

ABERRANT CRYPT FOCI OF THE COLON AS PRECURSORS OF ADENOMA AND CANCER

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ABSTRACT

Background Aberrant crypt foci of the colon are possible precursors of adenoma and cancer, but these lesions have been studied mainly in surgical specimens from patients who already had colon cancer.

Methods Using magnifying endoscopy, we studied the prevalence, number, size, and dysplastic features of aberrant crypt foci and their distribution according to age in 171 normal subjects, 131 patients with adenoma, and 48 patients with colorectal cancer. We also prospectively examined the prevalence of aberrant crypt foci in 11 subjects (4 normal subjects, 6 with adenoma, and 1 with cancer) before and after the administration of 100 mg of sulindac three times a day for 8 to 12 months and compared the results with those in 9 untreated subjects (4 normal subjects and 5 with adenoma). All 20 subjects had aberrant crypt foci at base line.

Results We identified 3155 aberrant crypt foci, 161 of which were dysplastic; the prevalence and number increased with age. There were significant ($P < 0.001$) correlations between the number of aberrant crypt foci, the presence of dysplastic foci, the size of the foci, and the number of adenomas. After sulindac therapy, the number of foci decreased, disappearing in 7 of 11 subjects. In the untreated control group, the number of foci was unchanged in eight subjects and slightly increased in one ($P < 0.001$ for the difference between the groups).

Conclusions Aberrant crypt foci, particularly those that are large and have dysplastic features, may be precursors of adenoma and cancer. (N Engl J Med 1998;339:1277-84.)

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ABERRANT crypt foci were described by Bird as lesions consisting of large, thick crypts in methylene blue-stained specimens of colon from mice treated with a carcinogen (azoxymethane).¹ Subsequently, they were identified in rat colon, appearing a few weeks after treatment with a carcinogen and becoming larger with time, with more marked nuclear atypia or dysplasia.² In the rat model, the formation of aberrant crypt foci was enhanced by cancer promoters (such as chenodiol) and suppressed by chemopreventive agents (docosahexaenoic acid and aspirin).³⁻⁵ Increased proliferative activity and K-RAS mutations of aberrant crypt foci were also demonstrated.⁶⁻¹³

Aberrant crypt foci similar to those in rodents have also been reported in colonic mucosa in humans.¹⁴⁻¹⁷

Patients with colon cancer had more aberrant crypt foci than patients with noncancerous lesions¹⁶ and 58 to 73 percent had K-RAS mutations.^{7,9,11} These results suggested that aberrant crypt foci are not only morphologically but also genetically distinct lesions and are precursors of adenoma and cancer. However, the studies mainly analyzed surgical specimens from patients with colon cancer or dissected colonic tissues obtained at autopsy with stereoscopic microscopy. Data are lacking on normal subjects or patients with adenoma, and such data could provide essential information about the relation of aberrant crypt foci to colon cancer.

Using magnifying endoscopy, we studied the prevalence, number, size, and dysplastic features of aberrant crypt foci and their distribution according to age in normal subjects, patients with adenoma, and patients with cancer and determined the prevalence of K-RAS mutations in the biopsy specimens. We also evaluated the chemopreventive effects of nonsteroidal antiinflammatory drugs (NSAIDs) on the formation of the foci in patients with heart disease or osteoarthritis and their therapeutic effect on existing foci.

METHODS

Subjects and Study Design

The study was approved by the ethics committee of Muroran Shinnittetsu Hospital, an affiliate of Sapporo Medical University. We enrolled 370 subjects: 49 with colorectal cancer, 142 with adenoma, and 179 normal subjects. Normal subjects were defined as subjects with no apparent lesions of the colon on endoscopy. All subjects provided written informed consent before enrollment.

