Pathology of colorectal adenomas: a colonoscopic survey

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SUMMARY The size, histological type, and grade of dysplasia of a large series of colorectal adenomas removed by colonoscopic polypectomy were matched against other variables such as anatomical site, age, sex, and number of adenomas per patient. Special emphasis was placed on the criteria for grading dysplasia in adenomas and the possible significance of severe dysplasia as a selective marker for increased colorectal cancer risk. The results showed that small adenomas (mostly with mild dysplasia) were evenly distributed throughout the colorectum but that adenomas showing severe dysplasia (mostly the larger tumours, >10 mm diameter) were concentrated in the left colon and rectum, particularly the sigmoid part which is also the segment with the highest risk of colorectal carcinoma in high risk populations.

Severe dysplasia in adenomas appears to be a selective histopathological marker for increased colorectal cancer risk. It is closely linked with increasing age and numbers of adenomas per patient, with the larger adenomas and particularly those with a villous component in their histology. Severe dysplasia and multiple adenomas could be valuable markers for selecting from the total adenoma population those most deserving of close surveillance in follow-up cancer prevention programmes.

Conceptually it would appear advantageous to think in terms of the dysplasia-carcinoma sequence in the colorectum rather than the polyp-cancer or adenoma-carcinoma sequence. The implications of these results in the study of the aetiology of colorectal cancer are discussed.

The increasing role of colonoscopy and polypectomy in the diagnosis and management of colorectal adenomas during the past decade has provided the histopathologist with an abundance of valuable material for study. This material is especially useful because, in most patients subjected to colonoscopy, the entire colorectum has been visualised at one examination and all polyps removed for histological diagnosis. Previous studies have relied on adenomas removed by proctosigmoidoscopy only, and surgical segments of bowel usually removed for carcinoma in which adenomas were a coincidental finding. Therefore, a colonoscopic survey should provide more detailed information about their distribution in the large bowel matched against other variables such as size, histological type, and grades of dysplasia. The results of such a clinical survey can then be compared with the figures given in various necropsy

reports. Emphasis in this study is also placed on the significance of grade of dysplasia, and especially severe dysplasia because the latter has been established as a valuable marker for increased cancer risk in ulcerative colitis as well as in the study of the epidemiology of adenomas.

Material and methods

During the eight-year period 1972 to 1979, 1167 adenomas were removed by colonoscopy from 675 patients (398 men and 277 women) either by snare polypectomy or the hot-biopsy-fulguration method.¹ The histological sections for 28 adenomas were missing, leaving 1139 adenomas available for study. From the same 675 patients a further 102 adenomas were removed by other methods, mostly by rigid proctosigmoidoscopy but a few by surgical excision. These were also included in the study, making a total of 1241 examined. Of these, 54 showing microinvasive carcinoma were excluded thus leaving a final total of 1187 adenomas for analysis.

All the removed adenomas were fixed in buffered 10% formaldehyde solution; the position of the stalk was identified, if possible, and the specimens were embedded on their sides in paraffin wax so that the tumour and stalk were orientated in their correct anatomical relationship to one another. In small adenomas (< 0.5 cm diam), only one level was cut; in larger adenomas however two or more levels were taken, according to the size of the specimen. Multiple semiserial sections were cut only in a minority of specimens to assess questionable examples of microinvasive carcinoma. All sections were stained by haematoxylin and eosin.

Size was measured on the histology slides in two dimensions and the arithmetic mean was calculated to represent the size of the tumours. Comparison of size measured in the fresh state and on histological slides showed that the size on the section was the same as, or only slightly smaller than, that in the fresh state because of the method of embedding the tumours. All the sections were examined by one of the authors (FK) and graded according to histological type and grade of dysplasia (see later).

The site of adenomas was identified from the colonoscopy records. The large bowel was divided into five segments: right colon (caecum and ascending colon); transverse colon; descending colon; sigmoid

colon; rectum. If indicated as splenic flexure or hepatic flexure, tumours at these sites were evenly allocated to either of the two adjacent segments. Age and sex of the patients were checked in the colonoscopy records or in the patients' notes.

Removal of rectal polyps by rigid proctosigmoidoscopy is often performed in the Outpatient Clinic or operating theatre rather than by colonoscopic polypectomy. In addition, removal of adenomas by proctosigmoidoscopy may have been performed at other hospitals before the patients attended St Mark's. For these reasons accurate comparison of the number of rectal and colonic adenomas was not possible. In order to make a proper comparative study of size, histological type, and grades of epithelial dysplasia between rectal and colonic adenomas a separate consecutive series of 270 rectal adenomas removed by rigid proctosigmoidoscopy during the four-year period 1976 to 1979 was also studied.

