

# Revisiting the Prognostic Impact of Family History in Colorectal Cancer by Retrospective Propensity Score Matching

YUSUKE MIZUUCHI<sup>1,2</sup>, YOSHITAKA TANABE<sup>2</sup>, KINUKO NAGAYOSHI<sup>1</sup>,  
KOJI TAMURA<sup>1</sup>, TAKA AKI FUJIMOTO<sup>1</sup>, KYOKO HISANO<sup>1</sup>, JINGHUI ZHANG<sup>1</sup>,  
SHUNTARO NAGAI<sup>2</sup>, KOHEI NAKATA<sup>1</sup>, KENOKI OHUCHIDA<sup>1</sup> and MASAFUMI NAKAMURA<sup>1</sup>

<sup>1</sup>Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan;  
<sup>2</sup>Department of Surgery, Kitakyushu Municipal Medical Center, Kitakyushu, Japan

**Abstract.** *Background/Aim:* Family history of colorectal cancer (CRC) is a known risk factor for CRC. However, its prognostic value in patients with CRC remains controversial. This study aimed to clarify the prognostic impact of a family history of CRC. *Patients and Methods:* We retrospectively reviewed the database from 1978 to 2018 and enrolled 3,655 consecutive patients with CRC. We investigated the clinicopathological factors of patients with CRC with and without a family history. After propensity score matching, we performed a survival analysis of patients with CRC with and without a family history. *Results:* Patients with CRC with a family history of CRC had a young onset (63.2 and 65.9;  $p < 0.001$ ), were more likely to be female (54.3% and 49.7%;  $p = 0.042$ ), had less symptomatic disease (76.9% and 80.8%;  $p = 0.008$ ), were more likely to have right-sided colon cancer (27.5% and 26.1%), and had less distant metastases (11.3% and 14.9%;  $p = 0.023$ ) and multiple CRCs (10.2% and 7.8%) compared with those without a family history of CRC. Prior to propensity score matching, CRC-specific survival analysis showed that a family history of CRC was a good prognostic factor ( $p = 0.022$ ). After propensity score matching, survival curves overlapped between the two groups. *Conclusion:* Patients with CRC with a family history of CRC had specific clinicopathological features including younger onset, female sex, proximal colon location, fewer symptoms, smaller number of distant metastases, likelihood of multiple diseases, and earlier cancer stage. Family history of CRC in patients with CRC was not a prognostic factor.

*Correspondence to:* Yusuke Mizuuchi, MD, Ph.D., Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Fukuoka, 812-8582, Japan. Tel: +81 926425441, Fax: +81 926425458, e-mail: mizuuchi.yusuke.295@m.kyushu-u.ac.jp

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Globally, colorectal cancer (CRC) is the third most common cancer type in men and the fifth most common in women (1) and its frequency is increasing. In Japan, CRC is the leading cause of death in women, and the third leading cause of death in men. Approximately 160,000 patients were newly diagnosed with CRC in 2016 and more than 50,000 patients died of CRC in 2018 (2). Among advanced CRC with distant metastases, prolonged survival was expected as a result of multidisciplinary therapies, such as surgery, chemotherapy, immunotherapy, and radiation, and the application of novel procedures such as laparoscopic surgery has been increasing to improve the treatment outcomes of CRC patients (3). However, patients with CRC still have a poor prognosis, and the 5-year overall survival rate of patients with advanced CRC is 23.7% in Japan (4).

Carcinogenesis is promoted by activating oncogenes as driver mutations and by inactivating tumor suppressor genes. Thus, cancer development is mediated by interactions between various gene mutations. Hereditary CRC is defined as the development of cancer in individuals with germline pathogenic variants of these cancer-mediated genes, such as *APC* (familial adenomatous polyposis; FAP), mismatch repair genes (Lynch syndrome), *STK11* (Peutz-Jeghers syndrome) and *PTEN* (Cowden syndrome). However, CRCs frequently occur in families who do not have evidence of known gene alterations related to inherited syndromes and account for 25%-30% of all patients with CRC. For instance, in patients clinically diagnosed with FAP by endoscopy, no variants of *APC* were detected in 20%-40% of these patients, and a number of them had germline gene mutations in *MUTYH*, *POLE*, *POLD1*, and *NTHL1* (5-7). However, only a very small number of genes responsible for familial CRC have been identified, partly because of the quality of genetic testing. Thus, these hereditary alterations of cancer-mediated genes have an important role in the development of familial CRC, but this is only one mechanism of CRC occurrence in these families, and other mechanisms such as DNA damage by radiation or toxic agents and epigenetic alterations have been suggested.

Familial CRC is generally defined as heterogeneous and includes unrecognized components of hereditary CRC, with seemingly sporadic forms frequently occurring in families. In these families, CRC can be triggered by the social environment (diet, living environment, smoking, and alcohol consumption); however, the detailed genetic mechanisms underlying its frequent occurrence are not well understood. While familial CRC can present a serious risk to patients as metachronous CRC develops, familial CRC also burdens patients with concerns about their relatives. Given these clinical and social problems, it is important to determine whether a family history of CRC has an impact on patient prognosis. Previous studies have shown that family history of CRC is a risk factor of colorectal neoplasia, ranging from benign tumors to malignancies, such as adenoma and adenocarcinoma (8, 9). Regarding the prognosis of CRC, a previous study showed no effect on survival in the whole cohort, whereas a subgroup analysis also showed that CRC family history was a poor prognostic marker in the younger cohort (age  $\leq 55$  years) (10). Another study demonstrated that CRC family history was a poor prognostic marker in female patients (11). Conversely, in Japan, the Japanese Society for Cancer of the Colon and Rectum demonstrated that the prognosis of patients with CRC with a family history was significantly better than that of patients with CRC without a family history, although there were no differences in the background clinicopathological factors between the two groups (12). However, the effect of CRC family history itself within second-degree relatives on cancer survival remains controversial. Thus, to correct for differences in clinicopathological factors, except for CRC family history, we retrospectively reviewed patients with CRC and examined the prognostic value of CRC family history using propensity score matching. The aim of this study was to evaluate the impact of CRC family history on prognosis compared with a propensity score-matched series of patients with CRC without a family history of CRC.

