



Biliary acids as promoters of colon carcinogenesis: a narrative review

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Objective: This review aims to analyze and summarize the possible effects of biliary acids (BAs) as promoters of colon carcinogenesis.

Background: Research on the biology of BAs represents a prime interest for gastroenterologists, and especially hepatologists. The increase of colorectal cancer (CRC) risk is principally related to prolonged, increased consumption of red meat and saturated fatty acids. In particular, these nutrients stimulate bile discharge, a mechanism that leads to increased concentrations of BAs above the physiological range. In this context, BAs can become tumor promoters as proven by many studies showing how increased BAs levels lead to changes in intestinal epithelium’s growth.

Methods: We analyzed and reviewed the recently published articles regarding bile acids and their influence on the onset and development of CRC. Another critical step includes comprehending the physical, chemical, biological, and clinical characteristics of secondary BAs.

Conclusions: Certain BAs as lithocholic acid (LCA) and deoxycholic acid (DCA), are potent inducers of colon carcinogenesis. Moreover, the association of increased intake of high lipid and red meat, low fiber intake, sedentary lifestyle could lead to CRC manifestation in the future of worldwide population and to increase overall mortality for gastrointestinal cancers.

Keywords: Colorectal cancer (CRC); lithocholic acid (LCA); deoxycholic acid (DCA); cancer stem cells (CSCs); diet

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Introduction

Biliary acids (BAs) are detergent-like amphipathic molecules synthesized in the liver from cholesterol, stored in the gallbladder, and released after food intake into the intestine. Nowadays the interest in BAs is increasing for gastroenterologists because of their critical role in several conditions such as liver and intestinal diseases (1). BAs are known to have multiple and significant functions: acting as a digestive surfactant that promotes the absorption of lipids, including fat-soluble vitamins, eliminating cholesterol and certain catabolites, participating in intestinal motility for fine regulation of bacterial flora. Almost fifty years ago, Berg noted that colorectal cancer (CRC) risk raised in the descendants who moved from rural to developed countries where the diet was characterized by meals enriched with saturated fatty acids and red meat. In fact, the close correlation with prolonged and increased consumption of saturated fatty acids and red meat has a crucial role in colorectal carcinogenesis (2). Recently, another cohort study investigating 55,487 Danish middle-aged men and women, suggested that CRC risk could arise without full adherence to healthy lifestyle recommendations (3).

Bayerdorffer's control study confirms that deoxycholic acid (DCA) levels were significantly increased in colorectal adenomas patients (4) finding a positive and strong association between colorectal adenomas and serum DCA, this occurs when DCA derived directly to the unconjugated fraction who is formed in the colon (5), in addition, the bile discharging is stimulated by a high-fat diet that leads to increased concentrations of BAs over the upper limit physiological range (6).

Various epidemiological nutrition studies show that subjects with high lipid and beef intake have increased levels of secondary bile acids like DCA and lithocholic acid (LCA) in feces, a similar pattern was seen in patients with CRC diagnosis (7,8). A high level of dietary fats stimulates increased primary bile acid production which forms secondary bile acids and these could be directly inductors of some gastrointestinal tumors or promoters that act on the growth of intestinal epithelium (9) (*Figure 1*).

We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/dmr-21-23>). Our review aims to analyze and summarize the possible effects of BAs as promoters of colon carcinogenesis.

Materials and methods

The research strategy is based on analyzing and reviewing principal recent research and articles regarding BAs and their influences on CRC. Another critical point has been to comprehend the physical, chemical, biological and clinical characteristics of secondary bile acids in the human. All downloaded papers were collected from PubMed Central, Medline, Scopus, CINAHL Complete, Google Scholar, Web of Science, and various open access journals.

The scientific core of this narrative review has been regrouped the principal articles of BAs physiology related to CRC disease, despite the limitation of narrative review because we didn't analyze according to metanalysis criteria which have an incredible statistical impact.

The quality of our work has been that of to summary the principal role of BAs in physiology and pathophysiology because the scientific web sites are full of information that is sometimes different from each other, with this work we have tried to revise the main works that have the most scientific impact and bring them together in a review.

According to us it could be useful other prospective studies that aim to analyze properly BAs in the development of colon cancer, better if the choice of patients is made with exclusion criteria of all genetic impairment related to colon cancer such Lynch Syndrome, familial adenomatous polyposis.

Because it is very important to understand the real impact of BAs at the net of this genetic disease.

