

## Bile Acids: Promoters or Carcinogens in Colon Cancer?

Carol Bernstein\*, Claire M. Payne and Harris Bernstein

Cellular and Molecular Medicine, College of Medicine, University of Arizona, Tucson, Arizona 85724-5044, USA

Since the 1970s it has been generally considered that bile acids are promoters of colon cancer, but lack carcinogenic activity. However, recent evidence indicates that bile acids do, indeed, act as carcinogens.

Substantial evidence from a variety of sources indicates that bile acids are involved in the etiology of colon cancer, although it has usually been assumed that they only act as promoters. The incidence of colon cancer, as well as mortality rate, varies dramatically across regions of the world. There is more than a 10-fold difference in incidence of colon cancer between countries [1,2]. Rates of colon cancer incidence among populations migrating from low-incidence to high-incidence countries change rapidly, and within one generation reach the rate in the high-incidence country. This could be seen, for instance, in a population migrating from Japan to Hawaii [3]. These changes in colon cancer incidence are thought to be largely due to changes in diet. There is a correlation between large increases in both meat and fat in the diet and large increases in incidence of colon cancer, graphed on an exponential scale [4].

The concentrations of the bile acids deoxycholic acid (DOC) and lithocholic acid are doubled in the colonic contents of human in response to a high fat diet, where the fat comes from red meat and milk products (butter, sour cream) [5] or from corn oil [6]. In populations with a high incidence of colorectal cancer, fecal concentrations of bile acids are increased [7-13], suggesting that increased exposure of the colonic lumen to high levels of bile acids plays a role in the natural course of development of colon cancer. The hydrophobic bile acids, DOC and lithocholic acid, appear to be the most significant bile acids with respect to human colorectal cancer [12].

Early experiments with rats indicated that bile acids have a promoting, but not carcinogenic effect. In those studies, bile acids enhanced the incidence of tumors when a potent carcinogen was also administered. In the first of these studies [14] the bile acids lithocholic and taurodeoxycholic acid were administered intrarectally; in the second study [15] DOC was administered intrarectally to germ free rats; in the third study [16] cholic acid and chenodeoxycholic acid were administered intrarectally; and in the fourth study [17] cholic acid was fed, but only over a 6 month period.

More recent experiments, however, have provided insight into the effects of bile acids on colonic epithelial cells suggesting a carcinogenic role for bile acids. In 2009, we reviewed 12 studies showing that exposure of colon cells to high physiologic concentrations of DOC induce formation of reactive oxygen species [18]. In this review we also summarized 14 studies showing that exposure of cells to bile acids increases DNA damage, and 26 studies showing that bile acids cause apoptosis. Surviving cells that retain un-repaired DNA damages, upon replication may give rise to daughter cells with mutations, including chromosome abnormalities (Figure 1). In addition, bile acids repress expression of proteins involved in the spindle assembly checkpoint, which likely contributes to aneuploidy [19].

Exposure of cells of normal colonic epithelial origin to DOC causes mitotic aberrations that are precursors to aneuploidy and are indicators of genome instability [19,20]. These precursors caused by DOC include micronuclei (Figure 2), chromosomes displaced from the metaphase

plate, lagging chromosomes and chromatin bridges.

Some of the bile acid-induced mutant/aneuploid cells likely acquire a growth advantage (e.g. apoptosis resistance). We showed that colonic epithelial cells grown in culture and repeatedly exposed to increasing concentrations of DOC developed resistance to apoptosis. These apoptosis-resistant cells were altered in expression of 839 out of 5,000 genes assessed by cDNA assay [21] and in 91 of 454 proteins detected by a proteomic analysis [22]. The cells with a growth advantage may form a defective field as suggested by the finding that expression of the anti-apoptotic protein Bcl-xL is increased in the colon mucosa adjacent to adenocarcinomas [23]. In addition, deletions of chromosome 1p were simultaneously found in both the distant normal-appearing mucosa of