We used endoscopy to assess the prevalence, number, size, and dysplastic features of aberrant crypt foci and their distribution according to age in 48 patients with colorectal cancer, 130 patients with adenoma, and 147 normal subjects. We determined the prevalence of aberrant crypt foci in 25 subjects with either heart disease or osteoarthritis who had been treated with NSAIDs, including 100 mg of sulindac (Clinoril, Banyu, Tokyo, Japan) three times daily and 220 mg of aspirin (Takeda, Tokyo, Japan) three times daily, for more than one year. We also prospectively examined the prevalence of aberrant crypt foci in 11 subjects (4 normal subjects, 6 patients with adenoma, and 1 patient with cancer) before and after the administration of 100 mg of sulindac three times daily for 8 to 12 months and compared the results with those in an untreated group (4 normal subjects and 5 patients

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TABLE 1. BASE-LINE CHARACTERISTICS OF THE SUBJECTS ACCORDING TO STUDY-GROUP ASSIGNMENT.*

CHARACTERISTIC	PREVALENCE STUDY			PROSPECTIVE STUDY OF SULINDAC†	
	NORMAL SUBJECTS (N=171)	PATIENTS WITH ADENOMA (N=131)	PATIENTS WITH CANCER (N=48)	TREATMENT GROUP (N=11)	CONTROL GROUP (N=9)
Age (yr)					
Mean ±SD	54.8±11.6	59.6±10.7	62.5±11.0	64.3±7.9	65.2±8.9
Median	53	58	61.5	63	66
Sex (M/F)	92/79	73/58	28/20	6/5	5/4
Treatment with NSAIDs (no. of subjects)‡	24	1	0	11	0

*The subjects were referred to our hospital for colonoscopy because of symptoms such as abdominal discomfort, distention, a feeling of tightness on defecation, or bloody stools. Normal subjects were defined as subjects with no apparent lesions of the colon on endoscopy.

†The treatment group received 300 mg of sulindac per day for 8 to 12 months after the diagnosis was made by endoscopy. The treatment group included four normal subjects, six patients with adenoma, and one patient with cancer; the control group included four normal subjects and five patients with adenoma. There were no significant differences in age or sex ratios between the two groups by Student's t-test and the chi-square test, respectively.

‡NSAIDs denotes nonsteroidal antiinflammatory drugs. The 25 subjects had either heart disease or osteoarthritis and had been treated with sulindac (300 mg per day) or aspirin (660 mg per day) for more than one year. The other subjects had not received NSAIDs routinely.

with adenoma). All 20 subjects were assessed for aberrant crypt foci twice in a period of 10 to 12 months. The base-line characteristics of the subjects are shown in Table 1.

Magnifying Endoscopy

A magnifying endoscope (model EC7-CM2, Fujinon, Tokyo, Japan) that magnifies objects by a factor of 40 and was equipped with an autofocus device was used throughout the examination. All subjects underwent total colonoscopy. In three consecutive subjects (a normal subject, a patient with adenoma, and a patient with cancer), the entire colon was washed with 0.5 percent glycerin, sprayed with 0.25 percent methylene blue solution, washed again with warm water, and examined for aberrant crypt foci. In the other subjects, only the lower rectal region was surveyed with this staining method. Typically, the entire procedure required no more than 30 minutes, including total colonoscopy (10 to 15 minutes) and examination for aberrant crypt foci (10 to 15 minutes). All procedures were recorded on videotape and evaluated by two independent observers who were unaware of the subjects' clinical histories.

Criteria Used for Endoscopic Diagnosis

Aberrant crypt foci were defined as lesions in which the crypts were more darkly stained with methylene blue than normal crypts and had larger diameters, often with oval or slit-like lumens and thicker epithelial linings.¹⁴⁻¹⁷ Dysplastic aberrant crypt foci were defined as crypts in which each lumen was compressed or not distinct, with an epithelial lining that was much thicker than that of normal surrounding crypts. Nondysplastic aberrant crypt foci were classified as hyperplastic or nonhyperplastic. Hyperplastic aberrant crypt foci were those with lumens shaped like asteroids or slits, whereas nonhyperplastic foci were those with oval or semicircular lumens.^{14,15}

Histologic Examination

A total of 105 biopsy specimens with aberrant crypt foci were obtained, and the foci were histologically classified into one of

three groups depending on the grade of dysplasia or hyperplasia according to previously described criteria.^{14,15,18,19} The specimens were graded by two independent pathologists who were not aware of the subjects' histories. The rate of diagnostic agreement between graders was 92.4 percent (97 of 105); the 8 biopsy specimens whose results were in dispute were not included in the evaluation of the accuracy of endoscopic diagnosis.