Discussing

Biological properties and functions of BAs

BAs were originally known only for their digestive role in the absorption of all types of dietary lipids and vitamins and in the emulsion process of the other biochemical molecules (10). More recently, they are considered to have a pleiotropic biological function: (I) into bile canaliculi, bile acids synthesis forms an osmotic pressure which is called as BA dependent-bile flow; (II) biliary lipids secretion is stimulated by bile acids (11) and their physical-chemical properties lead to the formation of mixed micelles along with phospholipids of bile and this leads to solubilization of some lipophilic compounds, cholesterol and to the emulsion of liposoluble vitamins leads to A-D-E-K

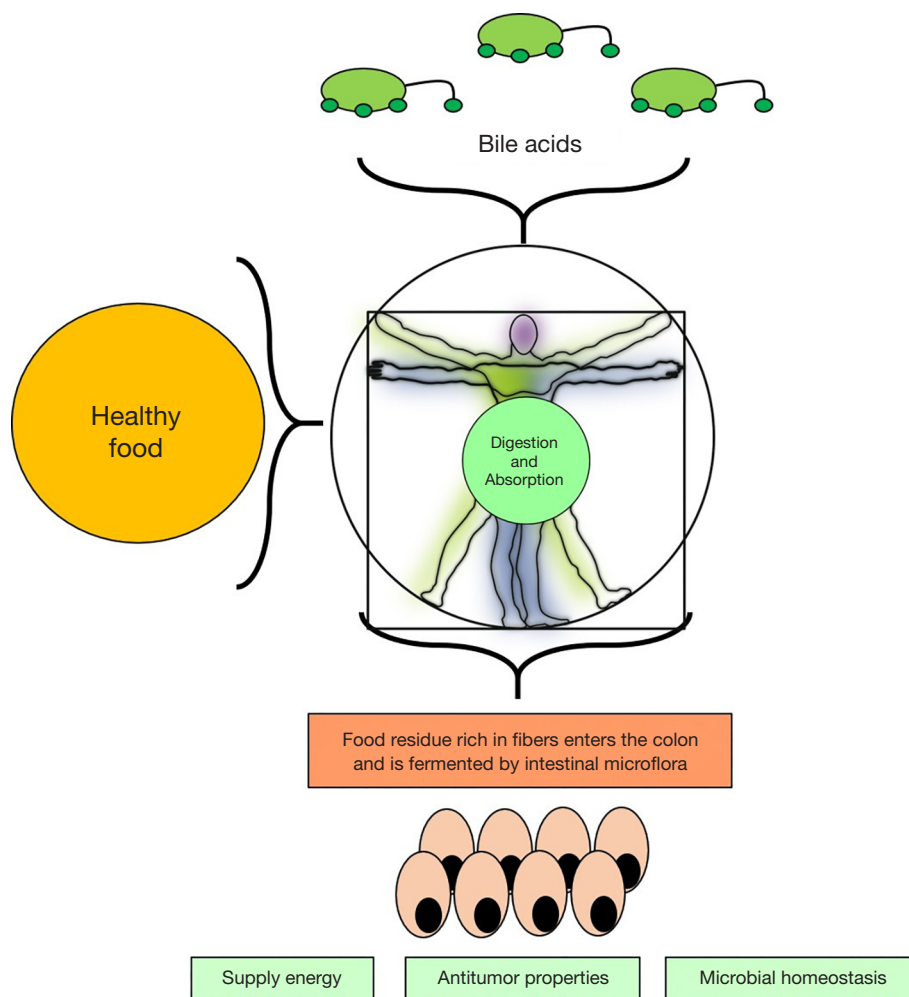


Figure 1 Effects of BAs and balanced diet on intestinal health.

vitamins absorption; (III) even free calcium is absorbed in intestine by BAs and this mechanism plays a crucial role in many biochemical reactions where calcium needed like muscle contraction, heart rate control and neuromuscular transmission. (12); (IV) releasing of cholecystokinin and the modulation of pancreatic enzyme secretion is under the control of BAs; (V) also the prevention of bacteria overgrowth in the small bowel is carried out by BAs which have a potent antimicrobial property (13,14).

The BAs' role as endocrine and paracrine signaler has been validated by the discovery of farnesoid X receptor (FXR) (15-17) and TGR5, specific BA membrane receptors (18,19). In addition to other functions such as the synthesis regulation of their own hepatic enzymes and intestinal and hepatic transport, BAs are extremely important for the adaptive responses to liver injury and cholestasis (20-23).

Nevertheless, a relevant and vastly unexplored function of BAs could be represented by their role in the control of energy metabolism (24).

