How Do Colorectal Cancers Develop?

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Background. **The aim of this study was to reveal (1) whether a flat adenoma is the precursor of a flat cancer and (2) the more frequent pathway in colorectal cancer development—a flat cancer or a polypoid cancer.**

Methods. **Clinical features and histologic characteristics of 97 flat early cancers, 138 polypoid early cancers, 60 advanced cancers involving the muscularis propria, and 185 flat adenomas were investigated.**

Results. **Of the flat cancers, 89.7% were not accompanied by residual adenoma and are considered to have arisen de novo. The distribution of flat adenomas and flat cancers was significantly different, and a follow-up of flat adenomas did not reveal any rapid growth or carcinomatous changes in the flat adenomas. The shape of advanced cancers involving only the muscularis propria almost matches that of flat early cancers. Fifty-two of 97 flat cancers and 19 of 138 polypoid cancers invaded the submucosal layer.**

Conclusions. **Flat adenomas are not considered to be precursors of flat cancers. Advanced cancers of the large intestine originate mainly from flat cancers arising de novo. The percentage of the advanced cancers that originate from flat cancers is estimated to be 71.2% (52 of 52+19) at a minimum. *Cancer* 1995;75:1534–8.**

Key words: colon, rectum, flat cancer, polypoid cancer, flat adenoma, histogenesis, de novo.

A very important discovery in the past decade has been the detection of many flat-type cancers in the large intestine.[1–4] This type of early cancer is considered one of the original forms of advanced colorectal cancers. Although another primitive form of advanced colorectal cancer (cancer in polyp) had been formulated in 1974[5] and was believed to be the only original form up to the early 1980s, we now have to determine which is the more frequent pathway for colorectal cancers to develop from a microscopic size to an advanced cancer.

In the current study our goal was to compare the incidence, clinical features, and histologic findings of flat adenomas, polypoid early cancers, flat early cancers, and advanced cancers involving the muscularis propria and determine the main route of cancer development of the human large intestine. The term "early cancers" here indicates those cancers that stay in the mucosa (intramucosal cancer) and those that involve only the submucosal layer, regardless of metastasis to the mesenteric lymph nodes. In contrast, "advanced cancers" in the current study refers to mean cancers involving the muscularis propria or deeper.

We focused our study on whether a flat adenoma is the forerunner of flat early cancers and investigated the ratio of advanced cancers of the colon and rectum that originated from either polypoid early cancers, flat early cancers, or flat adenomas.

Materials and Methods

We investigated 97 flat early cancers, 138 polypoid early cancers, and 60 advanced cancers involving the muscularis propria (MP cancer). All patients were treated at the Third Department of Surgery, University of Tokyo, from January 1984 to May 1993. About 20% (15.7–32.6%) of colorectal cancers that required an operation each year from 1988 to 1992 were flat cancers. One hundred eighty-five flat adenomas were treated during the same period. The location, size, and histologic characteristics of the flat cancers, polypoid cancers, MP cancers, and flat adenomas were investigated. Histologic examination was performed using hematoxylin and eosin after fixing the specimens in 10% buffered formaldehyde and embedding them in paraffin.

Flat adenomas and flat cancers were lesions whose heights did not exceed half their diameter. The summit of flat lesions seemed to be undulating. Ten flat lesions were composed of adenomas and carcinomas. These lesions were counted as flat cancers, regardless of the ra-

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Elevated type without depression 49 (23)

Elevated type with depression (Type A) 26 (18)

Elevated type with depression (Type B) 6 (6)

Flush type 3 (0)

Depressed type 13 (4)

carcinoma muscularis propria

muscularis mucosae

Figure 1. Classification of flat early cancers and numbers of cases identified in the current study. Numbers in parentheses mean the number of lesions involving the submucosal layer.

tio of adenomas and carcinomas. Early cancers were divided into two types by appearance: polypoid cancers and flat cancers. Polypoid cancers were tall tumors whose heights exceeded half their diameter. They have also been called peduncular, semipeduncular, and sessile cancers.