Detection of Point Mutations at K-RAS Codon 12

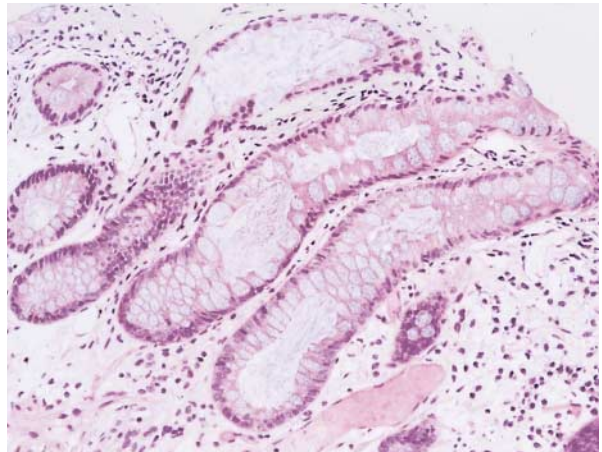
The point mutations at codon 12 of the K-RAS gene were analyzed by the polymerase-chain-reaction–restriction-fragment–length polymorphism method.²⁰

Figure 1. Endoscopic and Histologic Features of Aberrant Crypt Foci.

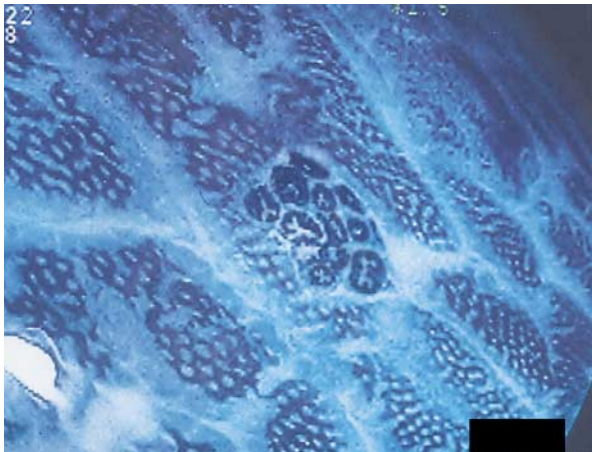
Endoscopy with methylene blue staining reveals a small focus consisting of four crypts with semicircular or oval lumens (Panel A). The aberrant crypts stained more darkly, were larger, and had a thicker epithelial lining and a larger pericryptal zone than normal crypts. Histologically, there was slight enlargement, irregularity, and elongation of the ducts, findings consistent with the previously reported features of aberrant crypt foci without dysplasia or hyperplasia (Panel B, hematoxylin and eosin, ×180). Panel C shows a medium focus consisting of 13 crypts, each with an asteroid or slit shape. Histologically, there was a serrated luminal pattern, characteristic of aberrant crypt foci with hyperplasia (Panel D, hematoxylin and eosin, ×150). Panel E shows a large focus with a deformed and slightly raised shape. The epithelial lining was thicker than those of the foci shown in Panels A and C, and each lumen was compressed or not distinct. Histologic examination revealed a loss of polarity, hyperchromatism of the nuclei, and stratification of the nuclei of crypt epithelium, findings in agreement with the previously reported features of dysplastic aberrant crypt foci (Panel F, hematoxylin and eosin, ×120).



