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Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK

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Summary

Background Flat and depressed colorectal tumours were originally thought to be unique to the Japanese population. Recently there have been reports of flat and depressed lesions in western countries but they have been thought to be uncommon.

Methods In this prospective study, 1000 consecutive patients attending for routine colonoscopy were examined for flat or depressed lesions. The examinations were done by one European colonoscopist using methods developed in Japan.

Findings 321 adenomas were found: 202 (63%) were polypoid, 36% (117) were flat and 2 (0·6%) appeared depressed. Most adenomas contained areas of mild or moderate dysplasia but 10% (31) were severely dysplastic. Six Dukes' A adenocarcinomas were identified together with 25 more advanced adenocarcinomas. The likelihood of Dukes' A cancer or severe dysplasia increased from 4% (3/70) in small flat lesions, to 6% (9/154) in small polyps, 16% (8/50) in larger polyps, 29% (14/49) in large flat lesions, and 75% (3/4) in depressed lesions. 54% (20/37) lesions containing severe dysplasia or Dukes' A carcinoma were flat or depressed.

Interpretation The polyp-carcinoma hypothesis prompts colonoscopists to search only for polypoid lesions when screening for cancer, and many early colorectal neoplasms may therefore be missed. Colonoscopists require training in the recognition of flat and depressed lesions to detect colorectal tumours in the early stages.

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Introduction

The adenoma-carcinoma hypothesis proposes that colorectal cancers arise from adenomatous polyps.[1] Morson[2] estimated that up to two-thirds of all colorectal carcinomas arise from adenomatous polyps, but was unable to explain the origin of the remainder. Japanese workers have reported the existence of flat and depressed tumours since the 1980's.[3–5] Retrospective reviews indicate that 12–40% of adenomas or early colorectal carcinomas appear flat, or as depressions, rather than polyps.[6] Outside Japan however, there have been few reports of such lesions.[7–9] Although there is a higher incidence of colonic cancer in Europe and the USA than in Japan, flat or depressed lesions have been regarded as rare in western countries. Lanspa et al,[10] suggested that flat adenomas might have the same prevalence as other adenomas in the USA, and that they may represent an early stage of adenoma formation. Fujii et al[11] reported that up to two-thirds of adenomas in a small prospective study of 210 patients in the UK, appeared flat or depressed.

The polyp-carcinoma hypothesis has led to the hope that screening to clear the colon of polyps would reduce the risk of colorectal cancer.[12] If flat and depressed tumours are commoner than previously thought, it would have important implications for cancer prevention programmes because these lesions are more difficult to detect. We have therefore undertaken a large prospective study to determine the prevalence and distribution of flat or depressed neoplasms in the UK.

Methods

1000 consecutive, unselected patients attending for routine colonoscopy in Leeds and Bradford were screened for flat or depressed neoplasms by a single colonoscopist (BJR). Informed consent was obtained from all patients. Mean age was 59 years (range 15–98) with a male/female ratio of 7/10.

All colonoscopies were done between June 1995 and March 1999, with a standard Olympus 200L colonoscope and the 200Z magnifying colonoscope. Bowel preparation included 2–5 L polyethylene glycol electrolyte solution in the morning before an afternoon examination, or the previous evening in those patients undergoing examination in the morning. Patients were sedated with midazolam (mean dose 4 mg), and 20 mg buscopan was given intravenously to patients who had no contraindication to its use. Patients were not preselected, and the indications were similar to other units in the UK (table 1). 938 (94%) of all examinations

	No of cases	Total number of adenomas or carcinomas found (% of examinations)
Change in bowel habit	261	57 (22%)
Polyp surveillance	163	108 (66%)
Anaemia	143	68 (48%)
Rectal bleeding	119	35 (29%)
Assessment of inflammatory bowel disease	98	4 (4%)
Abdominal pain	68	29 (43%)
Postsurgical cancer surveillance	66	28 (42%)
Surveillance for ulcerative colitis	42	8 (19%)
Other	40	15 (37%)
Total	1000	352 (35%)

