Duodenal adenomatosis in familial adenomatous polyposis

S Bülow, J Björk, I J Christensen, O Fause, H Järvinen, F Moesgaard, H F A Vasen, the DAF Study Group

Background: The prevalence of duodenal carcinoma is much higher in familial adenomatous polyposis (FAP) than in the background population, and duodenal adenomatosis is found in most polyposis patients. Aims: To describe the long term natural history of duodenal adenomatosis in FAP and evaluate if cancer prophylactic surveillance of the duodenum is indicated.

Methods: A prospective five nation study was carried out in the Nordic countries and the Netherlands. Patients: A total of 368 patients were examined by gastroduodenoscopy at two year intervals during the period 1990–2001.

Results: At the first endoscopy, 238 (65%) patients had duodenal adenomas at a median age of 38 years. Median follow up was 7.6 years. The cumulative incidence of adenomatosis at age 70 years was 90% (95% confidence interval (CI) 79–100%), and of Spigelman stage IV 52% (95% CI 28–76%). The probability of an advanced Spigelman score increased during the study period (p<0.0001) due to an increasing number and size of adenomas. Two patients had asymptomatic duodenal carcinoma at their first endoscopy while four developed carcinoma during the study at a median age of 52 years (range 26–58). The cumulative incidence rate of cancer was 4.5% at age 57 years (95% CI 0.1–8.9%) and the risk was higher in patients with Spigelman stage IV at their first endoscopy than in those with stages 0–III (p<0.01).

Conclusions: The natural course of duodenal adenomatosis has now been described in detail. The high incidence and increasing severity of duodenal adenomatosis with age justifies prophylactic examination, and a programme is presented for upper gastrointestinal endoscopic surveillance.

Duodenal polyps in familial adenomatous polyposis (FAP) were first described almost a century ago, duodenal carcinoma was reported in 1935 and the first series of upper gastrointestinal endoscopic screening was published in 1977. The increasing use of prophylactic examination and early colectomy has caused a substantial reduction in the incidence of colorectal cancer which has led to improvement in prognosis. Over the last decades, the reduction in the incidence of colorectal cancer which has led to improvement in prognosis. Over the last decades, the reduction in the incidence of colorectal cancer which has led to improvement in prognosis.
endoscopy to the nearest time point. Statistical calculations were done using SAS (v 8.2; SAS Institute, Cary, North Carolina, USA). A p value of less than 5% was considered significant.

**RESULTS**

**First endoscopy**

A total of 368 patients (182 males and 186 females) entered the study in Denmark (n = 108), Finland (n = 65), Holland (n = 35), Norway (n = 59), and Sweden (n = 101). Median ages at diagnosis of FAP, at colectomy, and at the first upper gastrointestinal endoscopy in the study were 25 years (range 6–67), 26 years (range 9–67), and 37 years (range 20–81), respectively. Seven patients had various types of local excision of duodenal polyps before entering the study. Fundic gland polyps were seen in 198 (54%), gastric adenomas in 37 (10%), and gastric hyperplastic polyps in nine (2%) patients. Duodenal polyps were seen in 228 patients, in whom histological examination showed adenomas in 209 and normal mucosa in 19. Random biopsies showed adenomatous tissue in 28 patients without visible polyps at endoscopy. In total, 238 patients (65%) had duodenal adenomas, of whom 12% were invisible. Median age at diagnosis of duodenal adenomas was 38 years (range 20–81). The Spigelman classification in 366 classifiable patients was stage 0, 123 (34%); stage I, 55 (15%); stage II, 97 (27%); stage III, 64 (17%); and stage IV, 27 (7%) (fig 1).

**Development of adenomatosis**

The median number of endoscopies was 4 (range 1–5; 131 with five endoscopies, 57 with four, 52 with three, 45 with two, and 83 with one), and the median follow up period was 7.6 years (range 0.5–10.4). The distribution according to Spigelman stage at the follow up endoscopies is shown in fig 1. During the observation period, 12 patients had open duodenotomy with polyp excision. The incidence of duodenal carcinoma, and the total incidence of carcinoma showed a significant increase over time (p = 0.0001) and time from diagnosis to entry (dichotomised at 15 years) in a Cox proportional hazards model, no significant effect of the covariates was demonstrated (p = 0.51, p = 0.98, and p = 0.53, respectively). The cumulative incidence by age in this group was 73% at age 70 years (95% CI 57–89).