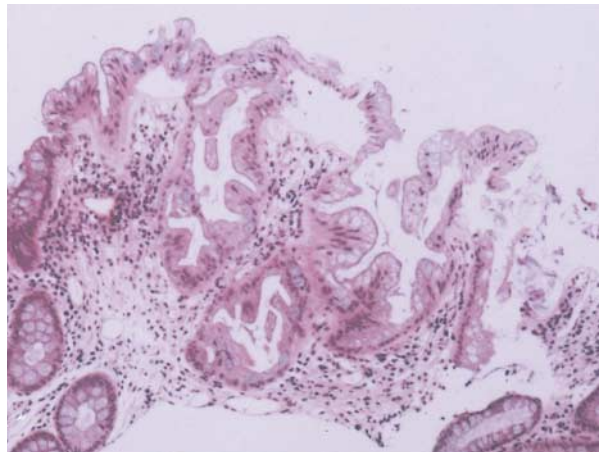
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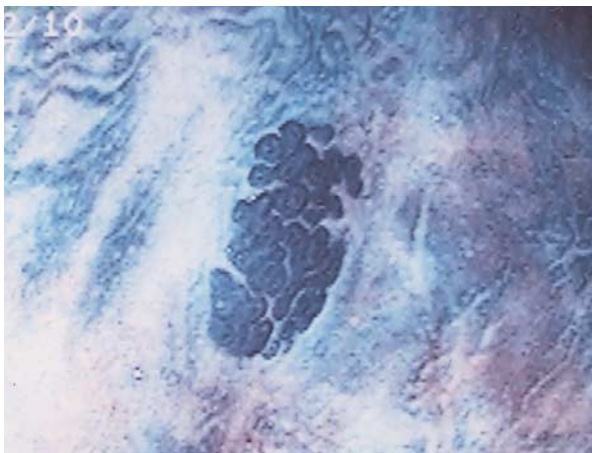
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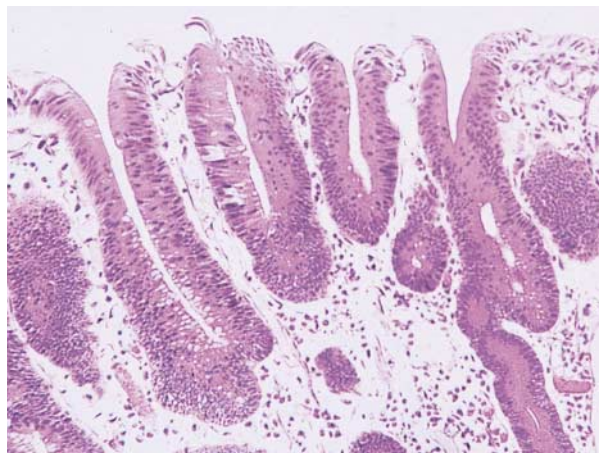
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D



E



F

Statistical Analysis

The prevalence and number of aberrant crypt foci in age-stratified groups of normal subjects, patients with adenoma, and patients with cancer were compared by age-adjusted logistic-regression analysis²¹ and the Wilcoxon rank-sum test,²² respectively. Correlations between the number of adenomas and the number or size of aberrant crypt foci were evaluated by Spearman's test. Data from the prospective study of the effect of NSAIDs on aberrant crypt foci were analyzed with use of Fisher's exact test with a dichotomous variable consisting of a group in which there was a reduction in aberrant crypt foci and a group in which there was not.²² All analyses were two-tailed.

The sensitivity and specificity of endoscopic diagnosis were calculated on the basis of the rates of agreement and disagreement with the histologic diagnosis.²³

RESULTS

Endoscopic and Histologic Features of Aberrant Crypt Foci

Using magnifying endoscopy, we found a total of 3155 aberrant crypt foci among 147 normal subjects, 130 patients with adenoma, and 48 patients with cancer. We examined the entire colorectal mucosa of one normal subject, one patient with adenoma, and one patient with cancer and found aberrant crypt foci, as defined previously with the use of stereoscopic microscopy¹⁴⁻¹⁸ — that is, crypts that were larger, thicker, and more darkly stained than normal crypts — in all three subjects. The aberrant crypt foci were mainly confined to the rectosigmoidal region: one of one focus in the normal subject, two of three foci in the patient with adenoma, and six of eight foci in the patient with cancer. On the basis of these findings and to minimize the examination time, we confined further examinations to the lower rectal region from the middle Houston valve to the dentate line. Figure 1 shows three representative endoscopic and histologic examples of the possible combinations of small, medium, and large foci with dysplasia, without dysplasia or hyperplasia, and without dysplasia but with hyperplasia.

