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RAPID COMMUNICATION

Depressed-type (0-IIc) colorectal neoplasm in patients with family history of first-degree relatives with colorectal cancer: A cross-sectional study

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Abstract

AIM: To investigate the correlation of depressed-type (0-IIc) colorectal neoplasm and family history of first-degree relatives (FDR) with colorectal cancer (CRC).

METHODS: This cross-sectional study was conducted from June 2000 to October 2002 at National Cancer Center Hospital East. Eligible patients undergoing initial total colonoscopy were surveyed regarding family history of CRC among FDR by a questionnaire prior to colonoscopic examinations. All endoscopic findings during colonoscopy were recorded and the macroscopic classification of the early stage neoplasm/cancer was classified into two types (0-IIc *vs* non 0-IIc). Odds ratios (OR) and 95% confidence intervals (CI) were calculated by univariate and multivariate logistic regression to estimate the association between macroscopic features and clinicopathological data including gender, age, and family history of FDR with CRC.

RESULTS: The OR of an association between family history of FDR with CRC and overall early stage neoplasm adjusted by gender and age was 1.85 (95% CI: 1.31-2.61, P = 0.0004), that for non 0-IIc neoplasm was 1.71 (95% CI: 1.22-2.41, P = 0.0017) and for 0-IIc colorectal neoplasm was 2.78 (95% CI: 1.49-5.16, P = 0.0031).

CONCLUSION: Our study shows a significant association between a family history of FDR with CRC and 0-IIc colorectal neoplasm. When patients with a family history of FDR with CRC undergo colonoscopy, colonoscopists should check carefully for not only polypoid, but also depressed-type (0-IIc) lesions.

Key words: Depressed-type; Family history; Colorectal cancer; First-degree relative; Colonoscopy

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INTRODUCTION

In Japan, colorectal cancer (CRC) is the third most important cause of cancer mortality and the incidence of CRC is increasing gradually[1]. The prognosis for patients with CRC is strictly dependent on early detection of premalignant and malignant lesions. Familial risk management is one of the important strategies for CRC prevention. There is evidence from cohort and case-control studies that people with close relatives with CRC have an increased risk of CRC and develop the disease at a younger age than those without a family history of CRC[2-4]. In clinical guidelines and rationale for CRC screening and surveillance in USA, approximate lifetime risk of CRC, when a first-degree relative (FDR) was affected with large bowel malignancy, was found to increase by 2-3 fold[5]. In addition, there is a report that a family history of CRC is a strong risk factor for adenoma growth[6,7].

However, previous studies concerning familial risk for CRC did not investigate the data from the perspective of macroscopic classifications of colorectal neoplasm. As the Paris endoscopic classification of superficial neoplastic lesions in the colon proposed, special attention is attached to depressed-type (0-IIc) lesions. Even when the diameter is small, 0-IIc lesions are often at a more advanced stage of neoplasia, with deeper invasion than other types of lesion[8,9]. However, to our knowledge, whether the risk of 0-IIc colorectal neoplasm is correlated with family history of FDR with CRC has not been investigated previously.

In this study, we therefore investigated the correlation of 0-IIc colorectal neoplasm and family history of FDR with CRC.

MATERIALS AND METHODS

Eligibility and exclusion criteria

Between June 2000 and October 2002, all patients undergoing initial total colonoscopy at National Cancer Center Hospital East were screened for eligibility for this study. The exclusion criteria were age < 50 years old, past history of surgical resection for CRC, past history of endoscopic treatment for colorectal neoplasm, family history of familial adenomatous polyposis or hereditary non-polyposis colorectal cancer, past history of inflammatory bowel disease and presence of either submucosal tumor, metastatic colorectal tumor or ischemic colitis. Informed consent was obtained from all patients.

Questionnaire of family history and past history

All patients had been asked for family history of CRC among FDR of patients by a questionnaire prior to colonoscopic examinations. Colonoscopists were kept unaware of this information until the end of the examinations.