Synthesis of BAs

Cholesterol is the molecular precursor of BAs, whose synthesis involves two major pathways, named classical and alternative, in addition to several other minor pathways not equally characterized (25). The classical or neutral pathway runs only in the liver and his intermediate metabolites are neutral sterols which are involved in the synthesis of two primary BAs, cholic acid (CA) and chenodeoxycholic acid (CDCA). Cytosol organelles such as mitochondria, peroxisomes, and microsomes are involved at different levels in the CA and CDCA biosynthetic reactions (26,27).

Physical and chemical characteristics of BAs

BA molecules contain the non-equivalent hydroxyl groups but their physical and chemical characteristics are mainly conferred by the carboxylic acid group distributed across the main chain structure. The special chemical structure of this organic chain has inspired its employment in several areas of research, including novel antibiotics (28-30), chiral templates (31), new soft material (32,33), anion (34-36), artificial ion channels and cation receptors (37), drug targeting vehicles (38), dendrons (39), molecular baskets (40), scaffolds for combinatorial chemistry (41), new surfactants (42), and others (43,44).

“The solubilization of an insoluble compound” is the unique capacity of BAs that leads to lipid transport and cholesterol excretion into the intestinal tract with poor absorption of the preformed micelles (small lipidic aggregates of less than 10 monomers). The amphipathic properties are related to the presence of both a hydrophilic and a hydrophobic side: the former is composed of the carboxylic side chain and the hydroxyl group, both oriented towards the α -side, while the β -side orientation is influenced by the methyl group (45). This double- α and β conformation confers a great surface activity where micelles are formed in aqueous solutions. In this way, the aggregates concentration is higher than the critical concentration value of a single monomer, these are known as critical micellar concentration (46). Freezing point measurements demonstrated that BAs act as 1:1 strong electrolytes below the critical micellar concentration (47).

The hydrophilic and hydrophobic properties differ within the different molecular types of bile salts, leading to different bile salts reactions with other substances depending on the balance between the various types of bile salts involved (48,49). Hydrophobic bile acids are potent inflammatory agents that cause injury to vital organs such as liver, intestine, and other tissues. Whereas hydrophilic bile acids are anti-inflammatory in nature. By inhibiting NF- κ B nuclear translocation and antagonizing NF- κ B-dependent induction of proinflammatory cytokines, bile acid activates FXR and TGR5 signaling pathways which suppress inflammation in macrophages, intestine, and hepatocytes (50-53).

Epidemiology of CRC in relation to BAs

According to the GLOBOCAN 2020 statistical data, more than 1.9 million new CRC (including anus) cases and 935,000 deaths were estimated to occur in 2020, representing

about one in 10 cancer cases and deaths. Overall, CRC ranks third in terms of incidence, but second in terms of mortality. Incidence rates are approximately 4-fold higher in transitioned countries compared with transitioning countries, but there is less variation in the mortality rates because of higher fatality in transitioning countries (54).

The appearance of CRC changes happens suddenly on populations migrating from low to high incidence countries: for example, the peak of CRC has already reached in people migrating from Japan to Hawaii (55). The “Japan-Hawaii migration” shows that the increase in CRC followed the moving population from “eastern diet-based fish” Country to “western diet-based meat” Country (56). BAs high level in feces indicates a major risk of CRC incidence, in these population (57-59) other data shows that association between epithelium colon exposition and increased levels of BAs lead to CRC, transforming BAs from physiological acids to potential tumor-promoting agents (60).

BAs as potential inducers of CSCs of the colon

The CSCs model proposes that a small fraction of CSCs proliferates within the tumor. These cells are capable of sustaining tumor growth and initiating carcinogenesis, as well as regenerating themselves (61).

Specific surface epitopes used to identify CSCs include CD133, CD166, EpCAM, CD44, CD24, and ALDHA1 (62-64). Some of those surface molecules are involved in tumor cell transformation, growth, and proliferation; moreover, CD44 and CD166 are associated with cross-mutation of primary CRC and increased risk of lymph node involvement and liver and lung metastatic progression (65).

Secondary BAs and CRC related to high lipids diet

The combination of low-fiber and high-fat levels in the diet is associated with increased levels of secondary BAs in feces and high incidence of CRC (66-68); moreover, increased fecal LCA/DCA ratio is associated with the presence of CRC (5,67-69). Over-consumption of a Western-style diet can represent a step linking BAs to CRC. This high-fat alimentary regimen brings excess calories, is enriched with highly saturated fats and processed carbohydrates but lacks mono-polyunsaturated fatty acids and plant-derived proteins and fiber. Following a high-fat diet, therefore, abnormally high levels of secondary BAs might unbalance the intestinal epithelial cells renewal.