Validity of Endoscopic Diagnosis

We assessed the validity of endoscopic diagnosis by examining the degree of agreement between this method and histologic diagnosis in 97 samples from 83 patients. The diagnoses were concordant in the case of 53 specimens without dysplasia or hyperplasia, 19 specimens without dysplasia but with hyperplasia, and 20 specimens with dysplasia. The results were discordant for five specimens. One focus that was defined histologically as nondysplastic and hyperplastic was defined endoscopically as nondysplastic and nonhyperplastic; two samples that were defined histologically as nondysplastic and nonhyperplastic were defined endoscopically as nondysplastic and hyperplastic; and two samples that were defined histologically as nondysplastic and hyperplastic were defined endoscopically as dysplastic. Therefore, the sensitivity of the diagnosis of nondysplastic, nonhyperplastic foci was 96.4 percent ($53 \div (53+2)$), the sensitivity of the diagnosis

of nondysplastic, hyperplastic foci was 86.4 percent ($19 \div (19+1+2)$), and the sensitivity of the diagnosis of dysplastic aberrant crypt foci was 100 percent ($20 \div (20+0+0)$). The respective specificities were 97.6 percent ($((19+20+2) \div (19+20+2+1))$), 97.3 percent ($((53+20) \div (53+20+2))$), and 97.4 percent ($((53+19+2+1) \div (53+19+2+2+1))$).

Among the 3155 aberrant crypt foci identified by endoscopy, 161 (5.1 percent) were dysplastic, 457 (14.5 percent) were nondysplastic and hyperplastic, and 2537 (80.4 percent) were nondysplastic and nonhyperplastic. These findings are consistent with those of previous studies that evaluated surgical specimens.^{19,24} Since most hyperplastic foci also had areas without hyperplasia, they were subsequently combined with the group of foci without dysplasia or hyperplasia.

Prevalence and Number of Aberrant Crypt Foci in Age-Stratified Groups

The prevalence and number of aberrant crypt foci according to age are shown in Table 2. The prevalence of aberrant crypt foci in normal subjects under the age of 40 was 10.0 percent, from 40 to 49 years of age it was 53.6 percent, and from 60 to 69 years of age it was 65.7 percent. Three of the four patients with adenoma who were under the age of 40 had aberrant crypt foci, and the prevalence increased gradually with age, reaching 90.2 percent by the age of 60. In patients with cancer, the prevalence was 100 percent in all age groups examined. Logistic-regression analysis showed that the difference among the three groups of subjects was significant ($P < 0.001$). When the age-stratified prevalence of dysplastic foci (Table 2) was compared with that of nondysplastic foci, the differences among the three groups of subjects were more marked: the estimated relative risks of dysplastic foci for patients with adenoma and patients with cancer, as compared with normal subjects, were 4.26 and 18.14, respectively, and the estimated relative risks of nondysplastic foci were 1.14 and 1.29, respectively. Results of the analysis of the numbers of aberrant crypt foci according to age were similar to those for prevalence (Table 2).

Correlation between the Number of Adenomas and the Number, Size, and Dysplastic Features of Aberrant Crypt Foci

There was a significant correlation ($r = 0.62$, $P < 0.001$) between the number of aberrant crypt foci and the number of adenomas (Fig. 2A). When the patients who had dysplastic foci were analyzed separately, an even stronger correlation was observed ($r = 0.85$, $P < 0.001$). Similarly, when aberrant crypt foci were classified according to the number of crypts per focus (small, 1 to 9 crypts per focus; medium, 10 to 19 crypts per focus; and large, 20 crypts or more per focus), there was a clear correlation between the num-

TABLE 2. PREVALENCE AND NUMBER OF ABERRANT CRYPT FOCI ACCORDING TO AGE.

VARIABLE	AGE					TOTAL
	<40 YR	40-49 YR	50-59 YR	60-69 YR	≥70 YR	
Prevalence of aberrant crypt foci*						
Normal subjects						
No. of subjects	20	28	35	35	29	147
Aberrant crypt foci (%)	10.0	53.6†	62.9	65.7	69.0	55.8
Dysplastic foci (%)	0	3.6	8.6	5.7	10.3	6.1
Patients with adenoma						
No. of patients	4	15	44	41	26	130
Aberrant crypt foci (%)	75.0	73.3	86.4	90.2	96.2	87.7
Dysplastic foci (%)	0	20.0	11.4	14.6	15.4	13.8
Patients with cancer						
No. of patients	4	4	11	14	15	48
Aberrant crypt foci (%)	100	100	100	100	100	100
Dysplastic foci (%)	50	75	54.5	50	46.7	52.1
No. of aberrant crypt foci						
Normal subjects						
Median	0.0	1.5	1.5	2.0	3.0	1.0
Interquartile range	0.0-0.0	0.0-3.0	0.0-3.0	0.0-3.0	0.0-5.0	0.0-3.0
Patients with adenoma						
Median	2.5	4.0	5.5	6.0	8.0	5.0
Interquartile range	1.0-5.0	0.3-5.0	2.0-10.0	3.0-15.3	4.0-16.0	2.0-14.0
Patients with cancer						
Median	39.0	25.0	27.0	25.5	26.0	26.5
Interquartile range	30.5-47.5	14.5-37.5	20.5-39.3	20.0-45.0	12.0-44.3	18.0-45.0
P value‡						
Normal subjects vs. patients with adenoma	0.03	0.04	<0.001	<0.001	<0.001	<0.001
Patients with adenoma vs. patients with cancer	0.02	0.009	<0.001	<0.001	<0.001	<0.001