Table 1: **Indications for colonoscopy**

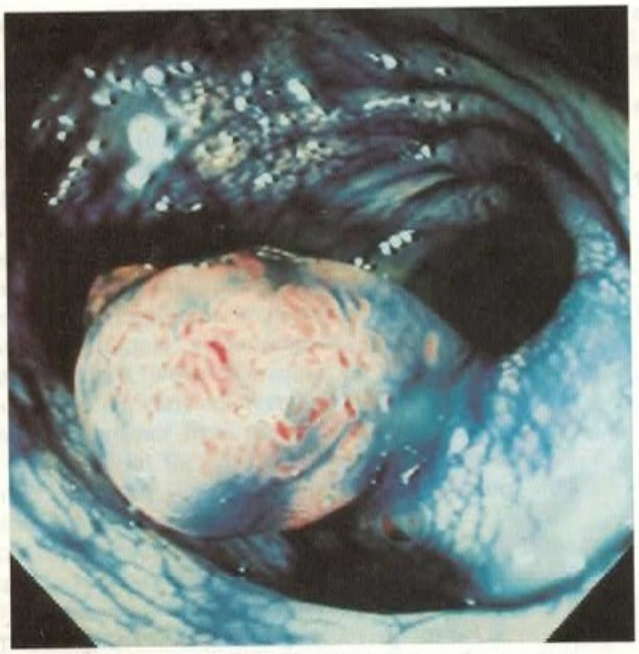

Figure 1: **Pedunculated colonic polyp**
15 mm in diameter, after dye spraying.

were completed to the caecum. The examination was stopped because of poor bowel preparation in 28 cases (3%), severe sigmoid diverticular disease in 12 patients (1%), and persistent looping of the endoscope in 22 (2%) of cases.

By contrast with colonic polyps (figure 1), flat adenomas (figure 2) and depressed lesions (figure 3) usually appear as patches of erythema or irregularity of a mucosal fold; dye spraying is then important in their recognition. In Japan, the use of methylene blue, crystal violet, and indigo carmine dye have all been described, and we used 0·2% indigo carmine dye. 3–6 mL of the solution was sprayed directly onto suspicious areas with a 20 mL syringe to allow a cushion of air to push the dye through the biopsy channel. After dye has been sprayed the size and shape of the lesion is usually clearly visible (figure 3).

We used the system proposed by the Japanese Research Society for Cancer of Colon and Rectum[13] in our macroscopical classification of lesions into mucosal polyps, flat elevations, and

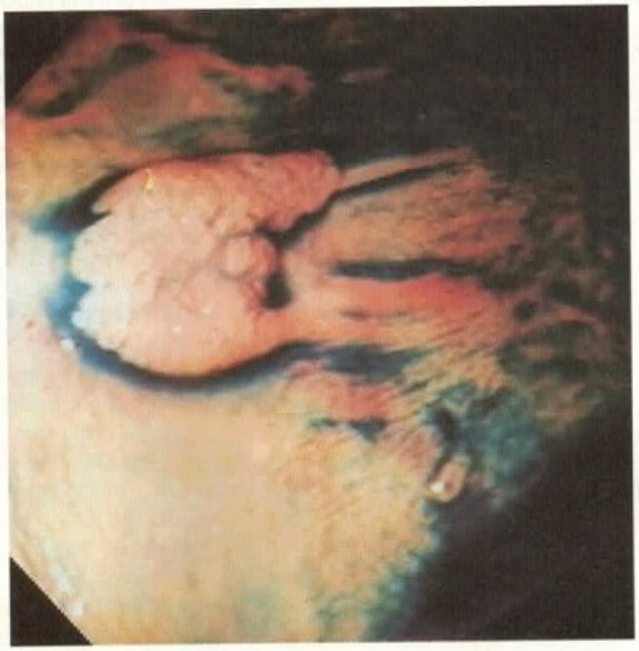

Figure 2: **Flat adenoma**
12 mm in diameter, after dye spraying. This lesion contained severe dysplasia on histological examination.