The pathogenic mechanism of colon carcinogenesis

induced by BAs involves the genotoxic effect exerted by CDCA and DCA in normal human colonic epithelial cells (HCoEpiCs): oxidative stress in CRC cells has been associated with genotoxic alteration of the DNA helix, which transforms normal cells into cancer cells (70). Damages caused by a prolonged exposition to BAs have been observed in the liver as well, with disruption of the normal apoptosis of hepatocytes (71-73).

DCA or LCA shows that the formation of CSCs is induced by secondary BAs and several markers of CSC's expression, spheroids formations, and pluripotency markers such as KLF4, OCT4, Nanog, SOX2, and EMT marker's levels such as Vimentin, Twist, Slug and Zeb2 are augmented in HCoEpiCs (74).

LCA and DCA regulate the expression of multidrug resistance (MDR) genes like *ABCG2* and *ABCB1* and can induce the transformation from normal HCoEpiCs to CSCs, suggesting additional roles in the pathogenesis of CRCs (75).

Muscarinic cholinergic receptors coupled to G proteins influence the CRC carcinogenesis mediated by BAs. These receptors are divided into five subtypes (M1R-M5R) and M3R is activated by LCA: this activation plays an important role in CRC progression (76,77). The simultaneous expression of mRNA of MMP1, MMP10, MMP3 in HCoEpiCs has an important role in the invasion of cancer that is accentuated by the concomitant increase of M3R expression in response to BAs. The worst biological and clinical outcomes in cancer patients are correlated to the over-expression of MMP2, MMP7, MMP1, MMP3, MMP13, and MMP9 (78-82).

Oncogenic effects of secondary BAs

The CRC lethality increases when invasion and metastasis occur and the tumor invasiveness depends on the histological phenotype of the metastatic cells. CRC growth and progression are promoted by secondary BAs, especially DCA. Another oncogenic effect is exerted by β -catenin: a protein related to the cadherin complex and involved in tumoral anoikis, a form of programmed cellular death related to the cellular detachment from the matrix.

The modulation of β -catenin can be regulated by DCA as well as the promotion of CRC growth and invasiveness: β -catenin, cyclin D1, and targeted genes of the urokinase-type plasminogen activator receptor (uPAR) are expressed in CRC and correlated to cancer invasion, growth, and metastasis. Significant increase of tyrosine phosphorylation

of β -catenin, induction of uPAR and urokinase-type plasminogen activator, and expression of cyclin D1 have been demonstrated when DCA's lower concentration enhances CRC proliferation and invasiveness. The DCA could induce uPAR and cyclin D1 expressions are markedly reduced by inhibition of β -catenin. The neutralizing antibodies are used to block uPAR that markedly suppress the DCA-induced CRC, cell proliferation, and invasiveness (9).

Protective diet against CRC

The CRC incidence is inversely proportional with the increased intake of vegetables and fruits because this food contains fibers that bind LCA and facilitate its excretion in the stool (83). Other protective factors include calcium supplementation and cholecalciferol, which can inhibit colorectal carcinogenesis caused by increased secondary bile acids and LCA detoxification following a feed-forward catabolic pathway named cholecalciferol receptor activated by LCA (84,85). The final step of the LCA detoxification is the saponification between insoluble calcium and free bile acids in the intestine lumen, these cytotoxic BAs are eliminated with stool and the colon mucosa is protected from CRC (86).

Summary and conclusions

BAs can promote tumor proliferation in human CRC. Their relationship with diet makes them an interesting target to modulate the risk for CRC associated with the consumption of high-risk food, common in the Western dietary regimen. The primary take-home message emerging from this review is that BAs, in particular DCA and LCA, are potent inducers of colon carcinogenesis and ultimately they play an important role in the progression of CRC. Moreover, BAs' co-carcinogenic activities may induce the proliferation of CSCs in the epithelium of the colon. Among the many epidemiological factors involved in CRC progression, diet is the principal inducer of BAs synthesis and therefore represents an ideal target for non-invasive preventive or treatment protocols.

Our secondary take-home message is elaborated on the consequences of uncontrolled diet and lifestyle. The association of increased intake of high-lipid and red meat, low fiber intake, and sedentary lifestyle could lead to CRC manifestation in the future of the worldwide population and to increase overall mortality for gastrointestinal cancers.

Further research should focus on understanding the

pathogenic pathways involving BAs, diet, and the molecular events promoting the onset and the progression of CRC.

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