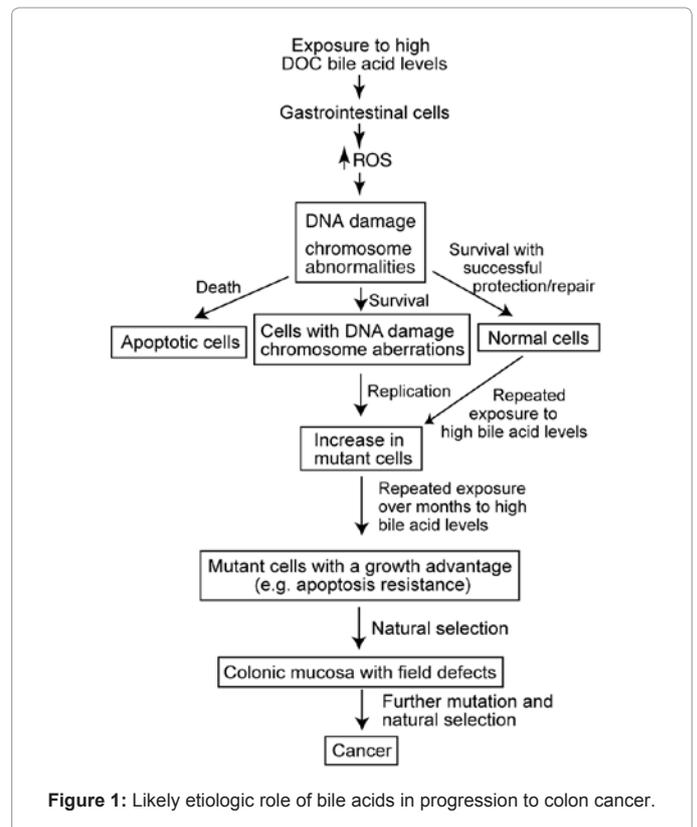


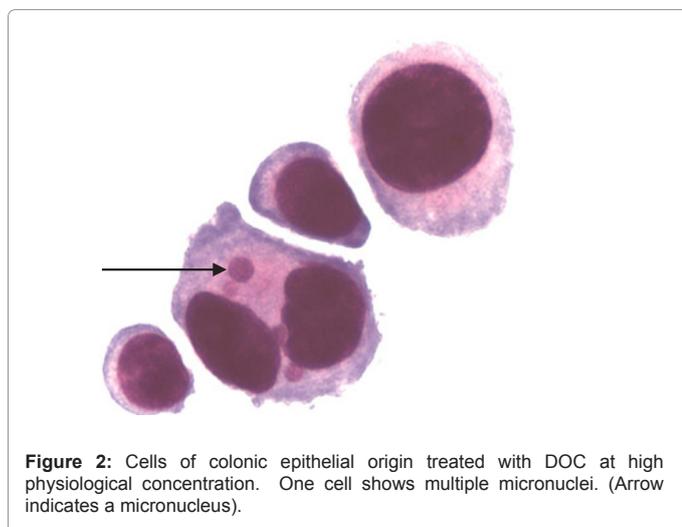
Figure 1: Likely etiologic role of bile acids in progression to colon cancer.

\*Corresponding author: Carol Bernstein, Cellular and Molecular Medicine, College of Medicine, University of Arizona, Tucson, Arizona 85724-5044, USA, E-mail: [bernstein3@earthlink.net](mailto:bernstein3@earthlink.net)

Received March 10, 2011; Accepted March 12, 2011; Published June 14, 2011

Citation: Bernstein C, Payne CM, Bernstein H (2011) Bile Acids: Promoters or Carcinogens in Colon Cancer? J Carcinogene Mutagene 2:101e. doi:10.4172/2157-2518.1000101e

Copyright: © 2011 Bernstein C, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.



**Figure 2:** Cells of colonic epithelial origin treated with DOC at high physiological concentration. One cell shows multiple micronuclei. (Arrow indicates a micronucleus).

76% of patients that also harbored 1p deletions in their cancer [24]. The molecular and cellular pathways associated with this deletion include, for example, pro-apoptotic molecules and DNA repair proteins [25]. Such defective fields, with further mutation and aneuploidy due to bile acids, and further selection, could give rise to a colon cancer (Figure 1).

Based on the finding that DOC induces genomic instability in cultured cells, we investigated whether DOC, at a high physiologic level, could be a colon carcinogen. Addition of 0.2% DOC for 8-10 months to the diet of wild-type mice resulted in fecal levels of DOC in mice comparable to fecal levels of DOC for humans eating a high fat diet. This level of colon DOC induced colonic tumors in 94% of the mice, including 56% with cancers [26]. This indicates that the bile acid DOC is a carcinogen, not merely a promoter. Furthermore, these results suggest that, in humans, the association of colon cancer with a high fat diet is mediated by persistent exposure to high physiologic levels of bile acids, especially DOC.