Almost all the patients in the colonoscopy series had barium enema study before colonoscopy either at St Mark's Hospital (St Mark's patients) or at other hospitals (cases referred only for colonoscopy). In referred cases when barium enema failed to visualise particular segments of colon (usually the right side), total colonoscopy was carried out but

Fig. 1 *Tubular adenoma. Haematoxylin and eosin $\times 10$.*

Fig. 2 Tubulovillous adenoma. Haematoxylin and eosin $\times 10$.

when the barium enema study was of sufficient quality and no polyps were seen in the right colon, total colonoscopy was not invariably performed. Using this policy total colonoscopy was performed in 60% of the cases and 601 patients were considered to have had adequate total examination of the large bowel by barium enema study and fiberoptic colonoscopy. There was no significant difference in the subsite distribution of colonic adenomas between "referred cases" and St Mark's cases. For this reason adenomas removed from referred patients and from St Mark's patients could be analysed together.

HISTOLOGY OF ADENOMAS

If the tubular pattern occupied more than 80% of the tumour it was classified as tubular (Fig. 1); with a villous pattern of more than 80% it was classified as villous (Fig. 2); the remainder were classified as

tubulovillous (Fig. 3).

Irrespective of histological type all adenomas can be graded by histological and cytological criteria into three grades of epithelial dysplasia (atypia)—mild, moderate, and severe, the latter being used synonymously with carcinoma-in-situ. However, there are reasons for avoiding the use of this term in surgical reports.² It is common to see differing grades of dysplasia within any one adenoma and in this study individual adenomas have been graded according to the part with the most advanced grade. Sometimes an area with one grade of dysplasia has a distinct boundary with the adjacent area showing a different grade but more often there is a gradual transition. A focus of severe dysplasia in an adenoma often shows an expansive growth pattern and a sharp boundary with the adjacent mild to moderate dysplasia. There have been other studies on grading dysplasia³⁻⁶ but it must be emphasised

Fig. 3 Villous adenoma. Haematoxylin and eosin $\times 10$.

that grading is a subjective assessment taking both structural and cytological changes into consideration.

GRADING OF DYSPLASIA

Mild dysplasia (Fig. 4)

The nuclei are elongated, larger than normal and slightly hyperchromatic with a fine chromatin pattern. They are arranged regularly at the base of the cells. Usually nucleoli are not seen. The amount of mucin is decreased and is confined to the luminal border of the cells. The number of mitotic figures is slightly increased. Pleomorphism and loss of polarity of the nuclei are not typical features of this category. The glandular arrangement is irregular with some branching but there is no further disorganisation of the glandular structure. Only occasional reversed goblet cells (intraepithelial goblet cells) may be seen. The distinction from moderate dysplasia

becomes blurred when the nucleoli begin to become stratified with some loss of polarity and the amount of mucin is further decreased.

Moderate dysplasia (Fig. 5)

This category can be defined as intermediate between mild dysplasia and severe dysplasia. The nuclei are elliptical rather than elongated and the chromatin is denser and tends to show a clumping pattern. There is nuclear pseudostratification and minor loss of polarity with some increase in the nuclear-cytoplasmic ratio. The amount of mucin is further decreased and reversed goblet cells are seen more often. An important change is the tendency towards pleomorphism of nuclei. The interglandular space is reduced and structural distortion of the crypts is more manifest, with folding of epithelial cells into the glandular lumen. This is different from the true intraglandular budding and bridging which are the features of severe dysplasia.

Fig. 4 *Mild dysplasia. Nuclei are regularly arranged on the basal side of the glands. There is some branching of the glands. Mucin is relatively well preserved. Haematoxylin and eosin $\times 120$.*

Fig. 5 *Moderate dysplasia. Nuclei are larger and show pseudostratification. Mucin is decreased. There is moderate structural abnormality. Haematoxylin and eosin $\times 120$.*

Fig. 6 Severe dysplasia. Nuclei are pleomorphic and show loss of polarity. Structural abnormality is marked, featuring intraglandular budding and bridging. Haematoxylin and eosin $\times 120$.

Fig. 7 Age and sex distribution of 675 patients.

