

Evidence for adenoma-carcinoma sequence in the duodenum of patients with familial adenomatous polyposis

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Abstract

Aims—To explore the association between duodenal adenoma and carcinoma in patients with familial adenomatous polyposis (FAP).

Methods—A multicentre survey of 1262 patients with FAP yielded 47 cases of duodenal cancer. The association between adenoma and cancer was assessed in these cases.

Results—Adenomatous tissue was found within duodenal cancer in 29 of 44 (66%) patients with FAP and in mucosa adjacent to duodenal cancer in 31 of 42 (73%) such patients. Adenomas were found as a component of, or adjacent to, duodenal cancer in 38 of 45 (84%) patients.

Conclusions—These observations support the existence of the adenoma-carcinoma sequence in the duodenum of patients with FAP. Factors associated with malignant change included villous histology, moderate or severe dysplasia, and the presence of stage IV duodenal polyposis.

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Nearly all patients with familial adenomatous polyposis (FAP) develop adenomas in the duodenum.^{1,2} Although the risk for duodenal cancer is significantly greater in patients with FAP than in the normal population,³⁻⁵ only about 5% of patients with FAP go on to develop duodenal cancer. Moreover, while it might be expected that the duodenum of patients with FAP conforms to the adenoma-carcinoma sequence,⁶ there is no evidence for this. This study aimed to document the association between adenomas and carcinomas in the duodenum of patients with FAP, and also to determine what factors might be associated with malignant change.

Methods

Two groups of patients were involved in this study. The first group (group 1) consisted of patients with FAP known by the St Mark's Polyposis Registry to have had duodenal cancer. The histopathology of these patients was reviewed retrospectively. The second group (group 2) consisted of patients with FAP with duodenal cancer, as revealed by a survey of upper gastrointestinal neoplasia in FAP conducted by the Leeds Castle Polyposis Group (LCPG) in the late 1980s.³ Participating groups in this survey were: Toronto General Hospital, Toronto, Canada; The Cleveland Clinic Foundation, Cleveland, Ohio, USA; the Rigshospitalet, Copenhagen, Denmark;

Helsinki University, Helsinki, Finland; New York Hospital-Cornell Medical Center, New York, USA; St Mark's Hospital, London; St Erik's Hospital, Stockholm, Sweden; Mayo Clinic, Rochester, USA; Johns Hopkins Hospital, Baltimore, USA; and Tokyo University Hospital, Tokyo, Japan. Some findings from this study have been published before, but the issue of adenomatous residue in duodenal cancer has not been addressed.³ Moreover, information from eight additional patients with FAP and duodenal cancer from St Mark's Hospital is presented here for the first time.

The number of patients who had an adenoma as a component of a duodenal cancer was recorded. The proportion of patients who had adenomas in mucosa directly adjacent to a duodenal cancer was also noted.

Results were assessed for each group separately and then for the two groups combined. Adenomas found as a component of cancer in the St Mark's group of patients were also classified according to whether they were tubular, tubulo-villous, or villous in architecture, and the degree of dysplasia was noted. The stage¹ of duodenal polyposis (where stage I equates with minimal duodenal polyposis and stage IV with severe duodenal polyposis) was calculated, where possible, for group 1 patients.

Results

GROUP 1

Histopathology was available for review in 12 patients (nine men, three women; average age 51.8 years, range 27-71 years). Of these 12 patients, an adenoma was a component of cancer in 10 cases, and 10 patients also had adenomas in mucosa adjacent to duodenal cancer (table).

In total, 11 of the 12 (92%) patients had either an adenoma as a component of a duodenal cancer or had adenomatous tissue present in mucosa adjacent to a duodenal cancer. Of the 10 adenomas found as a component of cancer, the histology was villous in eight, tubulo-villous in one, and tubular in one. The degree of dysplasia was moderate or severe in all but one of these cases.

Association between adenomas and duodenal cancer in patients with FAP

	Adenoma	
	As a component of cancer	In mucosa adjacent to cancer
St Mark's patients	10/12	10/12
LCPG patients	19/32	21/30

(LCPG = Leeds Castle Polyposis Group)

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Classification of the stage of duodenal polyposis was possible in eight of the St Mark's patients, and all eight had stage IV duodenal polyposis.

GROUP 2

Duodenal cancer was reported in 35 of 1250 patients with FAP (23 men, 12 women; average age 51.4 years, range 28–81 years). Of these 35 patients, 32 were evaluable in terms of assessment of adenomas as a component of cancer. Of these 32 patients, 19 had adenomas as a component of cancer. Only 30 of the 35 patients were evaluable in terms of assessment of the presence of adenomas in adjacent mucosa. Adenomas in adjacent mucosa were seen in 21 of these 30 patients (table 1).

In total, 27 of 33 (82%) evaluable patients either had an adenoma as a component of a duodenal cancer or had adenomatous tissue present in mucosa adjacent to a duodenal cancer.

BOTH GROUPS COMBINED

Adenomas occurred as a component of duodenal cancer in 29 of 44 (66%) patients and in mucosa adjacent to duodenal cancer in 31 of 42 (74%) patients. Adenomas were found as a component of, or adjacent to, duodenal cancer in 38 of 45 (84%) evaluable patients. Of the seven patients without such adenomas, one had an adenoma elsewhere in the duodenum. It is not known whether the remaining six patients had other duodenal adenomas.

Discussion

The question of adenomatous residue in duodenal cancer has not been addressed in patients with FAP before. In people without FAP, however, adenomas have been found in ampullary duodenal cancers in 18 of 22 cases,⁷ 20 of 109 cases,⁸ 53 of 58 cases⁹ and in 11 of 26 cases.¹⁰

The findings of our study strongly support the existence of the adenoma-carcinoma sequence in the duodenum of patients with FAP. Those patients most at risk for malignant change would appear to be those who display villous change or who have stage IV duodenal polyposis. These features are only found in a few patients with FAP.¹¹ More precise risk estimation may be provided by study at the molecular level. For example, a preliminary report suggests that K-ras codon 12 mutations occur late in the adenoma-carcinoma pathway, where they are found in large, moderately to severely dysplastic periampullary adenomas.¹² Another late change might be the presence of p53 mutations, as found in advanced colonic adenomas of patients with FAP.¹³ Even within the colon, such studies are in their infancy. For example, Ando *et al*¹⁴ have shown that while K-ras mutations correlate with the degree of dysplasia of colonic adenomas of patients with FAP, the mutation frequency in cancer was much lower than in severely dysplastic adenomas. Disease severity might also reflect functional differences resulting from the numerous mutations within the adenomatous polyposis coli (APC) gene on chromosome 5, each of

which can produce FAP.¹⁵ Such a scenario would mimic that which seems to occur in cystic fibrosis, in which there is good correlation between the type of mutation and the severity of the disease.¹⁶

Duodenal adenomas in patients with FAP are difficult to treat, and in most patients no treatment is required. However, intervention seems to be indicated in those patients who have developed stage IV duodenal polyposis or who have duodenal adenomas with villous histology or with moderate to severe dysplasia on biopsy. Until such time as it becomes possible to predict which patients will go on to develop such features, prophylactic drug treatment should continue to be explored.^{17,18}

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