Total colonoscopy

A preparatory solution of electrolytes and polyethylene glycol was administered orally to each patient. An anti-cholinergic agent was administered intramuscularly before each examination to prevent persistent colonic spasms, if there was no contraindication to its use. Total colonoscopies were performed using magnifying colonoscopes (CF200Z, CF240Z; Olympus Optical Co. Ltd, Tokyo, Japan). All detected lesions were diagnosed by magnifying colonoscopy using a non-biopsy technique to differentiate between hyperplastic polyps and adenomas[10,11]. When any neoplasm was suspected, 0.2% indigo carmine dye was sprayed on the area to highlight the lesions. All detected lesions were finally diagnosed by magnification with chromoendoscopy, and the lesions diagnosed as neoplasm were removed or biopsied to evaluate the histological findings. Lesions, diagnosed as hyperplastic polyps macroscopically or histologically, were excluded from this analysis.

Histological and macroscopic evaluation

Histological diagnoses were based on the classification of the World Health Organization (WHO)[12]. Intramucosal neoplasms, including intramucosal carcinoma and submucosal cancer that had spread through the muscularis mucosa into the submucosa, were defined as early stage neoplasm/cancer. Malignant lesions involving the muscularis propria or beyond on histological examination were classified as advanced cancer.

All endoscopic findings during colonoscopy were recorded at each examination. The macroscopic classification of early stage neoplasm/cancer was classified into two types (0-IIc *vs* non 0-IIc) using the system proposed by the Japanese Society for Cancer of the Colon and Rectum[13], which is nearly similar to the Paris endoscopic classification proposed in 2003[8]. In this study, type 0-IIc lesions included the combined type (0-IIc+IIa, 0-IIa+IIc, 0-Is+IIc)[9] and laterally spreading flat-type tumor[14,15]; so called "LST non-granular type" as described by Kudo in 1993[16]. Other macroscopic type lesions were classified as the non 0-IIc type.

Table 1 Initial colonoscopic findings of the patients

Patients without neoplasm	579 (36.5%)
Patients with neoplasm	1007 (63.5%)
Patients with only early stage neoplasm/cancer	651 (41.0%)
Patients with only advanced cancer	206 (13.0%)
Patients with both early stage neoplasm/cancer and advanced cancer	150 (9.5%)

Statistical analysis

Odds ratios (OR) and 95% confidence intervals (CI) were calculated by univariate and multivariate logistic regression to estimate the association between macroscopic features (early stage neoplasm/cancer, 0-IIc or non 0-IIc) and clinicopathological data including gender, age, family history of FDR with CRC. Two-sided *P* values less than 0.05 were considered statistically significant. Analyses were performed with Stata software (Version 9.0 for Windows, StataCorp LP. TX, USA).

RESULTS

A total of 2079 patients who underwent initial colonoscopy were screened; 1586 were enrolled in this study. Of 493 excluded patients, 297 were less than 50 years old, 84 had a past history of surgical resection for CRC, 62 had a past history of endoscopic treatment for colorectal neoplasm, 7 had a family history of familial adenomatous polyposis or hereditary non-polyposis colorectal cancer, 4 had inflammatory bowel disease; and the rest were excluded because of the presence of either submucosal tumor, metastatic colorectal tumor or ischemic colitis.

Patient characteristics

The study consisted of 1586 patients, including 1002 (63.2%) men and 584 (36.8%) women, with median age 63 (range, 50-96) years. There were 159 (10.0%) patients with a family history of FDR with CRC.

Detected neoplasm during colonoscopy

In 579 patients (36.5%), there were no neoplastic lesions detected on the initial colonoscopy. Colorectal neoplasm was found in 1 007 (63.5%) patients, among whom 651 (41.0%) patients had only early stage neoplasm/cancer, 206 (13.0%) patients had only advanced cancer, and 150 (9.5%) patients had both (Table 1). Furthermore, 775 (48.9%) patients had at least one non 0-IIc lesion and 63 (4.0%) patients had at least one 0-IIc lesion. The prevalence of 0-IIc colorectal neoplasm was 4.6% (95% CI: 3.3-5.9) in men and 2.9% (95% CI: 1.5-4.3) in women.