Severe dysplasia (Fig. 6)

The changes are very similar to those of invading adenocarcinoma. The nuclei are large and pleomorphic with an obvious increase in the nuclear-cytoplasmic ratio. The chromatin pattern is

either diffusely dark or open with clumping of the chromatin and one or more nucleoli can often be seen. The marked pleomorphism is associated with loss of polarity of the nuclei and an obvious increase in the number of mitotic figures. These are the most important features of this category. Little mucin is present and cannot be recognised as a clear droplet with haematoxylin and eosin staining. The glandular structure is very distorted featuring frequent intra-glandular bridging and budding with obliteration of the interglandular space, which gives the impression of glandular fusion. This condensed growth pattern is the so-called "glandular back-to-back" arrangement. In some cases, despite little evidence of intra-glandular budding and bridging, the nuclei are large and show severe pleomorphism and loss of polarity. In many adenomas areas of severe dysplasia have a distinct boundary with adjacent less severe, even mild, changes.

Results

AGE AND SEX DISTRIBUTION

Figure 7 shows the age and sex distribution of the 675 patients in this series. The mean ages were 61.1 yr for men and 59.1 yr for women. The peak inci-

Fig. 8 Age distribution of adenoma patients (this series) and carcinoma patients (South West Thames Cancer Registry).⁷

Fig. 9 Cumulative age and sex distribution.

dence for men is in the age group 60–65 yr and for women is in the 55–60 yr group. Compared to the age distribution of large bowel carcinomas,⁷ the peak incidence occurs about 10 years younger in our adenoma patients than in carcinoma patients (Fig. 8), a figure which lends support to the concept of the adenoma-carcinoma sequence.

Figure 9 shows the cumulative age and sex distribution; the number of younger women patients slightly predominates, or is about the same as that of younger men patients but as age increases from 50 yr to over 80 yr, the tendency is for men patients to predominate. This tendency is similar to that of the age-sex distribution of large bowel carcinoma in high-risk countries, as reported by Haenszel and Correa.⁸

DISTRIBUTION AND SITE OF ADENOMAS

Table 1 shows the site distribution of 1187 adenomas. The number of rectal adenomas should not be compared to the number in the colon because, as described previously, rectal adenomas are often treated separately from colonic adenomas. About half (47%) of adenomas removed were located in the sigmoid colon, the percentage decreases from the sigmoid proximally to the right colon (8.2%) in striking contrast to the distribution of adenomas in necropsy series.^{9–14} The figure for the right colon could be a slight underestimate because of those endoscopically irremovable adenomas not biopsied and subsequently treated by right hemicolectomy. Most reports of necropsy studies show a more or less even distribution with a slightly greater percentage in the right colon. It must be remembered, however, that adenomas found in necropsy studies were mostly smaller than those in our colonoscopic series.

Table 2 shows the size of 1187 adenomas by site. Colonic adenomas smaller than 5 mm show a comparatively even distribution but in striking contrast those measuring 5 to 10 mm and >10 mm are concentrated in the left colon; the difference is statistically highly significant. ($\chi^2 = 162.17$, $df = 8$, $p < 0.001$.)

A similar trend has been shown in other studies.^{11–13} The percentage of rectal adenomas measuring 6–10 mm (29%) and >10 mm (23%) are less than those of sigmoid colon adenomas within the same size group (approximately 39% for both). However, it should be mentioned that broad-based adenomas often measuring 3.0 cm across or even larger are more common in the rectum than in the sigmoid colon or descending colon. In the right colon and in the transverse colon, 67% of adenomas were <5 mm diameter excluding a small number of

Table 1 Distribution of adenomas (combined series)

Right colon	Trans colon	Desc colon	Sigmoid colon	Rectum	Total
8.2% (97)	13.6% (161)	18.7% (222)	47.0% (559)	12.5% (148)	100% (1187)

Table 2 Size and site (1187 adenomas)

Size	Right colon	Trans colon	Desc colon	Sigmoid colon	Rectum	Total
<5 mm	64.0% (62)	69.2% (111)	44.6% (99)	22.2% (124)	48.0% (71)	39.3% (467)
6–10 mm	18.5% (18)	17.4% (28)	31.1% (69)	38.8% (217)	29.0% (43)	31.6% (375)
>10 mm	17.5% (17)	13.4% (22)	24.3% (54)	39.0% (218)	23.0% (34)	29.1% (345)

large irremovable ones. Larger adenomas in the sigmoid colon and rectum may be detected more readily than large adenomas located in other parts of the large bowel because of easier accessibility to endoscopic examination.