*P<0.001 by logistic-regression analysis for the differences among the groups. When dysplastic aberrant crypt foci were analyzed separately, the estimated relative risks for patients with adenoma and patients with cancer, as compared with normal subjects, were 4.26 (95 percent confidence interval, 2.66 to 6.82) and 18.14 (95 percent confidence interval, 11.33 to 29.04), respectively. In contrast, when nondysplastic aberrant crypt foci were analyzed separately, the relative risks for patients with adenoma and patients with cancer, as compared with normal subjects, were 1.14 (95 percent confidence interval, 0.82 to 1.57) and 1.29 (95 percent confidence interval, 0.94 to 1.79), respectively.

†P=0.005 by the chi-square test for the comparison with the group of normal subjects under the age of 40.

‡The P values were calculated with the Wilcoxon rank-sum test.

ber of adenomas and the size of the foci ($r=0.49$, $P<0.001$) (Fig. 2B).

Location of Adenomas in Relation to Aberrant Crypt Foci

In 16 of 130 patients with adenoma (12 percent), no aberrant crypt foci were found in the lower rectal region. In 109 of the 114 patients with adenoma and aberrant crypt foci (96 percent), adenomas were found in the left colon. Thirteen of the 16 patients with adenoma who did not have aberrant crypt foci had adenomas in the right colon (9 in the ascending colon and 4 in the right half of the transverse colon).

Point Mutations of K-RAS at Codon 12 in Aberrant Crypt Foci and Adenoma

In nondysplastic aberrant crypt foci, the prevalence of K-RAS mutations in biopsy specimens was high in all three groups of subjects: normal subjects, 80 percent (16 of 20); patients with adenoma, 85 percent (23 of 27); and patients with cancer, 92 percent (22 of 24). The prevalence of K-RAS mutations in dysplastic aberrant crypt foci was lower both

overall (57 percent, 8 of 14 subjects) and in each group (normal subjects, 50 percent, 1 of 2; patients with adenoma, 60 percent, 3 of 5; and patients with cancer, 57 percent, 4 of 7).

Effect of NSAIDs on the Formation of Aberrant Crypt Foci

Only 1 of 25 patients (4 percent) who received NSAIDs for more than one year had an aberrant crypt focus (a small nondysplastic aberrant crypt focus and an adenoma were detected concomitantly). We prospectively administered sulindac to 11 subjects (4 normal subjects, 6 patients with adenoma, and 1 patient with cancer) with aberrant crypt foci (Fig. 3). After 8 to 12 months of follow-up, the number of foci significantly decreased in the group as a whole and completely disappeared in seven subjects. In contrast, in the untreated control group (four normal subjects and five patients with adenoma), the number of foci was either unchanged (eight subjects) or slightly increased (one subject, $P<0.001$ for the difference between groups) (Fig. 3).

