Jpn. J. Cancer Res. **90**, 1066–1070, October 1999

Chronic Active Disease Reflects Cancer Risk in Ulcerative Colitis

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There is an increased risk of developing colorectal neoplasia in ulcerative colitis (UC) and surveillance colonoscopy is recommended for early detection. We investigated the precise features of UC retrospectively to identify a subgroup with longstanding extensive UC at increased risk of neoplasia. From 1985 to August 1997, we experienced eight UC patients with colorectal cancer and eight with definite dysplasia. All 16 had extensive disease of seven years or more in duration. During the same period, 61 of 334 UC patients without colorectal neoplasia were available for detailed study, allowing evaluation of non-surgical patients with extensive colitis of seven years or more in duration. Basic clinical factors including family history of cancer, expressions of disease activity and durations of pharmacotherapy were investigated. Univariate analysis revealed four significant factors: intractability ($P=0.001$), periods of inflammation persisting for 3 months or more ($P<0.01$) and total durations of diarrhea ($P<0.01$) and hematochezia ($P<0.05$). The number of admissions and the duration of systemic steroid administration were higher in the neoplasia group but without statistical significance. Multivariate analysis revealed two significant factors: duration of diarrhea ($P<0.001$) and age at onset ($P<0.01$). Chronic active disease is a risk factor for colorectal cancer or dysplasia in extensive and longstanding UC.

Key words: Ulcerative colitis — Cancer risk — Dysplasia — Disease activity — Chronic inflammation

There is an increased risk of developing colorectal neoplasia in ulcerative colitis (UC). The consensus is that extensive colitis with a long duration[1–4] carries this risk. Surveillance with total colonoscopy and multiple biopsies is recommended to allow detection of such tumors at the earliest stage.[5, 6] However, surveillance colonoscopy is reportedly problematic in terms of efficacy and cost-effectiveness.[7, 8]

In most surveillance programs, patients with longstanding extensive UC were treated in the same way regardless of disease activity. However, if the chronically inflamed colon has an increased cancer risk, the surveillance program should be modified according to the disease activity of each patient. This would improve surveillance efficacy. To our knowledge, whether disease activity is related to the development of neoplasia in UC has not yet been examined in detail.

To clarify high risk factors for developing colorectal cancer and dysplasia in UC, we retrospectively compared longstanding extensive UC patients with and without cancer or dysplasia in terms of precise disease features.

PATIENTS AND METHODS

Patients with cancer or dysplasia (neoplasia group) From 1985 to August 1997, we experienced eight UC patients with colorectal cancer. These tumors did not resemble typical sporadic cancers morphologically. During the same period, another eight patients were diagnosed as having definite dysplasia. We excluded nine cases from the dysplasia group: in one, low grade dysplasia was recognized only once in the flat mucosa and no further dysplasia was detected. In the other eight, low grade dysplasia was seen in sporadic adenomas with pedunculated or sessile configurations. These patients were older than 50 years and their disease durations were less than seven years except in one case.

One rectal cancer patient was excluded because she had undergone total colectomy and ileorectal anastomosis for intractable UC nine years previously and her disease activity was difficult to assess according to the criteria described below. The remainder had an extensive disease of long duration (7 years or more).

Patients without dysplasia or cancer (control group) Between January 1985 and August 1997, 350 UC patients visited our department, of whom 16 had colorectal cancer or dysplasia, 95 had undergone surgery, 124 had limited colitis (not extending beyond the mid-transverse colon) and 35 had a short disease duration (less than 7 years). These 270 were excluded. In 19 of the remaining 80, we could not obtain a detailed history of the disease. The number of cases ultimately studied as control patients was thus 61 with longstanding total colitis.

Data collection In reviewing patients' records, the fol-

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lowing information was sought and abstracted for both the neoplasia and the control group.

Family history: Colorectal cancer in first and second degree relatives was recorded as positive (+) or negative (−).

Age at endpoint: Age at the first diagnosis of cancer or dysplasia for the neoplasia group. For control patients, age in August 1997 or, if the patient did not visit our clinic in August 1997, age at the last follow-up date was recorded. The duration of UC was calculated by subtracting the age at endpoint from the age at onset.

Disease activity was evaluated based on the following factors:

a. Intractability: Intractable cases were defined as those presenting at least one of the following features according to the proposal by the Research Committee for Intractable Intestinal Diseases sponsored by the Ministry of Health and Welfare, Japan,[9] and intractability was recorded as positive (+) or negative (−).

b. Severe attack: History of previous severe attack(s) was also recorded as positive (+) or negative (−).

c. Total duration of diarrhea: Only diarrhea exceeding 4 times a day was recorded as a positive finding.

d. The periods of inflammation persisting for 3 months or more: This includes mainly three states as follows:

(1) symptoms persisted without therapy.
(2) symptoms persisted despite therapy.
(3) symptoms subsided relatively quickly, but relapsed frequently.

e. Number of occasions and total duration (in months) of hospitalization were recorded.

Pharmacotherapy: The durations of treatment (in months) with sulfapyridine and systemic corticosteroids were recorded regardless of dosages. No other immunosuppressants were used in either patient group.