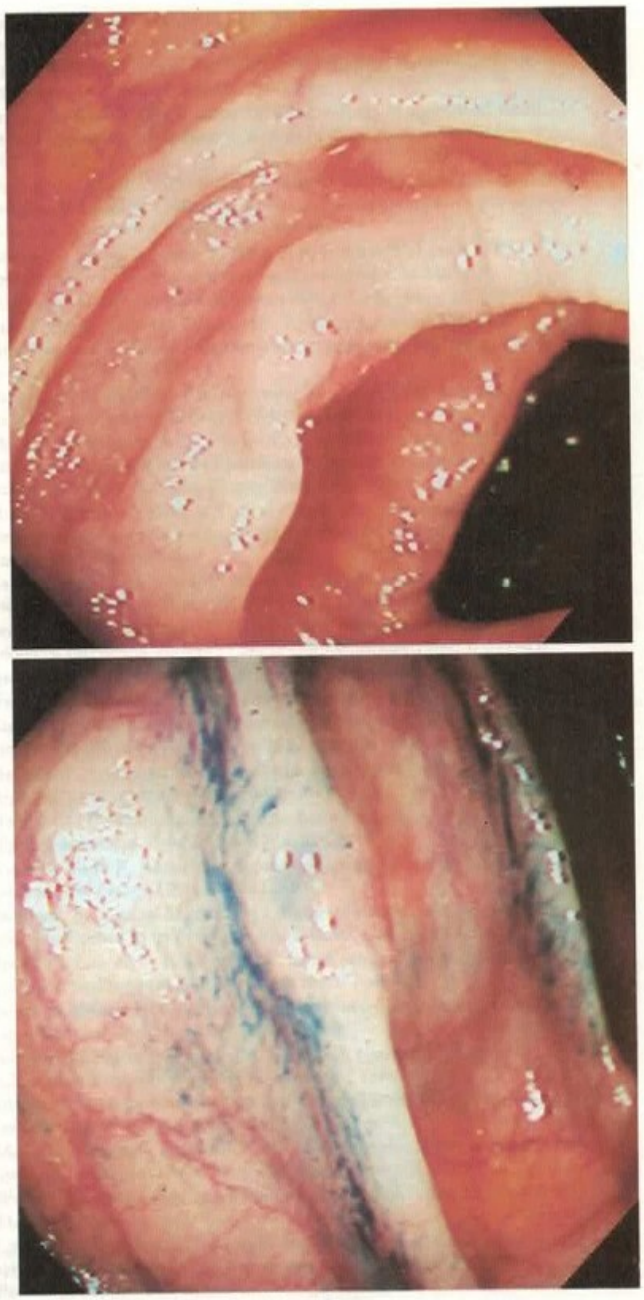

Figure 3: **Depressed adenoma**
6 mm in diameter, and containing areas of severe dysplasia. Before spraying (top panel), and after dye spraying (bottom panel).

depressions. There are several definitions of flat adenomas. Histologically these are usually defined as lesions with a height, as measured from the muscularis mucosa to the top of the lesion, of more than twice the height of the neighbouring mucosa.[14] A recent histological analysis of 37 small flat adenomas (less than 7 mm) by an image analyser system concluded that flat adenomas could be distinguished from small polyps by height alone.[15] These histological definitions of flat adenomas are, however, not applicable to colonoscopy. Macroscopically, we based our definition of flat adenomas on the criteria proposed by Sawada.[16] Flat adenomas were defined as mucosal elevations with a flat or slightly rounded surface and a height of less than half the diameter of the lesion. In practice, most flat adenomas were less than 2 mm in height and only very broad lesions were 5 mm high.

The diagnosis of dysplasia and adenocarcinoma was made according to the WHO system.[17] According to this classification severe dysplasia is characterised by considerable loss of nuclear polarity and irregular glandular architecture, but not breaching the muscularis mucosa. The malignant lesions were classified as early adenocarcinomas when the carcinoma cells infiltrated the

Appearance	Polypoid	Flat	Depressed	Total
Mild/moderately dysplastic adenomas	187	102	1	290
Severely dysplastic adenomas	15	15	1	31
Dukes' A carcinoma	2	2	2	6
Total	204	119	4	327

Table 2: **Correlation of appearance with histology**

submucosa but did not involve the muscularis propria.

We removed flat or sessile lesions less than 20 mm in diameter by endoscopic mucosal resection by inserting a needle beside the lesion and injecting 2–5 mL of saline into the submucosa to lift it above the surrounding mucosa.[18] Lesions that would not rise with submucosal injection of saline were referred for surgical resection. Once the lesion had been raised, a snare equipped with four sharp spikes, was applied over the lesion and closed. The snare was then relaxed slightly to allow the submucosa to retract and reduce the risk of perforation. The lesion was removed with a blend-current or cutting-current and the lesion retrieved with a five-pronged grasping forceps.

