Gastrointestinal intraluminal pH in normal subjects and those with colorectal adenoma or carcinoma

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Abstract

Recent evidence suggests that the production of colorectal carcinogens is facilitated when the pH of the colonic contents is alkaline. It follows that the colonic intraluminal pH of patients with colorectal neoplasms should be higher than in normal subjects. Gastrointestinal pH has been measured in 30 patients with colorectal cancer and 37 patients with benign colorectal adenomas (using a pH sensitive radiotelemetry capsule). These values have been compared with those recorded in 66 normal subjects. No differences in gastrointestinal pH were found and the results did not support the hypothesis that colonic pH plays a role in the aetiology of colorectal neoplasia.

Much evidence has accumulated to suggest that intraluminal carcinogens are important in the development of colorectal neoplasia. Hill et al[1] drew together epidemiological, histopathological, and metabolic data and concluded that the intraluminal degradation of cholesterol and primary bile acids by bacterial enzymes could lead to the production of intraluminal carcinogens.

In 1981 Thornton[2] reviewed the evidence relating to the aetiology of colorectal cancer and put forward a hypothesis. He suggested that a high colonic pH promoted, or at least facilitated, colonic bacterial degradation of primary bile acids and cholesterol to carcinogens and that intraluminal pH was influenced by the acidifying effect of dietary fibre fermentation in the colon.

There is evidence that the bacterial enzymes responsible for bile acid degradation are inhibited at a pH of less than 6·5.[3] [5] Colorectal cancer is uncommon in black Africans and they have lower faecal pH than white Africans,[6] and vegetarian Seventh Day Adventists (who also have a low risk of colorectal cancer) have faecal pH values lower than those of American patients with colorectal cancer.[7]

Increased dietary fibre may lead to a fall in faecal pH by its colonic fermentation to produce short chain fatty acids.[6] [8] [9] A reduced proportion of secondary bile acids in bile has been found after the administration of wheat bran[10] or lactulose,[5] and lactulose has been found to reduce colonic pH.[11]

This supports the idea that colonic acidification may reduce bile acid degradation in the colon. The pentose fraction of fibre is metabolised to produce short chain fatty acids[12] and its intake had an inverse relationship with mortality rates for colorectal cancer in a UK study.[13] It has been suggested, however, that there is no connection between the pentose fraction and

colorectal cancer but only with total non-starch polysaccharide.[14]

In a comprehensive review of recent hypotheses for the origin of colorectal cancer,[15] Bruce was unable to support enthusiastically the evidence in favour of a bacterial origin of colonic carcinogens but did find evidence to support the role of dietary fats and fibre as well as faecal pH.

SUBJECTS AND METHODS

A total of 133 pH studies were successfully performed. Sixty six normal volunteers completed the study (47 men, median age 26 years, range 21–82 years). None of the volunteers had any history of colorectal disease.

Thirty seven patients with benign adenomatous polyps underwent pH studies (24 men, median age 66 years, range 49–80 years). Nineteen had adenomas >1·5 cm in diameter and 10 had rectal polyps and 27 were in the colon. Thirty patients with adenocarcinoma of the colon or rectum completed pH studies (17 men, median age 62 years, range 50–76 years). Ten had Dukes's stage A tumours and there were 19 rectal tumours and 11 colonic tumours.

Intraluminal pH may be measured by the ingestion of a small pH sensitive radiocapsule (Remote Control Systems) which passes easily along the gastrointestinal tract, eventually being passed in the stool. Subjects wore an aerial belt around the abdomen which received the emitted signal from the capsule. This was connected to a portable receiver-recorder (John Caunt Scientific, Oxon) to allow ambulatory recording of pH data for up to 48 hours.[16]

Each subject swallowed the radiocapsule with the help of water after an overnight fast. Once the radiocapsule had left the stomach (associated with a pH reading greater than 5·0) normal diet was permitted. A surface location chart was kept to indicate the topographical position of the radiocapsule throughout the study. This was done by the use of a small directional detector which could localise the radiocapsule to within 5 cm.