Statistical analysis Factors possibly influencing the occurrence of colorectal neoplasia were compared between neoplasia group and control group: For continuous variables (i.e., age at onset, age at endpoint, duration of UC, admission, duration of hospitalization, duration of diarrhea, duration of hematochezia, inflammation over three months, months of steroid intake, and months of sulfapyridine), the difference in average values between groups was examined by means of *t*-tests with unequal variances. For dichotomous variables (i.e., family history, sex, intractability, and severe attack), the Pearson χ^2 test or Fisher's exact test was employed to examine group differences.

Cox proportional hazards regression analysis was used to investigate which of the factors predict the occurrence of neoplasia in UC patients. Patients were assumed to become at risk at the age of onset, while they may be censored or diagnosed with neoplasia as the endpoint. The outcome measure was the occurrence of neoplasia. All the factors listed in Table I, except for age at endpoint and duration of UC, were entered and removed with a significance level of $P<0.05$, either by the forward or the backward stepwise method. Family history of colorectal cancer, sex, intractability and the presence of severe attacks were modeled using binary dummy variables.

Statistical analyses were performed using Stata version 6.0 (StataCorp, College Station, TX).

Table I. Univariate Analysis of Factors Possibly Influencing the Occurrence of Colorectal Neoplasia in Longstanding Ulcerative Colitis

Items	Neoplasia group	Control group	*P*
Family history of colorectal cancer (% of presence)	0.0	1.7	0.792[a)]
Sex (male %)	59.0	62.5	0.800[b)]
Age at onset (average ages±standard errors)	34.3±3.6	28.4±1.7	0.157[c)]
Age at endpoint (average ages±standard errors)	49.3±2.9	43.5±1.8	0.105[c)]
Duration of UC (years)	15.0±1.5	15.1±0.7	0.962[c)]
Intractability (% of presence)	31.3	3.3	0.001[a)]
Severe attack (% of presence)	12.5	3.3	0.189[a)]
Admission (average numbers±standard errors)	2.1±0.8	1.1±0.2	0.256[c)]
Total duration of hospitalization (average months±standard errors)	4.47±1.9	2.12±0.4	0.266[c)]
Total duration of diarrhea (average months±standard errors)	71.1±17.9	10.8±2.0	0.004[c)]
Total duration of hematochezia (average months±standard errors)	74.5±20.8	21.1±3.0	0.022[c)]
Inflammation ≥3 months (average months±standard errors)	7.9±1.4	2.9±0.4	0.004[c)]
Systemic steroid (averages of total months of intake±standard errors)	41.4±13.2	20.6±3.7	0.148[c)]
Sulfapyridine (averages of total months of intake±standard errors)	121±22	119±9	0.920[c)]

a) Fisher's exact test.
b) Pearson χ^2 test.
c) *t*-test with unequal variances.

Table II. Risk Factors for Colorectal Neoplasia in Longstanding Ulcerative Colitis

Item	Classification	Frequency of neoplasia (%)	*P*
Total duration of diarrhea	≥50 months	9/10 (90)	<0.0001
	<50 months	7/67 (10)	
Intractability	+	5/7 (71)	0.0005
	−	11/70 (16)	
Total duration of hematochezia	≥75 months	8/16 (50)	0.0025
	<75 months	8/61 (13)	
Inflammation ≥3 months	≥5 years	12/25 (48)	<0.0001
	<5 years	4/52 (8)	
One or more of the above factors	+	13/26 (50)	<0.0001
	−	3/51 (6)	

Significant factors based on univariate analysis were classified for clinical application, e.g., patients with a total duration of diarrhea exceeding 50 months had a 90% possibility of developing neoplasia. Patients with one or more factors among the four significant factors accounted for 13/16 (81%) in the neoplasia group. Highly significant differences were noted for all items on χ^2 test.

Table III. Hazard Ratios of Factors Possibly Influencing the Occurrence of Colorectal Neoplasia in Longstanding Ulcerative Colitis

Factors	Hazard ratio[a)]	95% confidence interval	*P*
Total duration of diarrhea (/month)	1.015	1.007−1.023	0.000
Age at onset (/year)	1.081	1.028−1.138	0.003

a) Based on the stepwise application of the Cox proportional hazards model. In the Cox hazards model, all the factors listed in Table I were included, except for age at endpoint and duration of UC. Patients were assumed to become at risk at the age of onset, while they may be censored or diagnosed with neoplasia as the endpoint. Forward and backward selections of stepwise estimation provided the same results.

RESULTS

Univariate analysis (Table I) Univariate analysis revealed four significant factors: intractability (P=0.001), periods of inflammation persisting for 3 months or more (P=0.004) and total durations of diarrhea (P=0.004) and hematochezia (P=0.022). All of these factors represent disease activity. The average age at onset was higher in the neoplasia than in the control group, but the difference did not reach statistical significance (P=0.157). UC duration was nearly the same in the two groups (15.0 years vs. 15.1 years, on average). The duration of systemic steroid use was longer in the neoplasia group, but again the difference did not reach statistical significance (P=0.061).

