Original Article

EFFECT OF BOWEL BILE ACIDS AND DIETARY FAT ON LARGE BOWEL CARCINOGENESIS IN ANIMAL MODELS

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Summary

Epidemiologic and laboratory studies suggest that dietary factors, particularly high intake of fat and animal protein, and high concentration of bile acids and neutral sterols of the large bowel lumen are strongly associated with large bowel carcinogenesis. Such concepts guided our studies on animal models. Rats fed diets high in fat and/or protein had a higher incidence of DMH-induced large bowel tumors than rats fed standard diets. The source of fat and protein, animal vs. vegetable, had no major influence. High fat intake was associated with an increased excretion of fecal bile acids, particularly secondary bile acids, and neutral sterols. The repeated intrarectal doses of lithocholic acid or deoxycholic acid enhanced the development of MNNG-induced large bowel tumors in rats. Colostomized rats treated with intrarectal dose of MNNG had no tumors in the excluded segment. It suggests that luminal contents play a significant role in the induction of large bowel cancer. The results show that higher levels of bile acids in the large bowel lumen, resulting from high fat intake, exert a promoting effect on the development of large bowel cancer.

Key Words: bile acids on colon carcinogenesis, dietary fat on colon carcinogenesis.

Introduction

Epidemiologic studies have provided clues to survey etiologic factors involved in the development of large bowel cancer. Large bowel cancer incidence is high in Western Europe, North America and Australia, and low in Asia, Africa and South America except Argentina and Uruguay. Its increase among Japanese immigrants to Hawaii and California indicates that environmental factors rather than racial factors are of etiologic significance in the development of colon cancer. In Japan its recent increase is accompanied with westernized life-style, particularly dietary habits. Analytic epidemiology suggests that large bowel cancer incidence is associated with dietary factors, particularly high intake of fat and meat. The key question is how a high fat and meat diet translates into a high risk for large bowel cancer development in man. Hill et al., and Reddy et al. concluded that the suspected effect of dietary fat and meat on large bowel carcinogenesis may be related to change
in the metabolic activity of intestinal microflora and in the composition of bile acids and cholesterol metabolites in large bowel contents\textsuperscript{7,8}. They showed a strong association between dietary fat intake, fecal bile acids and cholesterol metabolites, and the risk of large bowel cancer among different populations. Furthermore, they indicated that patients with large bowel cancer excreted high levels of fecal secondary bile acids and cholesterol metabolites, compared to healthy controls.

Such epidemiologic and laboratory data on the etiology of large bowel cancer in man have led to the present studies in animal models. No apparent relation has been observed between diet-mediated agents responsible for colon cancer in man. Thus, experimental studies in animal models have some merit in assuming a link which may explain the complex sequence of events leading to large bowel cancer in man. A number of effective ways are now available to induce large bowel cancer readily in animals\textsuperscript{9,10}. The excellent and reliable methods to induce large bowel cancer in rodents are by parenteral administration of 1,2-dimethylhydrazine (DMH) or its analogs, or by the intrarectal administration of direct-acting alkyl nitrosamides, N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and N-methyl-nitrosourea\textsuperscript{11-13}. The lesions obtained are similar to the various types of neoplasms, adenocarcinoma and adenoma observed in the colon and rectum of man.

**Role of Fecal Stream on Large Bowel Carcinogenesis**

Female Donryu rats, at 7 weeks of age, received an intrarectal dose of 1.25 mg MNNG dissolved in 0.5 ml distilled water daily for 4 weeks. Thereafter, a colostomy was surgically established at the mid-portion of the distal large bowel. The distal segment approximately 4 cm long was excluded from contact with feces. All animals were killed at week 60 and examined grossly and histologically. Fig. 1 shows the large bowel segment showing tumor development. All control animals without colostomy had multiple tumors diffusely in the distal large bowel, which was bathed by the direct-acting carcinogen MNNG. None of animals with colostomies established at 10 weeks after the last instillation of MNNG, had tumors in the segment distal to the colostomy. The animals, however, developed tumors in the segment with fecal stream proximal to the colostomy portion with the same incidence to that in control animals. Animals in which the colostomy was performed at 20 weeks after the last instillation, had tumors also in the segment distal to the colostomy, but the tumors were smaller in number and size.

The results suggest that the luminal contents play a significant role, cocarcinogenic and/or promoting effects, on the induction of large bowel cancer. Similar findings were also obtained by Navarette and Spjut, Kanazawa et al. in colostomized rats receiving 3, 2-dimethyl-4-aminobiphenyl or MNNG\textsuperscript{14,15}. 

![Fig. 1. Large bowel tumor production by intrarectal instillation of MNNG, followed colostomy in rats (Narisawa, unpublished observation).](image-url)