Flat early cancers can be subclassified into five groups: an elevated type without any depression; Type A, an elevated type with depression; Type B, an elevated type with depression; a flush type; and a depressed type (Fig. 1). Type A, the elevated type with depression can be distinguished from Type B, the elevated type with depression, in that Type A has carcinoma cells on its outer shoulder of elevation, whereas the shoulder of Type B is composed of normal colonic mucosa, as described in our previous report.[1] These 97 flat cancers include 16 minute cancers (5 mm and smaller in diameter), which are classified as 6 elevated type without depression, 1 Type A elevated type with depression, 2 flush type, and 7 depressed type. Endoscopic imaging was given priority over the postoperative macroscopic features.

Polypoid cancers include either pure adenocarcinomas without any adenoma component or carcinomas in the adenoma that protrude into the intestinal lumen. It is sometimes difficult to discriminate minute lesions smaller than 5 mm in diameter as to whether they are flat or polypoid. In such cases, a tumor that seems to protrude as a dome is placed into the polypoid group, and tumors that impress in a trapezoidal fashion, that is, appear to have an undulating summit, are placed into the flat group.

Thirteen flat adenomas that were considered too difficult to be endoscopically removed were periodically followed up with use of the colonoscope, and biopsy specimens were taken. The observation period was from 17 to 38 months.

The data were analyzed by the chi-square test, and statistical significance was evaluated.

Results

Ninety-seven flat early cancers were observed in 87 patients; 138 polypoid early cancers in 125 patients; 60 MP cancers in 60 patients; and 185 flat adenomas in 164 patients, respectively (Table 1).

In all 97 flat cancers, 87 had no residual adenoma, and only 10 were accompanied by an adenoma (carcinoma in adenoma). Conversely, residual adenomas were histologically proved in 115 of 138 polypoid cancers. These figures indicate that most flat cancers arise de novo[6,7], and that the adenoma-carcinoma sequence[8] is still valid in polypoid cancers.

Adenocarcinoma involving the submucosal layer was seen in 52 of 97 flat cancers (53.6%) and in 19 of 138 polypoid cancers (13.8%). Flat cancers were aggressive, even if they remained smaller 10 mm in diameter, as they involved the submucosal layer in 16 of 38 cancers (42.1%). Lymphatic and venous invasion was found in 16, and metastasis to the mesenteric lymph nodes was found in 4 of 52 flat cancers involving the submucosal layer. In polypoid cancers, however, the rate of lymphatic and venous invasion was 10.5% (2 of 19), and no lymph node metastasis was found during the subsequent operation after snare polypectomy. Follow-up examinations failed, too, to reveal any metastasis or local recurrence.

Distribution in the large intestine showed significant differences between flat cancers and flat adenomas ($P < 0.01$, chi-square = 33.92) (Fig. 2). Of the flat cancers, 30 were found in the rectum, 33 in the sigmoid colon, and 7 in the descending colon, for a total of 70 of 97 flat cancers present in the distal colon and rectum. In contrast, 33 flat adenomas were observed in the cecum, 33 in the ascending colon, and 46 in the transverse colon; in total, 112 of the flat adenomas were present in the proximal colon. The chi-square value comparing the distribution of both lesions between the rectum to descending colon and the transverse colon to cecum was 27.23 ($P < 0.01$). This figure corresponds to 80% of the previous value (33.92).

Follow-up of 13 flat adenomas revealed no remarkable growth. The grade of atypia of the flat adenomas revealed in the biopsy specimens did not change, except in only one flat adenoma where carcinomatous change was proven in a patient who had multiple polyps of the colon.