## References

- Garcia M, Jemal A, Ward EM, Center MM, Hao Y, et al. (2007) *Global Cancer Facts & Figures 2007*. Atlanta, GA: American Cancer Society 52.
- Nystrom M, Mutanen M (2009) Diet and epigenetics in colon cancer. *World J Gastroenterol* 15: 257-263.
- Maskarinec G, Noh JJ (2004) The effect of migration on cancer incidence among Japanese in Hawaii. *Ethn Dis* 14: 431-439.
- Kono S (2004) Secular trend of colon cancer incidence and mortality in relation to fat and meat intake in Japan. *Eur J Cancer Prev* 13: 127-132.
- Reddy BS, Hanson D, Mangat S, Mathews L, Sbaschnig M, et al. (1980) Effect of high-fat, high-beef diet and of mode of cooking of beef in the diet on fecal bacterial enzymes and fecal bile acids and neutral sterols. *J Nutr* 110: 1880-1887.
- Stadler J, Stern HS, Yeung KS, McGuire V, Furrer R, et al. (1988) Effect of high fat consumption on cell proliferation activity of colorectal mucosa and on soluble faecal bile acids. *Gut* 29: 1326-1331.
- Hill MJ, Drasar BS, Hawksworth G, Aries V, Crowther JS, et al. (1971) Bacteria and aetiology of cancer of large bowel. *Lancet* 1: 95-100.
- Reddy BS, Wynder EL (1973) Large-bowel carcinogenesis: fecal constituents of populations with diverse incidence rates of colon cancer. *J Natl Cancer Inst* 50: 1437-1442.
- Crowther JS, Drasar BS, Hill MJ, MacLennan R, Magnin D, et al. (1976) Faecal steroids and bacteria and large bowel cancer in Hong Kong by socio-economic groups. *Br J Cancer* 34: 191-198.
- Hill MJ, Taylor AJ, Thompson MH, Wait R (1982) Fecal steroids and urinary volatile phenols in four Scandinavian populations. *Nutr Cancer* 4: 67-73.
- Jensen OM, MacLennan R, Wahrendorf J (1982) Diet, bowel function, fecal characteristics, and large bowel cancer in Denmark and Finland. *Nutr Cancer* 4: 5-19.
- Hill MJ (1990) Bile flow and colon cancer. *Mutat Res* 238: 313-320.
- Cheah PY (1990) Hypotheses for the etiology of colorectal cancer—an overview. *Nutr Cancer* 14:5-13.
- Narisawa T, Magadia NE, Weisburger JH, Wynder EL (1974) Promoting effect of bile acids on colon carcinogenesis after intrarectal instillation of N-Methyl-N'-nitro-N-nitrosoguanidine in rats. *J Natl Cancer Inst* 53: 1093-1097.
- Reddy BS, Narasawa T, Weisburger JH, Wynder EL (1976) Promoting effect of sodium deoxycholate on colon adenocarcinomas in germfree rats. *J Natl Cancer Inst* 56: 441-442.
- Reddy BS, Watanabe K, Weisburger JH, Wynder EL (1977) Promoting effect of bile acids in colon carcinogenesis in germ-free and conventional F344 rats. *Cancer Res* 37: 3238-3242.
- McSherry CK, Cohen BI, Bokkenheuser VD, Mosbach EH, Winter J, et al. (1989) Effects of calcium and bile acid feeding on colon tumors in the rat. *Cancer Res* 49: 6039-6043.
- Bernstein H, Bernstein C, Payne CM, Dvorak K (2009) Bile acids as endogenous etiologic agents in gastrointestinal cancer. *World J Gastroenterol* 15: 3329-3340.
- Payne CM, Crowley-Skillicorn C, Bernstein C, Holubec H, Moyer MP, et al. (2010) Hydrophobic bile acid-induced micronuclei formation, mitotic perturbations, and decreases in spindle checkpoint proteins: Relevance to genomic instability in colon carcinogenesis. *Nutr Cancer* 62: 825-840.
- Payne CM, Bernstein C, Dvorak K, Bernstein H (2008) Hydrophobic bile acids, genomic instability, Darwinian selection, and colon carcinogenesis. *Clin Exp Gastroenterol* 1: 19-47.
- Crowley-Weber CL, Payne CM, Gleason-Guzman M, Watts GS, Futscher B, et al. (2002) Development and molecular characterization of HCT-116 cell lines resistant to the tumor promoter and multiple stress-inducer, deoxycholate. *Carcinogenesis* 23: 2063-2080.
- Bernstein H, Payne CM, Kunke K, Crowley-Weber CL, Waltmire CN, et al. (2004) A proteomic study of resistance to deoxycholate-induced apoptosis. *Carcinogenesis* 25: 681-692.
- Badvie S, Hanna-Morris A, Andreyev HJ, Cohen P, Saini S, et al. (2006) A "field change" of inhibited apoptosis occurs in colorectal mucosa adjacent to colorectal adenocarcinoma. *J Clin Pathol* 59: 942-946.
- Ciacciulli A, Cosimelli M, Marzano R, Merola R, Piperno G, et al. (2004) Genetic and pathologic significance of 1p, 17p, and 18q aneusomy and the ERBB2 gene in colorectal cancer and related normal colonic mucosa. *Cancer Genet Cytogenet* 151: 52-59.
- Payne CM, Crowley-Skillicorn C, Bernstein C, Holubec H, Bernstein H (2011) Molecular and cellular pathways associated with chromosome 1p deletion during colon carcinogenesis. *Clin Exp Gastroenterol* 4: 75-119.
- Bernstein C, Holubec H, Bhattacharyya AK, Nguyen H, Payne CM, et al. (2011) Carcinogenicity of deoxycholate, a secondary bile acid. *Arch Toxicol*.