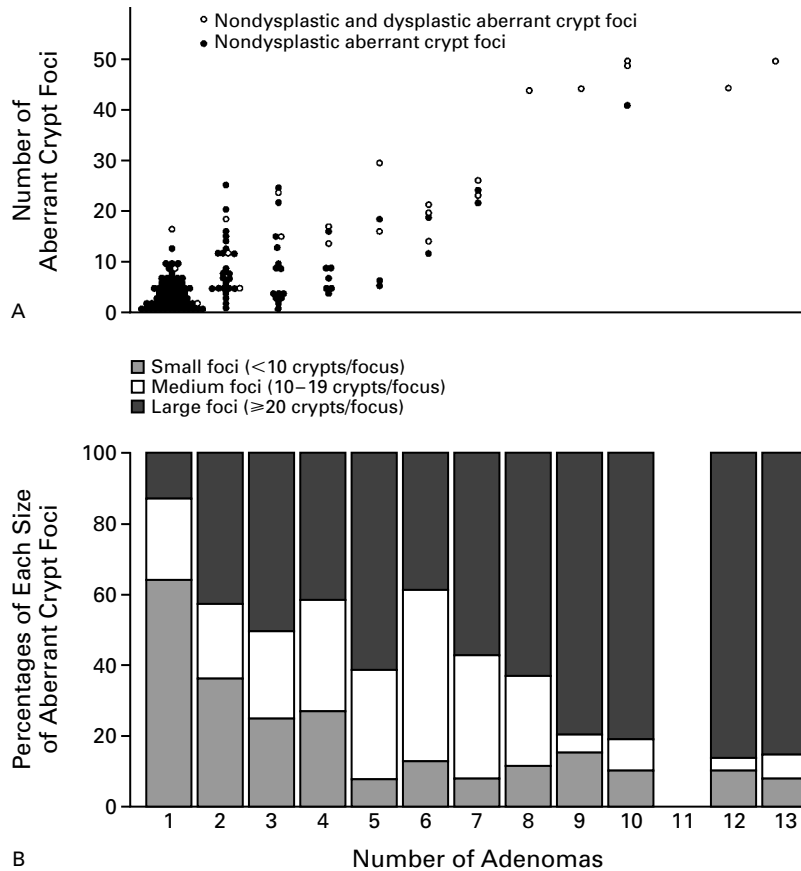


Figure 2. Correlation between the Number of Adenomas and the Number, Size, and Dysplastic Features of Aberrant Crypt Foci in Patients with Adenoma.

Panel A shows the relation between the number of adenomas and the number of aberrant crypt foci. A significant correlation was observed ($r=0.62$, $P<0.001$ by Spearman's test). When the patients who had dysplastic foci were analyzed separately, the correlation was stronger ($r=0.85$, $P<0.001$). Panel B shows the relation between the number of adenomas and the size of aberrant crypt foci. There was also a significant correlation ($r=0.49$, $P<0.001$ by Spearman's test).

DISCUSSION

Most of the aberrant crypt foci in our subjects were in the rectum and left colon. Therefore, for convenience, we confined our study to the lower rectal region from the middle Houston valve to the dentate line. We found lesions that were similar to the aberrant crypt foci previously observed by stereoscopic microscopy in surgical specimens from patients with cancer¹⁴⁻¹⁸ not only in patients with cancer, but also in normal subjects and patients with adenoma. Moreover, we were able to distinguish the subtypes of aberrant crypt foci: dysplastic, nondysplastic and hyperplastic, and nondysplastic and nonhyperplastic.^{14,15,19}

When differences in the prevalence and number of aberrant crypt foci among age-stratified groups of normal subjects, patients with adenoma, and patients with cancer were assessed by logistic-regression analy-

sis, significant stepwise increments in the prevalence from normal subjects to patients with adenoma and to patients with cancer were apparent, particularly in those with dysplastic aberrant crypt foci. In normal subjects, both the prevalence and the number of aberrant crypt foci in subjects under 40 years of age were very low and increased abruptly between the ages of 40 and 50, although there were not more than five aberrant crypt foci in any normal subject regardless of age. Conversely, patients with cancer had a consistently high prevalence and large numbers of aberrant crypt foci regardless of age. In patients with adenoma, the age-associated increment in the prevalence and number of aberrant crypt foci was intermediate. We also found that the number, size, and dysplastic features of aberrant crypt foci correlated with the number of polyps in patients