We took great care to prevent bleeding by applying a detachable snare[19] around thick stalks before removal and by applying metal clips to the epithelial defect after removal of large lesions.[20] Pedunculated polyps were removed by snare polypectomy, and lesions suspicious of more advanced disease were biopsied. Polyps smaller than 5 mm were treated by hot biopsy, where lesions are sampled using insulated diathermy forceps which destroys the base of the lesion with an electric current. As depressed lesions, larger than 10 mm, have a high incidence of invasive cancer,[21] we only attempted endoscopic resection in depressed lesions smaller than 10 mm in diameter. Specimens resected by endoscopy were pinned out and fixed in 10% formalin for 24–48 h.

Results

We identified a total of 321 adenomas in 225 patients, six Duke's A carcinomas in six patients, and 25 more advanced carcinomas in 24 patients. 111 lesions were treated by hot biopsy, 89 pedunculated lesions were removed by snare polypectomy, and 82 flat lesions were removed by endoscopic resection. 66 lesions were sampled by biopsy and, excluding the advanced carcinomas, four lesions were removed at surgery. There were several features that suggested the presence of cancer within a lesion. Flat lesions with a central depression, or those containing a single nodule, were likely to contain malignant cells infiltrating below the nodule or depressed area.

202 (63%) of all adenomas were polypoid, 117 (36%) were flat, and 2 (0·6%) appeared depressed. Most adenomas showed areas of mild or moderate dysplasia but 31 (10%) contained areas of severe dysplasia. Of the 31 severely dysplastic adenomas, 15 were polypoid, 15 were flat, and one appeared depressed. Two of the Dukes' stage A carcinomas were polypoid, two were flat, and two were depressed. No lesion showed intramucosal carcinoma without an adenomatous component (table 2). Two-thirds (134/204) of the polypoid lesions were situated between the splenic flexure and rectum compared with 54% (66/123) of the flat or depressed lesions.

Lesions containing areas of severe dyplasia and Dukes' A carcinoma may be regarded as early cancers, and failure to detect and treat these lesions is likely to lead to advanced colorectal carcinoma. Altogether there were 37 such lesions (31 severely dysplastic adenomas and six Duke's A carcinomas). The overall risk of a polypoid lesion containing early cancer was 8% (17/204) compared with 14% (17/119) for flat lesions.

Appearance	Proportion of lesions with early cancer (%)	Overall mean size (mm)
Polyps <10 mm	9/154 (6%)	5·7
Polyps ≥10 mm	8/50 (16%)	15·8
Flat lesions <10 mm	3/70 (4%)	5·1
Flat lesions ≥10 mm	14/49 (29%)	20·6
All depressed lesions	3/4 (75%)	9·0

Table 3: **Correlation of size with appearance and histology**

Lesions smaller than 10 mm in diameter, whether flat or polypoid, were unlikely to contain early cancer (table 3). The risk was 6% (9/154) in small polyps and 4% (3/70) in small flat lesions. Larger lesions were more likely to contain early malignant disease. The prevalence in larger polypoid lesions (10 mm or larger in diameter) was 16% (8/50) and 29% (14/49) in large flat lesions.

98 examinations were carried out to assess the activity of inflammatory bowel disease and four sessile adenomas (6–8 mm in diameter) were seen. Three contained areas of mild dysplasia, but one, situated in the rectum of a patient with active colitis, contained areas of severe dysplasia. 42 surveillance examinations were carried out in patients with quiescent ulcerative colitis affecting the whole colon. In this group eight adenomas were recorded; four were flat, (4 mm, 15 mm, 20 mm, and 25 mm in diameter); four were polypoid between 4–9 mm in diameter. Seven of these lesions were mildly dysplastic but the 20 mm flat adenoma contained areas of severe dysplasia.

The only serious possible complication was a colonic perforation, which happened in a patient with extensive ulcerative colitis who developed a toxic megacolon 24 h after the examination. There were no clinically significant complications related to polypectomy or endoscopic resection.

Discussion

Although up to two-thirds of colorectal carcinomas might develop from adenomatous polyps,[2,5] some workers have suggested that colorectal cancer can also develop de novo from normal mucosa.[22] In support of this de novo theory, several series of early colonic carcinomas, without evidence of concomitant adenomatous tissue, have been published.[23–25] In the largest series, 155 small carcinomas were identified without evidence of concomitant adenomatous tissue;[24] 59% of the lesions appeared polypoid and 34% appeared flat. Bedenne et al,[25] proposed the existence of two distinct types of colorectal cancer. An exophytic type accounts for 60% of cases and arises from the adenoma-carcinoma sequence; the remainder, an ulcero-infiltrating type, develops de novo.