SITE AND GRADE OF DYSPLASIA

Table 3 shows the relation between the grade of dysplasia and the site. The most striking difference is the high percentage (9.5%) of severe dysplasia in the left colon; 68% of adenomas with severe dysplasia are located in this part of the colorectum. Adenomas with moderate dysplasia, although more often seen, show a similar subsite distribution as adenomas with severe dysplasia. The difference is statistically highly significant. ($\chi^2 = 44.19$, $df = 8$, $p < 0.001$.)

The percentage of each grade of dysplasia in the rectum is more or less similar to that obtained from the series of all rectal adenomas removed at St Mark's Hospital from 1976 to 1979 (Table 4) and in this series similar to that in the descending colon. The unexpectedly small percentage of severe dysplasia in the right colon and rectum could be due to biased selection of patients.

HISTOLOGICAL TYPES OF ADENOMA

The majority of adenomas (81%) were classified as tubular; 16% as tubulovillous (intermediate) and only 3% as villous adenoma (Table 5). Except for the percentage of villous adenomas, these figures are not significantly different when compared with a previous report from this hospital.⁶ The smaller percentage of villous adenomas in this study compared to the surgical series reported by Muto *et al* is probably due to the fact that in this colonoscopic series there was a smaller number of rectal adenomas.

It has been stated that villous adenomas are located almost exclusively in the rectum.^{15,16} In contrast, our study has shown that both tubulovillous and villous adenomas are more widely distributed with only a slightly higher incidence in the rectum and in the sigmoid colon. The percentage in the right colon, although not significantly different, is slightly higher than in the transverse and the descending colon. Again, the data for tubulovillous and villous adenomas of the rectum in this colonoscopy series (including adenomas removed by other methods) are similar to those for the previous surgical series of rectal adenomas removed at St Mark's Hospital from 1976 to 1980 (Table 6).

Table 7 shows the percentage of the three histological types related to the age of patients. The percentage of tubulovillous and villous adenomas is greater among patients older than 70 yr compared

Table 3 Percentage grades of dysplasia by site (1187 adenomas)

Grade	Right colon	Trans colon	Desc colon	Sigmoid colon	Rectum	Total
Mild	94.9% (92)	90.7% (146)	86.0% (191)	74.8% (418)	84.5% (125)	81.9% (972)
Moderate	4.1% (4)	8.1% (13)	8.1% (18)	15.7% (88)	10.1% (15)	11.6% (138)
Severe	1.0% (1)	1.2% (2)	5.9% (13)	9.5% (53)	5.4% (8)	6.5% (77)

Table 4 Grades of dysplasia in rectal adenomas

	Mild	Moderate	Severe
Rectal adenomas in colonoscopic series	84.5% (125)	10.1% (15)	5.4% (8)
All rectal adenomas (1976-1979)	82.2% (222)	12.6% (34)	5.2% (14)

Table 5 Histological type by site (1187 adenomas)

Type	Right colon	Trans colon	Desc colon	Sigmoid colon	Rectum	Total
Tubular	83.5% (81)	89.4% (144)	85.5% (190)	78.8% (440)	69.6% (103)	80.7% (958)
Tubulo-villous	14.4% (14)	9.9% (16)	11.7% (26)	18.2% (102)	25.0% (37)	16.4% (195)
Villous	2.1% (2)	0.6% (1)	2.7% (6)	3.0% (17)	5.4% (8)	2.9% (34)

Table 6 Histological type of rectal adenomas

	Tubular	Tubulovillous	Villous
Rectal adenomas in colonoscopic series	69.6% (103)	25.0% (37)	5.4% (8)
All rectal adenomas (1976-1979)	70.7% (191)	23.0% (62)	6.3% (17)

Table 7 Histological type and age (1187 adenomas)

Type	<50 yr	51-70 yr	>71 yr
Tubular	84.6% (171)	81.9% (621)	73.4% (166)
Tubulovillous	12.4% (25)	15.9% (121)	21.7% (49)
Villous	3.0% (6)	2.2% (17)	4.9% (11)

to younger age groups. This difference is statistically significant. ($\chi^2 = 9.04$, $df = 4$, $0.01 < p < 0.02$.)

It may be contributing to the observation that the percentage of severe dysplasia in patients older than 70 yr is greater than that in the younger age groups.