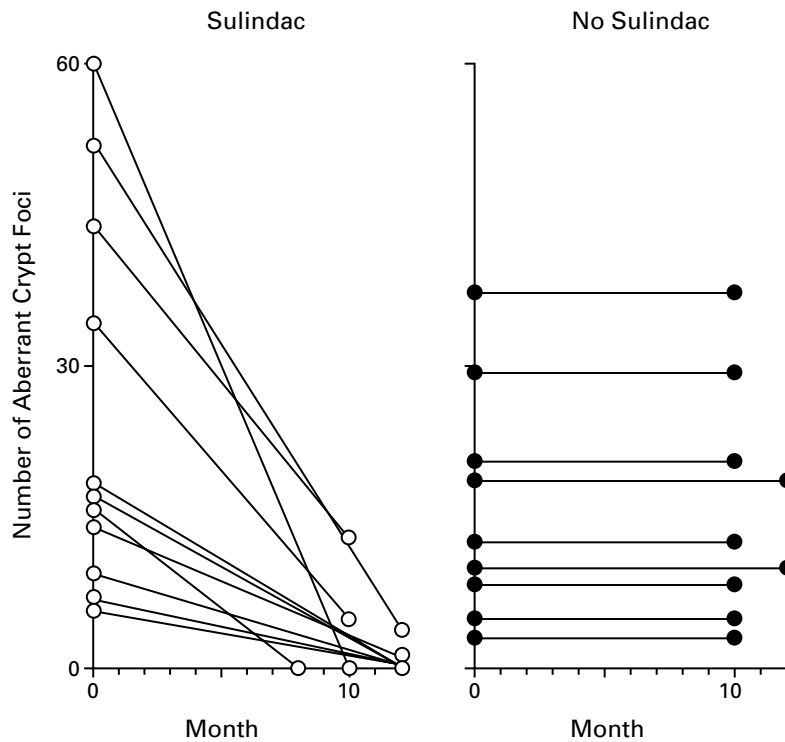


Figure 3. Effect of Sulindac on Aberrant Crypt Foci.

Eleven subjects with aberrant crypt foci were given 300 mg of sulindac per day, and nine subjects did not receive sulindac. After 8 to 12 months, the number of aberrant crypt foci was reassessed by endoscopy. The number of foci was markedly reduced in the subjects who received sulindac, and the foci completely disappeared in seven subjects. In contrast, in the nine control subjects, the number was either unchanged (eight) or slightly increased (one). There was a significant difference between the two groups ($P < 0.001$ by Fisher's exact test).

with adenoma. Moreover, in some patients, polyps overlapped aberrant crypt foci (data not shown). These results provide evidence to support the view that aberrant crypt foci, particularly those that are large and have dysplastic features, may be precursors of adenoma and cancer.

Since the prevalence and number of aberrant crypt foci increased with age, particularly after the age of 40, periodic endoscopic surveillance of patients is recommended. Furthermore, our observations that the increase in the number of foci occurred slowly and that many foci were no longer apparent after treatment with sulindac suggest that the feasibility of endoscopic monitoring every few years after treatment should be considered. Evaluation of additional patients is important.

Nondysplastic aberrant crypt foci had a relatively high prevalence of *K-RAS* mutations (80 to 92 percent). The prevalence of such mutations in dysplastic aberrant crypt foci was lower (57 percent). This difference suggests that genetic alterations other than those affecting *K-RAS* may be involved in the formation of dysplastic aberrant crypt foci.

The progression of adenoma to carcinoma is one

of the routes to colon cancer, and this sequence is commonly found in the left colon. Since aberrant crypt foci were present in almost all patients with adenoma or cancer and frequently appeared in the left colon, where polyps are often found,^{25,26} we hypothesize that aberrant crypt foci may eventually evolve into polyps and, subsequently, cancer. It should be noted, however, that they were not found in 12 percent of patients with adenoma (16 patients), most of whom had adenomas of the right colon. This finding is in accord with the suggestions of others that there is an alternative route of colon carcinogenesis^{27,28} that does not proceed from adenoma to carcinoma.

It has been reported that NSAIDs such as aspirin and sulindac reduce the risk of colon cancer by 40 to 50 percent.²⁹⁻³¹ Sulindac was shown to reduce the number and size of adenomas in patients with familial adenomatous polyposis.^{32,33} However, another study of patients with sporadic polyps found no chemopreventive effect of sulindac.³⁴ Although we did not examine many patients, we found that the prevalence of aberrant crypt foci was significantly lower in patients who received NSAIDs than in nor-

mal subjects and that the number of aberrant crypt foci was significantly reduced by the administration of sulindac. These findings should be evaluated in larger studies.

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