Table 1. Clinicopathologic Characteristics of Lesions

	Male patients	Female patients	Average age (yr)	Average size of lesions (mm)
Flat early cancers	54	33	63.2 ± 7.7	14.4 ± 9.5
Polypoid early cancers	78	47	61.8 ± 8.8	15.4 ± 6.9
MP cancers	37	23	62.5 ± 9.4	33.1 ± 14.0
Flat adenomas	99	65	63.1 ± 10.3	10.5 ± 5.9

MP cancers: advanced cancers involving the muscularis propria

The next step of analysis involved the MP cancers, which are at a slightly more advanced stage than early cancers and represent the earlier phase of advanced cancers. The shapes of MP cancers were analyzed from the point of view of whether they resembled the shapes of flat cancers or those of polypoid cancers. The shapes of MP cancers comprised four types: a protruded type (advanced type of polypoid cancers at the early cancer stage); an elevated type without ulcer (advanced type of elevated-type flat cancers without depression); an elevated type with ulcer (advanced type of elevated-type flat cancers with depression, Type A); and an ulcer-superior type (advanced type of depressed-type flat cancers or Type B elevated-type flat cancers with depression) (Fig. 3).

There were only 2 protruded types of 60 MP cancers; these were considered as originating from polypoid cancers. The other 58 MP cancers were divided into 25 of the elevated type without ulcer, 11 of the elevated type with ulcer, and 22 of the ulcer-superior type, all of which were considered as originating from flat cancers (Fig. 4).

Discussion

Polypoid adenomas or flat adenomas are considered to be forerunners of advanced colorectal cancers if the adenoma-carcinoma sequence is valid, whereas microscopic cancers[6] (carcinoma in situ) and flat early cancers are the pathologic type in force if colorectal cancers arise de novo.

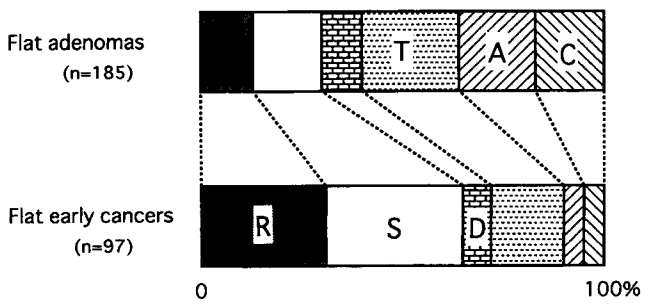

Figure 2. Distribution of flat adenomas and flat early cancers in the large intestine. R: rectum; S: sigmoid colon; D: descending colon; T: transverse colon; A: ascending colon; C: cecum.

It is unlikely that polypoid adenomas develop directly into advanced cancer through polypoid cancer (carcinoma in adenoma), because there is a great discrepancy in shapes between polypoid cancers and colorectal advanced cancers. It is also unreasonable to interpose flat cancers between polypoid cancers and advanced cancers, because flat cancers do have a IIIs-type pit pattern[9], which has much smaller round pits (0.03+/−0.01 mm in diameter) than pits of normal crypts (0.07+/−0.02 mm in diameter). If a carcinoma occurs in the polypoid adenomas and loses its elevation while replacing residual benign tumors, flat cancers originating from a polypoid cancer should not have a pit pattern on their surface. The histogenesis and development of colorectal cancers, therefore, have attracted the attention of colorectal surgeons, endoscopists, and pathologists, even after the adenoma-carcinoma sequence was formulated.

Flat adenomas[10] had come to be recognized as playing a key role in solving the above discrepancy in shapes. Following this, flat cancers[1] appeared as another candidate for an original form of colorectal cancer. Several articles,[2–4,11,12] mainly from Japanese researchers, have proven that there are numerous flat cancers in the large intestine in humans. It is now necessary to clarify whether flat adenomas or flat cancers represent the primary beginnings of colorectal cancers.

