluble fraction, while causing more hydrophobic secondary bile acids to partition predominantly into the water-insoluble fraction [40]. Bile acids in the water-soluble fraction are thought to be most important in inducing biological effects. Since no colonic bile acid transporters have been identified and labeled bile acids are not taken up by colon cancer cells in vitro, it is presumed that these amphipathic molecules exert their effects by perturbing plasma membranes [36]. In this regard, DCA is known to deplete cholesterol from plasma membranes, whereas UDCA antagonizes these effects [41,42]. Lipid rafts, cholesterol-rich lipid domains in the plasma membrane, are platforms that regulate membrane-initiated signaling [43]. Changes in the cholesterol composition of lipid rafts alter these signals. The opposing effects of UDCA and DCA on lipid raft composition may be central to their effects on colonic tumorigenesis. While there are no known colonic bile acid transporters, the recent identification of a membrane receptor for bile acids suggests that bile acids might activate membrane receptors to induce their effects. TGR5, a G protein-coupled bile acid membrane receptor is expressed in numerous tissues including the intestine and macrophage [44]. TGR5 has recently been implicated in Barrett’s esophageal cancer, but its role in colon cancer has not been examined [45]. Other bile acid receptors such as Farnesoid X Receptor (FXR) and Constitutive Androstane Receptor (CAR) are intracellular and would require a bile acid uptake mechanism [46]. Interestingly, FXR appears to function as a tumor suppressor in the AOM and Min mouse models [47].

The chemopreventive effects of UDCA are detected as early as the aberrant crypt focus (ACF) stage in premalignancy. ACF are the earliest detectable putative precursors of colon cancer in the AOM model and in humans harboring colonic neoplastic lesions [48,49]. We demonstrated that UDCA inhibited colonic hyperproliferation and ACF progression in the AOM model [50]. UDCA concomitantly decreased cyclin D1, a key positive cell cycle regulator. UDCA also suppressed Cox-2 up-regulation in AOM colonic tumorigenesis [50]. Cox-2 is the rate-limiting enzyme for prostaglandin biosynthesis and intimately involved in colonic carcinogenesis.

![Figure 4](image.png)

**Figure 4** Opposite effects of deoxycholic acid (DCA) and ursodeoxycholic acid (UDCA) on epidermal growth factor receptor (EGFR) signaling and Cox-2 expression in colorectal cancer.

Cyclin D1 and Cox-2 are up-regulated by p21K-ras, encoded by K-ras a proto-oncogene frequently mutated in colon cancer. We demonstrated that UDCA inhibited the development of tumors with mutant or activated wild type p21K-ras [51]. UDCA also suppressed AOM-induced Cox-2 by both p21K-ras-dependent and p21K-ras-independent pathways [51]. More recently, we demonstrated that transcription factor CCAAT/enhancer-binding protein (C/EBP) and stress mitogen-activated protein kinase (MAPK) p38 are important for Cox-2 induction by DCA and inhibited by UDCA in colon cancer cells [52].

Epidermal growth factor receptors (EGFR) reside in lipid rafts and are important activators of p21K-ras [53]. We have shown that EGFR controls colonic tumor development and progression [54,55]. We also showed that a Western diet, which is known to increase fecal DCA, required EGFR for Cox-2 induction [56]. In this regard, the bile acid membrane receptor TGR5 has also been shown to transactivate EGFR in gastric cancer cells [57]. Furthermore, in normal mouse colon UDCA inhibited EGFR signals [58]. While in the AOM model, tumor-promoting CA activated EGFR signaling, chemopreventive UDCA inhibited this pathway (Fig. 4) [59,60]. These results are in agreement with the ability of UDCA to inhibit extracellular signal regulated kinase (ERK) activation by DCA in human colon cancer cells [61]. UDCA may block EGFR signals in part by accelerating ubiquination and down-regulation of this receptor [39]. In addition, UDCA can block NFK activation, which may play a major role in the anti-inflammatory and anti-neoplastic actions of this cytoprotective bile acid (Fig. 4) [62]. NFK up-regulates expression of inducible Nitric Oxide Synthetase (iNOS) and Cox-2 that are implicated in colonic tumorigenesis [63,64]. Taken together, these studies suggest that differential effects of DCA and UDCA on growth factor and inflammatory signals likely mediate their opposing effects on colonic tumor promotion and tumor inhibition, respectively.

**Conclusion**

Evidence from experimental animal models and human studies suggest that UDCA exerts chemopreventive activity against colorectal carcinogenesis [28,65]. Studies in vivo...
in the AOM model, and in vitro in colon cancer cells, moreover, indicate that UDCA inhibits EGFR signals and Cox-2 up-regulation in colon carcinogenesis. UDCA, in combination with other chemopreventive agents, has also been shown to inhibit tumor development in other experimental genetic and chemical models of intestinal tumorigenesis [66,67]. These synergistic chemopreventive actions suggest that combination therapy involving UDCA could enhance efficacy, while reducing untoward side effects. Based on studies in animals, UDCA and NSAID might effectively inhibit sporadic colon carcinogenesis. In the colitis-related colon cancer model, UDCA, but not sulfasalazine, is able to suppress colon adenocarcinoma development [68]. Studies in humans also suggest that the combination of UDCA and 5-aminosalicylate might block the development of UC-associated colon cancer [28,30,65,69]. The use of a new amino acid derivative of ursodeoxycholate, N-γ-Glutamyl-UDCA, that increase colonic delivery of UDCA, could be an interesting therapeutic option [70]. Randomised controlled clinical trials will be needed, however, to test the safety and efficacy of such chemopreventive strategies.

Conflict of interest statement

No conflict.

References