The pH data were analysed as previously reported[16] and mean pH values calculated for the proximal small bowel (the first hour of small bowel recording), the distal small bowel (the final hour of small bowel recording), the intervening mid small bowel, the proximal colon (the first four hours of the colonic part of the recording), the distal colon (the last four hours of the colonic recording, provided the radiocapsule had travelled beyond the splenic flexure), and the intervening 'mid colon.' Each subject completed a dietary history questionnaire to establish their normal fibre intake.

Comparisons were made between each of the

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TABLE I Mean (SD) gastrointestinal pH in patients with adenomas and carcinomas and in normal subjects (n=133)

Site	Normal (n=66)	Adenoma (n=37)	Carcinoma (n=30)	Combined neoplasia (n=67)
Proximal small bowel	6·6 (0·5)	6·6 (0·5)	6·8 (0·5)	6·7 (0·4)
Mid small bowel	7·4 (0·4)	7·2 (0·6)	7·1 (0·6)	7·2 (0·5)
Distal small bowel	7·5 (0·5)	7·4 (0·5)	7·3 (0·5)	7·4 (0·6)
Whole small bowel	7·3 (0·3)	7·1 (0·5)	7·1 (0·5)	7·1 (0·5)
Right colon	6·4 (0·6)	6·6 (0·7)	6·4 (0·7)	6·5 (0·6)
Mid colon	6·6 (0·8)	7·0 (0·7)	6·7 (0·7)	6·8 (0·6)
Left colon	7·0 (0·7)	7·3 (0·8)	7·3 (0·8)	7·3 (0·8)
Whole colon	6·6 (0·7)	7·0 (0·7)	6·7 (0·7)	6·8 (0·7)

study groups and the effect of site, type, and stage of tumour together with age, sex, and dietary fibre intake were examined by analysis of variance.

This study was fully approved by the Ethical Committees of the University of Nottingham and Nottingham University Hospital. All radio-capsules were recovered at the completion of the studies, none remaining lodged proximal to neoplastic lesions.

Results

Mean pH values for each of the subject groups are given according to anatomical sites in Table I. The normal pH profile showed a rise in pH from the proximal small bowel to the distal small bowel followed by a noticeable drop in pH as the radiocapsule entered the caecum. Thereafter, the pH again increased as the radiocapsule passed to the distal colon. No significant differences associated with age (Table II) or sex were found by analysis of variance.

A similar pattern was seen in the patients with colorectal adenomas or carcinomas. There were no significant differences among the three groups when compared at each of the anatomical sites. Combining the adenoma and carcinoma patients to give a 'neoplasia' group again failed to show any significant differences (analysis of variance).

With the number of subjects in the adenoma, carcinoma, and normal groups the chance that a real difference of 0·5 pH units would have gone undetected (with an accuracy of 95%) was <5%. If the real difference had been 0·7 pH units then the chance that this would have gone undetected (with an accuracy of 99%) was <1%. By combining the adenoma and carcinoma groups the chance that a rectal difference of 0·5 pH units would have remained undetected (with an accuracy of 99%) was <1%.[17]

Further analysis of the data from the adenoma

TABLE II Mean (SD) gastrointestinal pH and age in normal subjects

Site	Age <40 yrs	Age >40 yrs
Proximal small bowel	6·7 (0·6)	6·5 (0·4)
Mid small bowel	7·4 (0·4)	7·3 (0·3)
Distal small bowel	7·5 (0·5)	7·4 (0·5)
Whole small bowel	7·3 (0·3)	7·2 (0·4)
Right colon	6·4 (0·6)	6·4 (0·4)
Mid colon	6·7 (0·9)	6·6 (0·5)
Left colon	7·1 (0·7)	6·9 (0·9)
Whole colon	6·7 (0·7)	6·5 (0·5)

patients failed to show any significant differences according to polyp size or site and no differences were found according to stage or site of the tumour in the carcinoma patients.