Table 2 Odds ratio (OR) for early stage colorectal neoplasm calculated by univariate and multivariate analyses

	No. of early stage neoplasm	Univariate analysis			Multivariate analysis		
	(*n* = 801)	Crude OR	95%CI	*P*-value	Adjusted OR	95%CI	*P*-value
Gender							
Female	230	1	1.66-2.51	<0.0001	1	1.64-2.50	< 0.0001
Male	571	2.04			2.03		
Age (yr)							
< 60	248	1	1.04-1.58	0.018	1	0.96-1.47	0.11
⩾ 60	553	1.29			1.19		
Familyhistory of FDR with CRC							
No	701	1	1.25-2.46	0.001	1	1.31-2.61	0.000
Yes	100	1.76			1.85		

Table 3 Odds ratio (OR) for non 0-IIc colorectal neoplasm calculated by univariate and multivariate analyses

	No. of non 0-IIc lesions	Univariate analysis			Multivariate analysis		
	(*n* = 775)	Crude OR	95%CI	*P*-value	Adjusted OR	95%CI	*P*-value
Gender							
Female	221	1	1.65-2.50	< 0.0001	1	1.63-2.49	< 0.0001
Male	554	2.03			2.02		
Age (yr)							
< 60	240	1	1.03-1.57	0.023	1	0.95-1.45	0.14
⩾ 60	535	1.27			1.18		
Family history of FDR with CRC							
No	680	1	1.17-2.28	0.004	1	1.22-2.41	0.002
Yes	95	1.63			1.71		

Table 4 Odds ratio (OR) for 0-IIc colorectal neoplasm calculated by univariate and multivariate analyses

	No. of 0-IIc lesions	Univariate analysis			Multivariate analysis		
	(*n* = 63)	Crude OR	95%CI	*P*-value	Adjusted OR	95%CI	*P*-value
Gender							
Female	17	1	0.91-2.83	0.09	1	0.92-2.90	0.08
Male	46	1.61			1.63		
Age (yr)							
< 60	20	1	0.64-1.89	0.73	1	0.61-1.82	0.86
⩾ 60	43	1.1			1.05		
Family history of FDR with CRC							
No	49	1	1.46-5.04	0.004	1	1.49-5.16	0.003
Yes	14	2.72			2.78		

In terms of age, the prevalence was 4.1% (95%CI: 2.9-5.3) in men and 3.7% (95% CI: 2.1-5.3) in women. These data showed that there was no statistical difference in frequency of 0-IIc colorectal neoplasm among gender and age. In addition, there were 14 (8.8%) patients with 0-IIc lesions and a family history of FDR with CRC.

Association between early stage, non 0-IIc, 0-IIc colorectal neoplasm and variables

Univariate analysis demonstrated that gender, age, and the family history of FDR with CRC were significantly associated with the prevalence of early stage and non 0-IIc colorectal neoplasm. On multivariate analysis, gender and the family history of FDR with CRC were significantly correlated with early stage and non 0-IIc colorectal neoplasm, although there was no significant association between non 0-IIc colorectal neoplasm and age (Tables 2 and 3). Univariate and multivariate analyses demonstrated that only a family history of FDR with CRC was significantly correlated with 0-IIc colorectal neoplasm, whereas gender and age were not found to be significant (Table 4). The OR of association between 0-IIc colorectal neoplasm and family history of FDR with CRC adjusted by gender and age was higher than that of non 0-IIc