Risk factors based on univariate analysis (Table II) The frequencies of neoplasia in the group with total durations of diarrhea exceeding 50 months and intractability were 90% and 71%, respectively. For those with an index of inflammation of 3 months or more per year for at least 5 years, the frequency of colorectal neoplasia development was 48%. Patients with one or more factors among the four significant factors had a neoplasia rate of 50% and comprised 13/16 (81%) in the neoplasia group.

Multivariate analysis (Table III) The hazard ratio (HR) for developing neoplasia was 1.015 (95%CI: 1.007−1.023), when the UC patients had diarrhea for one month longer. Age at onset was also statistically related to the occurrence of neoplasia: a HR of 1.081 (95%CI: 1.028−1.138) for the patients when compared with those who became UC at younger ages by one year. Forward and backward estimation of Cox regression models produced the same result.

DISCUSSION

Our results indicated that chronic active disease is a risk factor for developing colorectal neoplasia in UC. Inflammation is speculated to be a factor promoting neoplasia development in UC,[10] and our results are in agreement with this hypothesis. This reflects the tendency for patients with the chronic continuous type to be at high risk for developing colorectal cancer.[11] However, Pinczowski *et*

al.[12] suggested that higher disease activity has a protective effect against carcinogenesis. To our knowledge, few data are available concerning the relation between disease activity and carcinogenesis in UC. Further study is necessary.

The present results are readily applicable to clinical management, e.g., a patient with one of the positive factors listed in Table II is recommended to undergo closer surveillance while a patient with no factors requires less frequent surveillance colonoscopy. Considering that most patients receive surveillance colonoscopy at an interval of 1–3 years,[5, 13–18] patients with a positive risk factor are better surveyed annually at a minimum. If the duration of diarrhea exceeds 50 months, prophylactic colectomy may even be considered, as the present results indicate an estimated 90% probability of developing neoplasia in such patients.

The results of multivariate analysis in this study showed that the total duration of diarrhea is positively associated with the occurrence of neoplasia. A patient is more likely to develop neoplasia with a HR of 1.015 when compared with another who had diarrhea for a month less. This implies that a patient with diarrhea for a period of 50 months has a HR of 2.11 ($=1.015^{50}$) when compared with a patient without it. Furthermore, later onset of UC, i.e., the older age at onset, was associated with a higher risk of developing neoplasia, independent of the duration of diarrhea in UC patients. A patient who is diagnosed as UC at older age by a year had a HR for neoplasia of 1.081. This implies that a patient who suffered from UC at a ten year older age has a HR of 2.18 ($=1.081^{10}$) when compared with the other patients. Thus, shorter duration of diarrhea and earlier onset of UC were protective against the occurrence of neoplasia. The results of univariate analysis in our study showed that there was no statistically significant difference in the average ages of UC onset between the neoplasia group and the control, while the former had significantly longer duration of diarrhea on a group basis. However Cox regression analysis revealed that age at onset also increased the likelihood of developing neoplasia.

Certain risk factors other than disease extent and duration have been reported. Prior *et al*.[19] and Ekbon *et al*.[1] reported patients with early onset to be at increased risk, while Kvist *et al*.[2] and Greenstein *et al*.[3] reported that cancer risk did not appear to be increased by an early onset. In the present study, we found later onset is a risk factor for neoplasia. Further investigation is required to determine this risk. Smoking is a possible influencing factor.[12] As this study was retrospective, we could not retrieve smoking data in most cases. Although primary sclerosing cholangitis is known to be a risk factor for neoplasia,[20] none of our patients had this disorder. To our knowledge, no other factor has been established as conferring a risk.

Pharmacological therapy may also play a role in carcinogenesis. Pinczowsky *et al*. showed that sulfapyridine therapy might exert a protective effect, preventing or delaying the development of neoplasia,[12] while Lashner *et al*. reported that malignant transformation was promoted by sulfapyridine therapy because this drug induces folate deficiency.[21] In the present study, sulfasalazine was not relevant to the development of neoplasia. For steroids, the duration of therapy was longer in the neoplasia than in the control group, but the difference fell short of statistical significance on both univariate and multivariate analyses. Since disease activity was higher in the neoplasia group, the difference in steroid use may be attributable to differences in disease activity.

The factors employed in the present study may reflect chronicity rather than severity. We did not investigate diarrhea frequency or hematochezia quantity. However, numbers of admissions and total durations of hospitalization appear to represent rather severe disease, which showed a limited relation to neoplasia development on multivariate analysis. Therefore, we speculate that the development of colorectal neoplasia is more closely related to the chronicity than to the severity of inflammation.

The present study has a further weakness: the problem of bias. This study is not based on the entire UC population but on a subset followed at a university hospital. The analysis is also retrospective and involves a rather small number of patients, possibly leading to bias. A larger prospective population-based study should be performed.

In conclusion, chronic active disease, as represented by diarrhea, correlates with the development of colorectal cancer and dysplasia. Surveillance programs should be modified according to the individual patient's disease activity and prophylactic colectomy might be considered for high risk patients, if closer surveillance colonoscopy is difficult to perform.

(Received March 31, 1999/ Revised June 18, 1999/2nd Revised July 6, 1999/Accepted July 10, 1999)

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