An alternative explanation is that some carcinomas have an especially aggressive growth pattern, quickly destroying the neighbouring adenomatous tissue. Muto showed that flat lesions had a higher frequency of aneuploidy than did the polypoid type.[26] Outside Japan, there have also been reports that flat adenomas were ten times more likely to contain high grade dysplasia than polypoid adenomas.[27] The clinical and pathological features of four extended kindreds with the hereditary flat adenoma syndrome suggest that this is a variant of familial adenomatous polyposis.[28]

Our large prospective study confirms the presence of flat and depressed neoplasia in the UK. Our data suggest that the risk of cancer in flat adenomas was similar to that of protruded lesions when the lesions were smaller than 10 mm in diameter. However, larger flat lesions and depressed lesions were almost twice as likely as protruded lesions, of similar size, to contain areas of severe dysplasia, or foci of invasive carcinoma.

Although only four depressed lesions were recorded, one contained areas of severe dysplasia and two were Dukes' A

carcinomas. The average size of these depressed lesions was only 9 mm and they were all situated proximal to the splenic flexure. Similar findings have been published by Kudo et al,[21] who found the risk of severe dysplasia in small depressed lesions (6–10 mm) was 50%.

It is noteworthy that patients least likely to harbour a neoplastic lesion were those with inflammatory bowel disease; this may be because they were, on average, 10 years younger (49·8 years) than other patients (59·3 years).

The recognition that colorectal cancer can appear flat or depressed has important implications. The polyp-cancer hypothesis prompts colonoscopists to concentrate on polypoid lesions when screening for tumours, and a proportion of flat early colorectal neoplasms may therefore be missed. Evidence from the two largest studies suggest that this is indeed the case. The National Polyp Study[29] reported on the 6 year follow-up of 1418 patients after repeated colonoscopies to clear all polyps.

This study did not incorporate a control arm but, if the background age-specific and sex-specific incidence of colorectal cancer is used as a control group, removal of all polyps would have failed to prevent up to 24% of all subsequent carcinomas. The National Polyp Study does not elaborate on the detailed appearances of the five carcinomas that were missed, other than to provide data on sizes (6 mm, 8 mm, 15 mm, 15 mm and 25 mm), but the cancers were unusually small, suggesting more aggressive characteristics. The larger Veterans Affairs study of 32 702 patients showed that endoscopy prevented only 50% of all subsequent colorectal cancers. Some patients had, however, only been examined with the flexible sigmoidoscope. Western colonoscopists require training in the recognition of flat, elevated and depressed lesions in order to detect colorectal tumours in their early stages.

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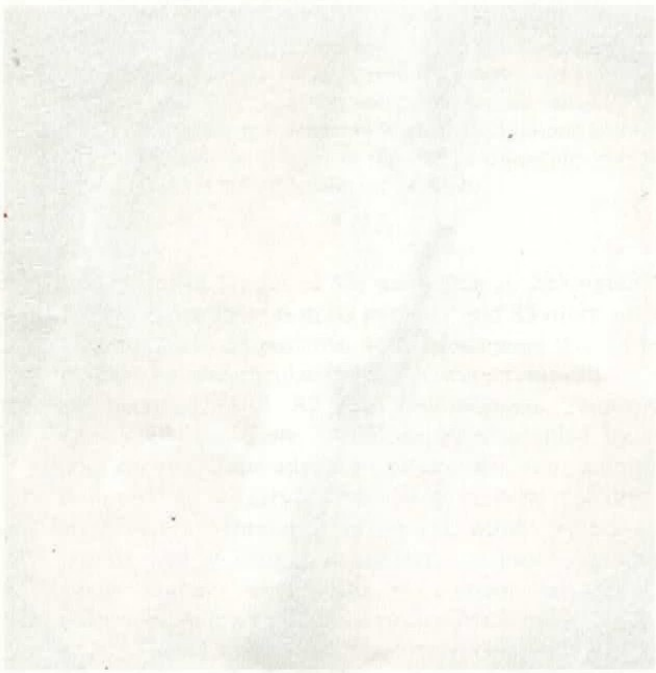

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