The current study produced four items of evidence that contradict the notion that flat cancers develop from flat adenomas. First, only 10.3% of the flat cancers were accompanied by a residual adenoma, though most flat cancers have no erosion or ulcers. Second, the location of the flat cancers resembles that of advanced colorectal cancers, whereas flat adenomas are observed most frequently in the proximal colon. This finding was revealed through our observations through total colonoscopies. Third, the average age of patients with flat cancer is almost identical to those with flat adenomas. If flat adenomas progress to flat cancers, the average age of patients with flat adenomas should be younger than those with flat cancers. Finally, there is no remarkable

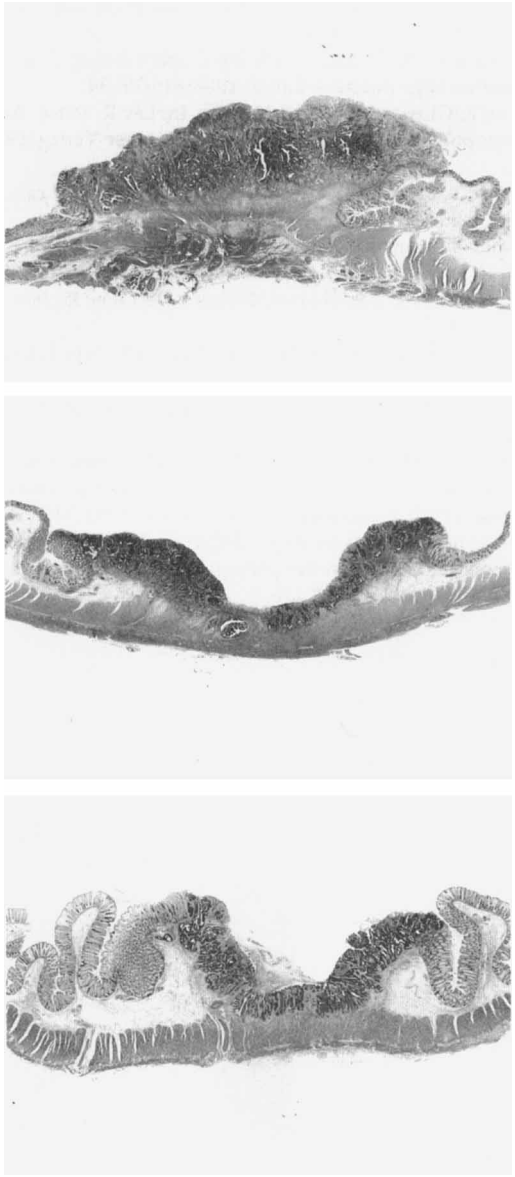

Figure 3. Classification of macroscopic features of advanced cancers involving the muscularis propria. (Top) Elevated type without ulcer, (middle) elevated type with ulcer, (bottom) ulcer-superior type.

increase in size nor any histologic malignant change in the flat adenomas observed during this period. We therefore conclude that flat adenomas seldom develop into flat cancers. Flat cancers occur in the flat mucosa as a minute intramucosal cancer and progress laterally and vertically.

Analysis of the shapes of MP cancers also reveals that their shapes closely resemble those of flat cancers. This finding supports the notion that flat cancers are the beginning of advanced colorectal cancers. In MP cancers, the rate of ulcer-superior shapes is higher than the rate of flat cancers, including the elevated type with depression, Type B, and the depressed type. This phenomenon might be explicable as a change reflecting the cancer progression.

With this in mind, we can arrive at an estimate of the percentage of advanced cancers that originate from flat cancers. Simply comparing the total numbers of flat cancers and polypoid cancers shows that 41.3% of advanced cancers of the large intestine originate from flat cancers. However, cancers remaining in the mucosal layer are considered to be safe and noninvasive. It is reasonable to compare invasive cancers of both groups between two fixed points that correspond exactly to the muscularis mucosae and the muscularis propria. Of the 52 flat cancers and 19 polypoid cancers involving the submucosal layer and failing to display any invasion into the muscularis propria, 71.2% (52 of 52 + 19) of advanced colorectal cancers originated from flat cancers.

The real number of flat early cancers is 97, which includes 52 cancers (53.6%) involving the submucosal layer. In contrast, only 19 of 138 polypoid cancers were invasive. The question then arises as to why the percentage of both cancers involving the submucosal layer should show such different values.