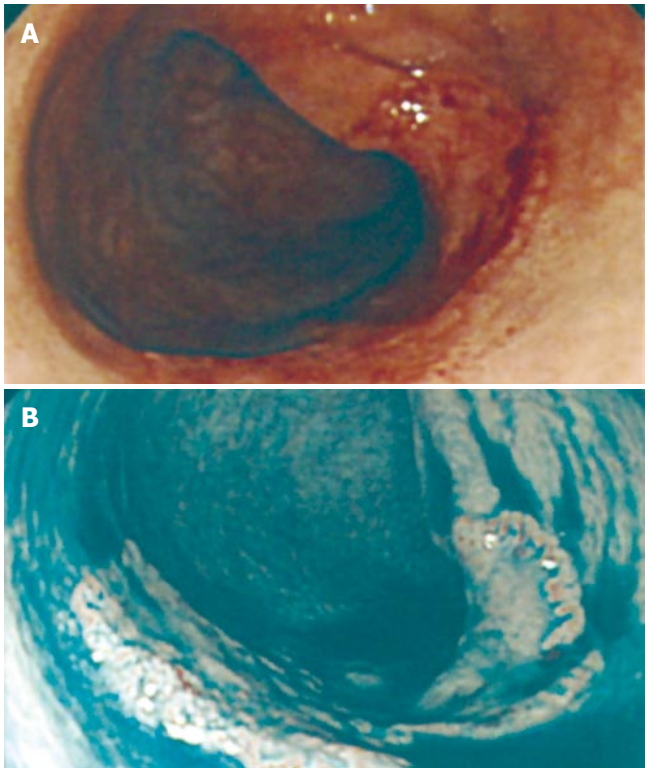

Figure 1 Superficial depressed lesion (0-IIc). **A**: A superficial depressed lesion (0-IIc) of the transverse colon, 27 mm in diameter. Initially it was recognized as a broad patch of erythema and deformity of the haustrum. The patient demonstrated a family history of CRC. His mother had a past history of sigmoid colon cancer at age of 65 years. **B**: After dye spraying, an absolutely depressed area could be clearly identified, with a slightly elevated margin.

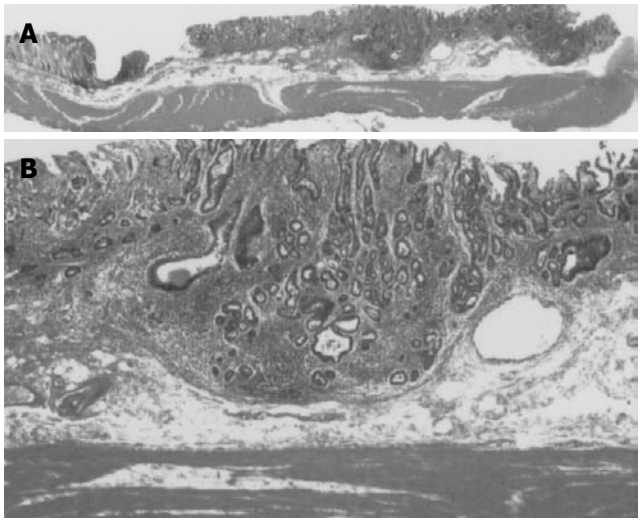

Figure 2 Histological findings. **A**: Low-power histological view of a cut section of the resected specimen confirmed Dukes' A (T1 stage) carcinoma with invasion to the submucosa. **B**: High-power histological view confirmed a well differentiated adenocarcinoma invading 1000 μm below the muscularis mucosa.

colorectal neoplasm (OR = 2.78, 95% CI: 1.49-5.16, P = 0.0031 *vs* OR = 1.71, 95% CI: 1.22-2.41, P = 0.0017).

DISCUSSION

Colorectal neoplasm with superficial morphology is broadly classified into two types, such as polypoid type and non-polypoid type[8,13]. In terms of polypoid type neoplasm, the adenoma-carcinoma sequence has formed the rationale for CRC screening and prevention in Western countries[5,17]. In addition, it is also known that familial risk management is one of the important strategies for CRC prevention due to its associations with bowel malignancy[5] and adenoma growth[6,7]. Almendingen *et al*[7] reported a significant association between family history of FDR with CRC and adenoma growth (adjusted OR = 3.9, 95% CI: 1.2-13.4). In the present study, family history of FDR with CRC was significantly correlated with non 0-IIc colorectal neoplasm (OR = 1.71, 95% CI: 1.22-2.41, P = 0.0017), which tends to show a result similar to previous reports. However, these data are mainly based on the polypoid type colorectal neoplasm.