Dietary fibre intakes were similar in each of the three study groups (normal subjects: median (range) 22 (8–62) g/day; adenoma patients: median (range) 19 (8–60) g/day; carcinoma patients: median (range) 23 (11–38) g/day) and no correlation was found between subjects' colonic pH values and the estimation of their dietary fibre intake.

Discussion

No differences have been shown in small bowel or large bowel intraluminal pH among normal subjects and those with colorectal neoplasia. Tumour site, size of adenoma, and stage of carcinoma did not exert any influence.

The colonic pH hypothesis[2] suggested that alkaline pH in the colon could be associated with neoplastic change, and Hill[18] suggested that the step at which the particular effect of pH could act was to promote enlargement of small adenoma to form larger (potentially malignant) adenomas.

If colonic pH plays a role in the initiation or promotion of neoplastic changes in the mucosa, then differences might have been expected between normal subjects and subjects with adenomas or carcinomas. The exact stage at which pH exerts its influence might have determined the point of difference to be between normal mucosa and small adenoma, small and large adenoma, large adenoma and early carcinoma or early and advanced carcinoma. No such point was found.

Why have these results failed to support Thornton's hypothesis?[2] The hypothesis rests heavily on the assertion that the important bacterial enzymes are inhibited at low pH, and he cites two studies to support this.[3 4] The data in these studies relate only to qualitative in vitro studies on a limited range of bacteria and enzymes. The effect of pH was only seen in relation to the initial pH of the culture medium, not its eventual steady state (or 'working' pH). Whether these bacteria would be inhibited in human colons is not clear and, furthermore, there may be compensatory changes in other groups of colonic bacteria taking over from the inhibited bacteria. The in vitro studies cannot take any account of this potential for change in the bacterial flora which may occur in the colon.

As the radiocapsule passed through the gastrointestinal tract it measured the pH of the intraluminal contents in contact with the measuring electrode. This will have reflected the pH of the bacterial environment within the bowel. It was clearly not a measure of mucosal pH, however, apart from on those random occasions when the radiocapsule would have been in contact with the mucosa. If the chain of events leading to carcinogen production takes place at the mucosal surface then mucosal pH would be more important but it seems unlikely that this should be so. Bacterial metabolic activity is likely to be concentrated in the medium containing the substrates which they require, rather than on the mucosa peripheral to them.

If carcinogenesis is a long term process occurring over years rather than months and colonic pH varies with diet within weeks,[19] the colonic pH responsible for the process of carcinogen production over some period in the past may have been quite different from that measured by the time of detection of the neoplasia. Diet may well have changed in response to bowel symptoms over a period of some weeks before diagnosis and this may have confounded the detection of differences in pH. Taking a 'high fibre diet' is widely thought to be good for disorders of the bowel and could have led to a misleading colonic acidification.

It may be that those within the group of normal subjects with alkaline colons are more at risk at some time in the future of developing a colorectal neoplasm, by which time change in dietary habits may have given them a quite different gastrointestinal pH profile.

The relation between colonic pH and epithelial cell proliferation rates has been investigated in rats. Dietary fibre supplements were shown to both reduce colonic pH and increase cell proliferation rates,[20] but these pH measurements were made at laparotomy in anaesthetised animals. It has since been shown, however, that dietary fibre supplements are protective against azoxymethane induced colorectal tumours in rats.[21] It is difficult to relate the results of these rodent studies to the aetiology of colorectal cancer in man.

The failure to show an association between raised colonic pH and subjects with colorectal neoplasia must cast doubt on Thornton's hypothesis.[2] Although there may be deficiencies in the hypothesis, it may be the timing of these measurements in relation to the time of carcinogen production that accounts for the lack of correlation.

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