The first answer to this lies in the character of the flat cancers. Flat cancers showed a high rate of invasion into the submucosa (42.1%), even when their sizes were smaller than 10 mm in diameter. The rate of metastasis to the lymph nodes (7.6%) and lymphatic and venous invasion (30.8%) in flat cancers involving the submucosa also clearly betrays the aggressive nature of flat cancers. The next answer is found in the anatomic distance from the carcinoma and the muscularis mucosae. In the case of polypoid cancers, the upward growth of residual adenomas lying between the carcinoma and the muscularis mucosae offsets the downward invasion of carcinomas.

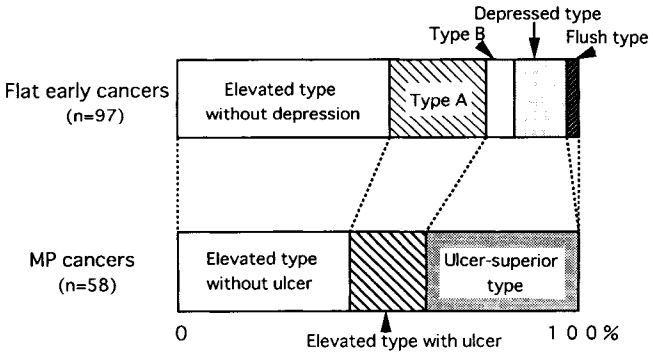

Figure 4. Comparison of macroscopic features of flat cancers and advanced cancers involving the muscularis propria. The incidence of the ulcer-superior type increases in advanced cancers. MP cancers: advanced cancers involving the muscularis propria; Type A: elevated type with depression; Type B: elevated type with depression.

Considering the ability of these aggressive flat cancers, more than 71.2% of advanced cancers will have then developed from flat cancers. Furthermore, the data in the current study include the period before 1988, when the percentage of flat cancers in all cancers treated by operation reached about 20%. Therefore, this figure, 71.2%, will increase.

References

1. Kuramoto S, Oohara T. Flat early cancers of the large intestine. *Cancer* 1989:64:950–5.
2. Hunt DR, Cherian M. Endoscopic diagnosis of small flat carcinoma of the colon: report of three cases. *Dis Colon Rectum* 1990;33:143–7.
3. Iishi H, Tatsuta M, Tsutsui S, Imanishi K, Otani T, Okuda S, et al. Early depressed adenocarcinomas of the large intestine. *Cancer* 1992:69:2406–11.
4. Shimoda T, Ikegami M, Fujisaki J, Matsui T, Aizawa S, Ishikawa E. Early colorectal carcinoma with special reference to its development *de novo*. *Cancer* 1989;64:1138–46.
5. Morson BC. The polyp cancer sequence in the large bowel. *Proc R Soc Med* 1974;67:451–7.
6. Kuramoto S, Oohara T. Minute cancers arising *de novo* in the human large intestine. *Cancer* 1988;61:829–34.
7. Lev R. Glossary and abbreviations. In: Lev R, editor. Adenomatous polyps of the colon. New York: Springer-Verlag, 1990: 130–1.
8. Muto T, Bussey HJR, Morson BC. The evolution of cancer of the colon and rectum. *Cancer* 1975;36:2251–70.
9. Muto T, Kamiya J, Sawada T, Konishi F, Sugihara K, Kubota Y, et al. Small "flat adenoma" of the large bowel with special reference to its clinicopathologic features. *Dis Colon Rectum* 1985;28: 847–51.
10. Kudo S, Ushiyama M, Miura K, Takano Y, Fujii T, Ohtsuka K. Flat and depressed type of early colorectal cancer: infiltrative form and growth pattern [in Japanese]. *Shokakigeka* 1991;14: 277–95.
11. Herrera I, Hanna S, Castillo N, Petrelli NJ. Primary *de novo* adenocarcinoma of the colon measuring 8 mm in diameter with lymph node metastasis. *Dis Colon Rectum* 1991;34:275–9.
12. Matsumoto T, Iida M, Yao T, Fujishima M. Role of nonpolypoid neoplastic lesions in the pathogenesis of colorectal cancer. *Dis Colon Rectum* 1994;37:450–5.