Effects of Diet on the Fecal Excretion and Bacterial Modification of Acidic and Neutral Steroids, and Implications for Colon Carcinogenesis

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Abstract

Diet-induced changes in the excretion and fecal concentration of bile acids have been associated with enhancement or reduction of chemically initiated colon carcinogenesis in experimental animals. Dietary lipid increases the excretion and fecal concentration of bile acids. Certain types of dietary fiber such as pectin and lignin also increase fecal sterol output. However, the predominant effect of food-derived fiber (e.g., wheat bran) is to increase stool bulk and, hence, reduce the concentration of fecal sterols. Although it has been suggested that the tumor-promoting activity of bile acids is enhanced following bacterial dehydroxylation, dietary factors appear to have limited effect on bacterial flora or acidic sterol degradation in the colon.

Demographic studies have shown high correlations between per capita intake of meat and fat and incidence of colorectal cancer (2). Other data have suggested that consumption of dietary fiber may be protective (2, 36). Population differences in fat, fiber, and meat consumption are reflected in the pattern of fecal excretion of cholesterol, bile acids, and their bacterially modified derivatives. The effects of dietary manipulations on the concentration and composition of fecal steroids are discussed below with regard to large bowel carcinogenesis.

Bile Acids

Acidic sterols have been shown to act as cocarcinogens in animal studies whether ingested (34), rectally instilled (29), surgically diverted through the colon (4), or adsorbed to cholesterolamine (32). The mechanisms by which bile acids enhance colonic carcinogenesis are not well understood. Free bile acids produce a number of biological changes in intestinal mucosal cells (9). There is evidence that bile acids influence the growth and morphology of cultured human fibroblasts and increase the turnover of intestinal mucosal cells (35). By acting as mitogens, bile acids may increase the effectiveness of any of a host of mutagenic agents. The secondary bile acids, deoxycholic acid and lithocholic acid, produced by bacterial dehydroxylation of cholic and chenodeoxycholic acids (Chart 1) appear to have greater promoting activity than the corresponding primary bile acids (37). However, bacterial metabolism of bile salts is not an absolute requirement because tumor enhancement was observed in germ free animals (37). Hill et al. have demonstrated in vitro that colonic anerobes of the coccobacillary species can, through a series of nuclear dehydrogenation reactions, convert bile acids into carcinogenic phenanthrenes (10, 13, 14, 42). However, such metabolites have not been isolated in vivo, and rectal installation of bile acids alone did not result in tumor formation. In certain population studies, the fecal deoxycholate or total bile acid concentration correlated with the incidence of large bowel cancer (15) as did the ratio of secondary to primary bile acids (39). However, inconsistencies have been reported (18). Bacterial strains in the stools of low-risk populations showed reduced capacity for 7α-dehydroxylation of bile acids (27). In case control studies, colon cancer patients were shown to have higher concentrations of fecal bile acids, increased stool pH, and greater activity of 7α-dehydroxylase and cholesterol dehydrogenase enzymes (Ref. 15; Table 1). Elsewhere, these results were not confirmed (28).

Cholesterol

Partial correlation analysis of data on diet and colon cancer incidence in different populations has suggested that dietary cholesterol is more strongly related to the disease than is intake of fat or fiber (24). An increase in cholesterol consumption tends to result in enhanced fecal neutral steroid output, although this is not a consistent effect in different individuals (31, 33). Fecal bile acid excretion is less often increased by dietary cholesterol in man. Cholesterol is excreted in the stool predominantly in a bacterially modified form. An enzymatic reduction of the sterol double bond to yield coprostanol is followed by an oxidation of the 3α-hydroxyl group to give coprostanone (Chart 2). Certain individuals show a reduced tendency to modify cholesterol (43). In a comparison of individual excretion patterns in countries with differing large bowel cancer rates, Hill and Aries revealed reduced bacterial modification of cholesterol in low-risk populations. Data from Reddy and Wynder (39) has also indicated reduced excretion and bacterial degradation of cholesterol in low-risk populations. However, other studies have not revealed differences in the concentration or composition of fecal neutral steroids in populations differing in colon cancer incidence (18). At the present time, the significance of the fecal concentration and bacterial modification of cholesterol in the etiology of large bowel cancer is not clear.