During the follow up period, four patients (1.1%) developed a duodenal carcinoma, and the total incidence of carcinoma was 6/368 (1.6%; 95% CI 0.3–2.9%). Median age at diagnosis

![Figure 1](http://gut.bmj.com/)  
**Figure 1** Spigelman classification in classifiable patients in relation to time after entry into the study.

![Figure 2](http://gut.bmj.com/)  
**Figure 2** Cumulative incidence of adenomatosis development.
of duodenal cancer in the six patients was 52 years (range 26–58) and the cumulative incidence rate was 4.3% at age 57 years (95% CI 0.1–8.9%). Spigelman stages at the previous endoscopies in the four patients who developed duodenal cancer were I–II, IV–III–IV–III, III–II–IV, and IV–IV–IV–IV, respectively. Among 27 patients with Spigelman stage IV at the first endoscopy, two (7%) later developed a carcinoma compared with 2/339 (0.7%) with Spigelman stages 0–III (p<0.01). The cumulative crude five year survival after duodenal cancer was 44% (95% CI 22–67).

DISCUSSION

The present study is the largest series of FAP patients followed prospectively with regular upper endoscopy. The advantages of the study were that it was based on five national polyposis registers with a high completeness of registration, it included a 10 year study period, and random biopsies were taken in patients without visible duodenal polyps. The disadvantages were the use of forward viewing endoscopy and decreasing patient compliance throughout the study period. The former may have led to underestimation of the stage of adenomatosis whereas decreasing patient compliance may have had the opposite effect as it cannot be ruled out that more patients with advanced duodenal adenomatosis continued to participate in the study.

Findings at the first endoscopy demonstrated that the prevalence of duodenal adenomatosis was 65%. This is similar to values of 58–74% in major series in the literature, which are comparable concerning age at diagnosis of FAP and at the first endoscopy (table 2). It is interesting that 12% of adenomas were diagnosed only histologically and this underlines the importance of multiple random biopsies in patients without visible polyps. It has been stated that side viewing endoscopy is the ideal procedure for evaluation of duodenal adenomatosis but as this procedure is only used routinely by endoscopists performing ERCP, we considered the standard use of side viewing endoscopy to be unrealistic in this multicentre study. In our opinion, future studies of the natural course or treatment of duodenal adenomatosis should include a combination of forward and side viewing endoscopy as well as random biopsies. We found the same proportion of adenomatosis Spigelman stage IV as in the Swedish study, in contrast with the Finnish result of only 2%. Median age of patients in the latter study was four years younger, and an updated analysis showed 3.6% Spigelman stage IV, thus indicating that the difference is probably not real (H Järvinen, personal communication).

The follow up examinations confirmed the results of the Nordic studies and showed that the lifetime risk of duodenal adenomatosis is approaching 100%. We found a lifetime risk of Spigelman stage IV of 52%, with a broad confidence

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**Table 1:** Estimated cumulative probabilities (probability that the stage is less than or equal to 0, 1, 2, or 3) for Spigelman stages for patients entering with and without adenomas, and with time from diagnosis to entry dichotomised at 15 years (familial adenomatous polyposis (FAP) time)

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*Including multiple random biopsies from mucosal folds in patients without visible polyps.
*Including multiple biopsies from polyps.
Table 3  Patient series, including results of upper gastrointestinal endoscopy follow up

| Author et al. | Year | Endoscopy type | No of patients | Findings at first endoscopy | Age at diagnosis of FAP (years) | Duodenal cancer (% of all patients) | Cumul. incidence (cumul. risk) of duodenal cancer at 75 y (%/1000) | Duodenal adenomas (% of all patients) | Cumul. incidence (cumul. risk) of duodenal adenomas at 70–75 y (%/1000) | Duodenal Spigelman stage IV at 70–75 y (% of all patients) | 
|--------------|------|----------------|-----------------|----------------------------|-------------------------------|----------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|-----------------------------------------|------------------|
| Bülow et al. | 1992 | SV + FV        | 71              | 14 20 41 2        | 58                            | 2.0                             | 1.4                                   | 2.0                                   | 4.5                                   | 0.4                                     | 0.9              |
| Debinski     | 1995 | SV             | 111             | 2 3 4 7 10 17 50  | 58                            | 2.0                             | 1.0                                   | 1.7                                   | 5.0                                   | 0.5                                     | 1.7              |
| Heiskanen     | 1998 | SV + FV       | 140             | 2 3 4 7 10 17 50  | 58                            | 2.0                             | 1.0                                   | 1.7                                   | 5.0                                   | 0.5                                     | 1.7              |
| Bülow et al. | 2002 | FV             | 180             | 2 3 4 7 10 17 50  | 58                            | 2.0                             | 1.0                                   | 1.7                                   | 5.0                                   | 0.5                                     | 1.7              |

*FV, forward viewing endoscope; SV, side viewing endoscope.