GRADE OF DYSPLASIA AND HISTOLOGICAL TYPE
The percentage of the different histological types in relation to degree of dysplasia shows that as the his-

Table 8 Percentage grades of dysplasia by histological type (1187 adenomas)

Grade	Tubular	Tubulovillous	Villous	Total
Mild	88.2% (845)	57.9% (113)	41.2% (14)	81.9% (972)
Moderate	7.7% (74)	26.2% (51)	38.2% (13)	11.6% (138)
Severe	4.1% (39)	15.9% (31)	20.6% (7)	6.5% (77)

Table 9 Grade of dysplasia (%) and number of adenomas (601 patients)

Grade	1	2	3	4
Mild	73	63	59	51
Moderate	13	20	24	24
Severe	14	17	17	25

Table 10 Multiplicity and age (601 patients)

	<50 yr	51-70 yr	>70 yr	Total
Single	56.4% (66)	49.0% (190)	43.8% (42)	49.6% (298)
Multiple	43.6% (51)	51.0% (198)	56.2% (54)	50.4% (303)

tological type becomes more villous severe dysplasia becomes more common (Table 8). This trend is similar to that shown in other studies.^{4,6}

SIZE AND GRADE OF DYSPLASIA

The influence of the size of adenomas on grade of dysplasia shows a similar trend to that previously reported from this hospital.⁶ As the size of adenomas increases so does the grade of dysplasia in agreement with previous study.^{4,15,17} Size is the simplest and most practical indicator and is closely related to grade of dysplasia.

MULTIPLICITY OF ADENOMAS

The numbers of adenomas per patient for this series in which there was total examination of the large bowel was 50% with one adenoma, 24% with two, 14% with three and 12% with four or more. Investigation of the relationship of size and number of adenomas per patient showed that with increasing number there is a trend towards a greater percentage of adenomas with severe dysplasia (Table 9). With increasing age of patient there is also a trend for the percentage of patients with multiple adenomas to increase (Table 10).

Discussion

Colorectal adenomas can be defined as well demarcated, circumscribed lumps of epithelial dysplasia (atypia) with or without a stalk, usually polypoid but occasionally flat, which can be categorised into three histological types: tubular, tubulovillous and villous.¹⁸ The histology of these three types of adenoma has been well documented, but it is important to remember that these are not clear cut categories, being only different manifestations of a spectrum of abnormal tissue architecture.¹⁹

The degree of dysplasia of adenomas can be graded subjectively into mild, moderate and severe, the latter being closest to invasive carcinoma. Severe dysplasia is used synonymously with carcinoma-in-situ. Although there are differences the cellular features of dysplasia in adenomas have much in common with the dysplasia seen as a consequence of long-standing ulcerative colitis and the chronic colitis caused by *Schistosoma japonica*.^{20,21} Similar changes of focal or diffuse epithelial dysplasia are seen in the stomach²² and in the squamous mucous membrane of the oesophagus.²³ Moreover, it has been pointed out²⁴ that the word "dysplasia" has general applicability in the description of histopathological precursor lesions for cancer in a variety of epithelial surfaces both within and without the gastrointestinal tract. Conceptually it now appears advantageous to think in terms of the dysplasia-carcinoma sequence in the colorectum rather than the polyp-cancer or adenoma-carcinoma sequence.

Kalus²⁵ reported that the incidence of severe dysplasia in adenomas (he used the term "carcinoma-in-situ") was 6.1% in patients with benign lesions only, whereas the incidence rose to 47% in adenomas associated with carcinoma in the same segment of the colon. From this result he concluded that the diagnosis of severe dysplasia in an adenoma should be followed by careful search for frank adenocarcinoma in any remaining colon. In another study of necropsy material in two different communities in Japan by Sato *et al*.²⁶ it was shown that adenomas are more often found in a high colorectal cancer risk community (Akita—30%) than in a low risk community (Miyagi—18.3%). These authors also showed that the adenomas found in the high risk community (Akita) more often exhibited severe dysplasia than in the low risk community (Miyagi). These studies suggest that severe dysplasia in adenomas might be useful as a selective marker for increased colorectal cancer risk.

Hill *et al*.²⁷ described an hypothesis for the aetiology of colorectal cancer in which they suggested that three factors operated in the process of carcinogenesis. Factor E1 was considered to be the fac-

tor which produces small adenomas. The second factor E2 makes the smaller adenomas become bigger. The third factor C induces carcinoma in a high proportion of large adenomas. This factor is considered to be ubiquitous and to play no part in determining the differences in the risk of developing carcinoma in large adenomas. Following this hypothesis, we suggest that patients who have small and only mildly dysplastic adenomas may be exposed to factor E1 but not E2 and these patients are considered to have a low cancer risk. On the other hand patients who have adenomas with severe dysplasia are considered to have intensified factor E2 and consequently a high cancer risk.