Factors Influencing Activity of Bacterial Steroid-active Enzymes

Populations with high colon cancer rates have been shown to have a greater preponderance of fecal anaerobic bacteria, including nuclear dehydrogenation coccobacilli (1). However, these findings have not been consistent, and studies on the relationship of individual dietary variables to fecal flora and colonic cancer risk have produced little meaningful or consist-
and undegraded cholesterol are recovered in ileal effluent. By contrast, construction of an intraabdominal ileal reservoir (continent ileostomy) permits intestinal stasis, growth of anaerobic bacteria, and increased duration of contact between bile acids and bacteria. In about 40% of patients with a continent ileostomy, dehydroxylation of bile acids or cholesterol degradation occurs (19).

The concentration of fecal bile acids may play a role in the induction of bacterial enzymes from *Clostridium, Bacteroides,* and *Bifidobacterium.* The extent of *in vitro* steroid degradation by fecal dehydrogenases and 7α-de-oxygenase is elevated at alkaline pH (25). Acidification of colonic contents in hamsters by p.o. administration of lactulose resulted in a decrease in the bacterial modification of fecal cholesterol and alteration in the spectrum of fecal acidic sterols (41). Similarly, the reduced fecal steroid degradation in a population at low risk for colon cancer has been related to the acidity of their stools (1). Cecal fermentation of certain types of dietary fiber may be expected to decrease colonic pH.

**Dietary Effects on the Pattern of Fecal Steroid Excretion**

Biliary secretion of bile acids is enhanced by a diet high in long-chain fatty acids (40). Cummings *et al.* (8) showed that a more than 2-fold increase in dietary fat resulted in a parallel increase in fecal bile acid excretion. Substitution of polyunsaturated for saturated fat results in a further enhancement of fecal acidic sterol output which may or may not be maintained under steady-state conditions (5, 30). Hence, the observed relationship between fat intake and colon cancer incidence may be wholly or partially mediated by effects on fecal bile acid concentration. Dietary fat does not, however, appear to alter the activity of bacterial enzymes active in the degradation of bile acids (8).

**Dietary Cholesterol increases fical neutral steroid excretion**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percentage Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal bile acid concentration</td>
<td>Increased</td>
</tr>
<tr>
<td>Stool pH</td>
<td>Increased</td>
</tr>
<tr>
<td>7α-Dehydroxylation</td>
<td>Increased</td>
</tr>
<tr>
<td>Cholesterol dehydrogenase</td>
<td>Not different</td>
</tr>
</tbody>
</table>

**Chart 1.** Bacterial modification of bile acids. Hydrolysis of conjugated bile acids (glyco- or tauro-) by cholanoylglycine hydrolase may be followed by 7α-dehydroxylation to yield lithocholate or deoxycholate. Alternatively, the primary bile acids may undergo 7α-hydroxydehydrogenation to give a keto derivative. The latter is a reversible reaction.

**Chart 2.** Bacterial modification of cholesterol. An enzymatic reduction of the sterol double bond of cholesterol yields coprostanol. This may be followed by an oxidation of the 3α-hydroxy group to give coprostanone.
in certain individuals but does not consistently increase acidic stool output in humans (31, 33). Although meat protein consumption has been linked with colon cancer, fecal steroid output or degradation is not altered (7).

Dietary fiber also influences the excretion, concentration, and bacterial modification of fecal steroids, but the effects vary with the type of fiber. In terms of carcinogenic potential, the concentration of bile acids is of greater significance than overall output. Some dietary fibers have significant capacity to increase fecal bile acid output either due to sterol adsorption (i.e., lignin) (22) or partitioning of bile acids into an intraluminal gel phase (i.e., pectin, guar) (21). Since these fibers have little stool-bulking capacity, fecal bile acid concentration is concomitantly increased. Other fiber-rich foods, such as oat bran, enhance fecal bile acid excretion (23) but also increase stool volume so that bile acid concentration is little affected. Finally, particulate fibers, including wheat bran, do not significantly alter total steroid output (20, 22). However, fecal bulk is increased, resulting in a major decrease in fecal steroid concentration.

The effect of dietary fibers on fecal steroid degradation by bacterial enzymes in humans is relatively minor. Pectin or oat bran did not significantly alter the extent of cholesterol degradation in human stool (21, 22). Variable effects have been reported for wheat bran (3, 20). In animal studies, lignin potentiated the inhibitory effect of lactulose on cholesterol degradation (41).

In summary, dietary fat increases and stool-bulking fiber decreases fecal steroid concentration (Table 2). These changes are associated with enhancement (38) or reduction of chemically induced carcinogenesis in animal models (11). Although some data have suggested that bacterial modification of fecal steroids may directly potentiate or be associated with an increase in promoting activity, such an effect is as yet poorly documented. Further studies are required on the interaction of bacterial enzymes and fecal steroids in the genesis of colonic carcinoma.

References


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