Celecoxib. In small series, sulindac had little23 or no effect,24 25 trials have included sulindac, calcium, calciferol, and seems promising but has not yet been validated. 20

It is possible that severe degree of dysplasia should add more points to the total Spigelman score and therefore we propose that validation of the Spigelman classification should be undertaken. This could be done in the setting of a multicentre study under the auspices of the Leeds Castle Polyposis Group.

The overall incidence of 1.6% for duodenal carcinoma in this five nation study is similar to most other series10 12 15 but lower than in a recent 10 year follow up study from St Mark’s Hospital.17 During follow up, carcinoma developed in 2/26 patients with Spigelman stage IV at their first endoscopy compared with 3/11 in the Swedish study14 and 4/11 in the St Mark’s study.17 These values are small and probably not different, thus indicating a higher risk of carcinoma development in patients with Spigelman stage IV with time. It is possible that severe degree of dysplasia should be used in a small number of patients for rectal adenomatosis or desmoid tumours. The influence of this on the development or progression of duodenal adenomatosis is however considered minimal.14 Therefore, we believe that our results are valid and indicate that the Spigelman stage will progress with time and patient age, as recently indicated.15 The unchanged distribution of histological type with time was expected but the lack of change in degree of dysplasia is surprising and conflicts with the increasing proportion of patients with Spigelman stage IV with time. It is possible that severe degree of dysplasia should add more points to the total Spigelman score and therefore we propose that validation of the Spigelman classification should be undertaken. This could be done in the setting of a multicentre study under the auspices of the Leeds Castle Polyposis Group.

The ideal treatment of duodenal adenomatosis includes complete and lasting destruction of adenomas with a minimum risk of complications and no functional problems. Such a treatment is not yet available but several options have been tried. Endoscopic treatment with Nd-YAG laser or electrocautery implies a risk of perforation and pancreatitis, and requires repeated endoscopies.19 Photodynamic therapy seems promising but has not yet been validated.20 Duodenectomy with polypectomy is feasible but inevitably leads to recurrence.17 Radical surgical treatment has included total pancreatico-duodenectomy (Whipple’s operation), which is presently used only in patients with carcinomas. A less comprehensive procedure is recommended as a cancer prophylactic operation in patients with severe adenomatosis: pylorus sparing or pancreas sparing duodenectomy result in a lower incidence of complications and a good quality of life.21 Pharmacological trials have included sulindac, calcium, calciferol, and celecoxib. In small series, sulindac had little12 or no effect,24 25 and calcium and calciferol had no effect.22 A randomised controlled trial showed that celecoxib 800 mg daily resulted
in a reduction in duodenal adenomatosis but there are as yet no long term results concerning adenomatosis development or a cancer protective effect.

Several studies have tried to identify a genotype-phenotype relation between specific mutation sites of the APC gene and the severity of duodenal adenomatosis but the results have been inconsistent. Five studies indicated correlations with mutations in codon 157–416, codon 279–1309, exon 15, after codon 1400, and exon 10–15, respectively, whereas two studies found no correlation between mutation sites and the severity of adenomatosis or carcinoma development. During the last decades, endoscopic surveillance of the duodenum has been recommended. An evaluation of the effect of such a policy showed a lifetime risk of 3–5% of duodenal cancer, and decision analysis demonstrated that regular surveillance resulted in an increase in life expectancy of seven months. Endoscopic ultrasonography has been recommended in patients with Spigelman stages III–IV to ensure that invasive growth has not occurred. A recent study presented a detailed surveillance programme, including endoscopy at intervals of 1–5 years depending on the Spigelman stage. Patients with stages II and III are considered for chemoprevention and endoscopic treatment, and those with stage IV should be offered a pancreas preserving duodenectomy.