As the Paris endoscopic classification of superficial neoplastic lesions in the colon proposed, special attention should be focused on depressed-type 0-IIc lesions[8], which are now widely recognized in Western countries as well as in Japan. This recognition has important implication, as the proportion of CRC is likely to be higher in these lesions than in other types, and these lesions tend to be more advanced at the time of diagnosis, despite being smaller[18-23]. Furthermore, it is certainly more difficult to detect 0-IIc colorectal neoplasm than polypoid type lesions during colonoscopy. They usually appear only as patches of erythema or irregularity of the mucosal fold (Figures 1 and 2), so colonoscopists should develop an understanding of the 0-IIc lesion[9]. At the same time, it is very important to identify risk factors for 0-IIc colorectal neoplasm, so if patients with some risk factors for these lesions undergo colonoscopy, we could be more alert to recognizing the lesions. However, it has not been reported whether the risk of 0-IIc colorectal neoplasm is correlated with any patient characteristics, including family history of FDR with CRC.

In the present study, 0-IIc colorectal neoplasm was detected in 63 patients (4.0%), which is nearly similar to data (1.94%-5%) reported by other institutes in Japan[8,9]. More importantly, our study showed a significant correlation with family history of FDR with CRC and 0-IIc colorectal neoplasm (OR = 2.78, 95% CI: 1.49-5.16, P =0.0031), suggesting the possibility of a genetic contribution to the occurrence of 0-IIc colorectal neoplasm. Recently, two major pathways for colorectal neoplasm are highly suspected. Compared to the polypoid lesions arisen in the pathway of adenoma-carcinoma sequence, depressed-type (0-IIc) lesions are proposed to arise in *de novo* pathway and show rapid growth. Molecular biology also suggests that depressed-type lesions are likely to have early *P53* and delayed K-*ras* mutations distinct from the former pathway[24,25]. Moreover, there tends to be high microsatellite instability occurrence in *de novo* cancers compared to early cancers with adenoma[25]. It is also noteworthy that Ricciardiello *et al*[26] have reported there is higher degree of microsatellite instability among patients with family history of FDR with CRC. These results may support our positive association between depressed-type colorectal neoplasm and family history of FDR with CRC.

In addition, the pathway of depressed-type lesions evolving rapidly into a small flat invasive carcinoma is hypothesized to be a major route in hereditary non-polyposis colon cancer (HNPCC)[8], for which the genes hMSH2, hMLH1, and others have been identified as being responsible. In our study, multivariate analysis stratified by age showed higher OR of association between 0-IIc colorectal neoplasm and family history of FDR with CRC in patients before age of 60 years than those after age of 60 years (OR = 4.06, 95% CI: 1.48-11.14, $P = 0.006$ *vs* OR = 2.28, 95% CI: 1.02-5.06, $P = 0.04$), whereas our colleagues previously reported that depressed-type lesions were predominant in the right colon[27]. These characteristics are similar to HNPCC, and further molecular genetic research for depressed-type 0-IIc lesions and HNPCC is required. However, to our knowledge, the association between a family history of FDR with CRC and 0-IIc colorectal neoplasm has not been investigated previously even on NPS (National Polyp Study in USA). The limitation of this study is that the prevalence of patients with neoplasm in this study was higher (63.5%) than that in the general population because of a characteristic of our cancer center hospital, because even we selected the patients who undergo initial total colonoscopy at our hospital, many patients are introduced from general hospital for further examination because of suspicion of colorectal cancer. Although the statistical analysis in this study could avoid these biases, this association should be confirmed in a prospective multicenter study.

In conclusion, the present study demonstrates a significant association between the family history of FDR with CRC and 0-IIc colorectal neoplasm. When patients with a family history of FDR with CRC undergo colonoscopy, colonoscopists should pay attention to not only polypoid, but also depressed-type (0-IIc) lesions.

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