Our results have shown that the larger adenomas with severe dysplasia are mostly concentrated in the left colon and rectum, but particularly the sigmoid part. On the other hand, small adenomas with mild dysplasia showed a more or less even distribution throughout the large bowel. It would appear that the factor which produces small adenomas with mild dysplasia operates relatively evenly throughout the colorectum and that the factor which makes small adenomas larger and more dysplastic is particularly concentrated in the sigmoid part. Haenszel and Correa²⁸ reported that the ratio of sigmoid colon carcinoma to rectal carcinomas (S/R) increases from low-risk countries to high-risk countries. In 1975 the same authors reported that the site of rectal carcinoma was higher in a high-risk community of New Orleans than in the low cancer risk community of Cali, Colombia.²⁹ There are two other reports from the USA which show an increase in the ratio of colonic carcinomas to rectal carcinomas during the last 30 yr.^{30,31} Although most of the reports of surgically removed carcinomas in high cancer risk countries show a higher incidence of carcinomas in the rectum than in the sigmoid colon,^{7,32-34} necropsy studies have shown that the percentage of sigmoid colon carcinomas is greater than that of rectal carcinomas^{12,35,36} possibly because the number of undiagnosed sigmoid colon carcinomas is greater than those of rectal carcinomas.³⁴ Since it is probable that the true distribution of large bowel carcinomas is shown in the necropsy studies it can be concluded that in countries with a high colorectal cancer risk carcinomas are more frequently present in the sigmoid colon than in the rectum, which closely correlates with the site distribution of adenomas with severe dysplasia as reported here.

There are reports relating increased numbers of adenomas to increased cancer risk.^{6,37} For example, Muto *et al* reported that as the number of adenomas per patient increased so did the percentage of patients with invasive carcinoma. If the genesis of large bowel carcinoma is considered according to

the hypothesis of Hill *et al*,²⁷ it can be inferred that when the factor which produces adenomas (E1) is intensified, the number of adenomas per patient will increase. In his epidemiological study published in 1978,³⁸ Hill tabulated the prevalence of various factors among countries with various grades of cancer risk deduced from the incidence of adenomas and carcinomas. In this Table both factor E1 and E2 are present in high risk countries and both are normally absent in low risk countries. In other words these factors usually appear together. From this result we can deduce that if there are multiple adenomas present in patients where E1 is intensified, factor E2 would also be intensified, making some adenomas larger and more dysplastic. Our results on the relation between grades of dysplasia and the number of adenomas per patient support this theory. Patients with multiple adenomas tend to have a greater risk of developing severe dysplasia which suggests that these patients have a higher cancer risk than the patients with solitary adenomas. The evidence that the greater the number of adenomas per patient the greater the cancer risk is supported by the example of familial polyposis coli in which there are thousands of adenomas per patient, with an almost 100% risk of developing carcinoma.

It is well known that there is a higher colorectal cancer risk with increasing age. We have confirmed previous reports^{13,17,39} of a relation between age and severe dysplasia which, although not statistically significant, demonstrates a trend. Persons over 70 yr old are particularly prone to a high incidence of severe dysplasia and consequently can be considered to be those with the highest cancer risk. Table 10 also demonstrates the trend that as age increases the percentage of patients with multiple adenomas becomes greater.

Colorectal adenomas are common and most of them never become malignant. In other words the adenoma is a very dilute marker of increased colorectal cancer risk. The objective must be to search for more selective markers of especially high cancer risk by studying the histopathological features of adenomas. It is already well established that those >10 mm diameter, tumours with a pronounced villous component and adenomas with severe dysplasia have the greatest malignant potential, but in this study evidence is presented which suggests that severe dysplasia *per se* may be the most selective marker of increased cancer risk and that this is closely linked with the site distribution of colorectal cancers, numbers of adenomas per patient, and increasing age. Severe dysplasia and multiple adenomas could be valuable markers for selecting from the total population of patients with adenomas those most deserving of close surveillance in

follow-up cancer prevention programmes, but this could only be satisfactorily demonstrated by prospective studies.

The concentration of severely dysplastic adenomas in the left colon and rectum suggests that the short flexible fiberoptic colonoscope might prove to be especially valuable in the design of cancer detection and cancer prevention programmes because it is easier to use than the long instrument and theoretically should detect the majority of adenomas destined to become cancerous. Detection of lesions in the more proximal colon could be left to investigation by air contrast barium enema studies. A combination of these endoscopic and radiological techniques might prove to be the most effective screening procedure.

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