The present results indicate that regular endoscopic surveillance of the duodenum should be offered to all FAP patients, and our proposed surveillance programme is shown in table 3. The first endoscopy should be carried out at the age of 30 years and include multiple random biopsies taken from the duodenal mucosa in patients without visible polyps. We find the present evidence of endoscopic therapy too weak to justify a general recommendation outside specialised centres. Endoscopic ultrasonography is recommended for evaluation of patients with Spigelman stage IV, severe dysplasia, or large adenomas in order to ensure that invasive growth can be ruled out. In order to delay progression to Spigelman stage IV, it seems justified to treat patients with stage III with celecoxib 800 mg daily. Patients with Spigelman stage IV should be informed about cancer prophylactic surgery. Endoscopic surveillance (including endoscopic ultrasonography) and chemoprevention are recommended at intervals of three months in patients who are not suitable or refuse surgery.

In conclusion, the long term natural history of duodenal adenomatosis in FAP is now known in detail and it has been documented that the incidence and severity of adenomatosis increase with age. There is thus convincing evidence to justify recommendation of regular endoscopic surveillance in all FAP patients. Furthermore, a high risk group for carcinoma development (Spigelman stage IV) has been identified. Chemoprevention with celecoxib may prove to delay worsening of duodenal adenomatosis. Patients with Spigelman stage IV should be offered prophylactic surgery, with pancreas preserving or pylorus sparing duodenectomy being the procedures of choice. We propose that the surveillance programme should be evaluated prospectively in an international multicentre study.

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O Fausa, The Norwegian Polyposis Register, Rikshospitalet, Oslo, Norway
H Järvinen, The Finnish Polyposis Register, Helsinki University Central Hospital, Helsinki, Finland
H F A Vasen, The Dutch Polyposis Register, The Netherlands Foundation for the Detection of Hereditary Tumours, Leiden, the Netherlands

APPENDIX

The DAF Study Group included: H Järvinen, A Kahri, and J-P Mecklin (Finland); T Alm, J Björk, R Hultcrantz, and C Rubio (Sweden); S Norheim Andersen, A Bakka, and O Fausa (Norway); G Griffioen, F Nagengast, GJA Offerhaus, and H Vasen (the Netherlands); S Bülow, LI Christensen, H Hojén, F Moesgaard, AM Mogensen, and LB Svendsen (Denmark).

EMH Matthus-Vliegen, P de Ruyter, and B Tal (Holland)
and L-K Enander, K Furugård, D-A Hallbäck, and H-O Håkansson (Sweden).

REFERENCES

A 44 year old woman was admitted with a two week history of colicky abdominal pain, vomiting, and constipation. Past medical history included Ehlers Danlos syndrome type IV with a history of spontaneous retroperitoneal haemorrhage treated conservatively. She was also known to have large uterine leiomyomas for which she was on hormonal therapy and was awaiting a hysterectomy.

On the fourth day of admission she developed severe colicky abdominal pain, persistent vomiting, gross abdominal distension, and obstipation.

GI Snapshot

Large bowel obstruction due to a benign uterine leiomyoma

Question

A 44 year old woman was admitted with a two week history of colicky abdominal pain, vomiting, and constipation. Past medical history included Ehlers Danlos syndrome type IV with a history of spontaneous retroperitoneal haemorrhage treated conservatively. She was also known to have large uterine leiomyomas for which she was on hormonal therapy and was awaiting a hysterectomy.

On examination she had abdominal distension with generalised vague tenderness and some suprapubic fullness. Digital rectal examination revealed an empty rectum with a large pelvic mass bimanually palpable anteriorly.

Chest x ray was normal but supine abdominal x ray revealed faeces filled distended loops of large bowel with minimal air in the rectum. Routine blood tests were within normal limits. She was initially treated conservatively with laxatives and enemas which did not improve her symptoms. On the fourth day of admission she developed severe colicky abdominal pain, persistent vomiting, gross abdominal distension, and obstipation.

See page 430 for answer.

Correspondence to: Mr A S Fawole Department of Academic Surgical Gastroenterology, St James’s University Hospital, Beckett St, Leeds LS9 7TF, UK; pamshina@aol.com

R P C Chaparala
A S Fawole
N S Ambrose

Department of Academic Surgical Gastroenterology, St James’s University Hospital, Leeds, UK

A H Chapman

Department of Radiology, St James’s University Hospital, Leeds, UK
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R P C Chaparala, A S Fawole, N S Ambrose and A H Chapman

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