## Patients and Methods

We retrospectively reviewed a prospectively maintained surgical database between January 1978 and December 2018 and enrolled 4,445 consecutive patients with CRC who underwent colorectal surgery at our institute. The eligibility criterion was histologically proven CRC adenocarcinoma. Exclusion criteria included the following: 1) clinical or genetic diagnosis of either FAP, Lynch syndrome, or other hereditary CRC ( $n=58$ ); 2) underwent stoma creation without resection of the primary lesion ( $n=112$ ); 3) colitic cancer associated with inflammatory bowel disease ( $n=27$ ); 4) appendiceal carcinoma ( $n=63$ ); 5) other malignancy including hematopoietic, lymphoid tissues, bone and soft tissue ( $n=416$ ); 6) emergency surgery ( $n=88$ ); 7) lack of information about family history ( $n=117$ ) including duplication. Patients with metachronous or multiple synchronous CRCs were included in this study.

We retrospectively collected data from the medical records of patients with CRC. Clinical data included age, sex, symptoms,

family history, serum tumor markers (carcinoembryonic antigen and CA19-9 levels), multiple CRCs, tumor locations, and distant metastatic organs (the liver, lung, and peritoneum). Tumor location was defined as the tumor site of the main tumor (right-sided colon including cecum, ascending colon, and transverse colon; left-sided colon including descending colon, sigmoid colon, and rectosigmoid junction; and rectum including upper and lower rectum). Multiple CRC included both metachronous and synchronous CRCs. Pathological data included histological grade (tumor differentiation defined as well differentiated, moderately differentiated, or poorly differentiated adenocarcinoma), and T and N stage of the main tumor. Tumor location and pathological tumor staging were classified in accordance with the 8th Edition of the TNM Classification of Malignant Tumours (UICC TNM) including earlier part of the study period (13). Family history was also collected from the medical charts. Our institute has adopted a questionnaire to collect medical history including family history since the 1980s, which is why there is relatively little information about family history. Patients with CRC with a family history were defined according to whether they had first- or/and second-degree relatives with CRC or not. To minimize the impact of various biases and confounding factors, we performed a propensity score-matched analysis, as previously described (14). Propensity scores were generated using perioperative characteristics including age, sex, tumor location, presence of symptoms, tumor markers, pathological stage, and distant metastatic organs. Propensity scores were matched using a caliper width of 0.01 multiplied by the standard deviation of values calculated using a logistic regression model. Each patient with a CRC family history was matched to a patient without a CRC family history using a one-to-one nearest neighbor matching algorithm without replacement. After matching, 493 patients were included in each group. The study protocol was approved by the Ethical Advisory Committee of Kitakyushu Municipal Medical Center before the study was initiated (approval number: 201901070). The informed consent requirement was waived because of the retrospective nature of this study, in which patient data were anonymized. All procedures conformed to the ethical guidelines of the Japanese Government and the Declaration of Helsinki.

Statistical analysis was performed using the following method. Correlations between two variables were analyzed using the chi-square test or Fisher's exact test, where appropriate. For survival analysis, CRC-specific survival (CSS) was adopted as the primary endpoint and set to the date of death and last follow-up date in surviving patients. The last follow-up date was June, 2022. To analyze the survival impact of CRC family history, we compared other potential prognostic variables. The survival correlation was presented by Kaplan–Meier analysis and the curves were compared using the log-rank test. Equivalency of CRC survival after propensity score matching was evaluated by comparing Cox proportional hazards models before and after propensity score matching. Continuous variables were expressed as the median and the range was assessed using the Mann–Whitney *U*-test. A *p*-value of  $<0.05$  was considered to indicate a statistically significant difference. All statistical analyses were performed using the JMP software (16<sup>th</sup> version; SAS Institute, Cary, NC, USA).

## Results

*Clinicopathological characteristics of familial CRC.* Table I shows the characteristics of the patients with and without a CRC family history. Among 3,655 patients with CRC who

Table I. Clinicopathological factors before propensity score matching.

Factors	FCRC (n=549)	SCRC (n=3,106)	p-Value
Sex (Male)	273 (49.7%)	1,672 (54.3%)	<b>0.042</b>
Age (range)	63.2 (16-92)	65.9 (17-97)	<b>&lt;0.001</b>
Symptomatic disease	422 (76.9%)	2,540 (80.8%)	<b>0.008</b>
CEA >5 ng/ml	109 (34.4%)	1,335 (37.7%)	0.795
CA19-9 >37 ng/ml	36 (11.9%)	511 (16.2%)	0.098
Multiple CRC	56 (10.2%)	233 (7.8%)	<b>0.037</b>
Primary lesion			0.316
Right side	151 (27.5%)	811 (26.1%)	
Left side	243 (44.3%)	1318 (42.4%)	
Rectum	155 (28.2%)	977 (31.4%)	
Distant and/or peritoneal metastasis	62 (11.3%)	462 (14.9%)	<b>0.023</b>
Peritoneal metastasis	19 (3.5%)	125 (4.0%)	0.524
Liver metastasis	48 (8.7%)	311 (10.0%)	0.35
Lung metastasis	7 (1.3%)	71 (2.3%)	0.098
TNM classification			
0	18 (3.3%)	87 (2.8%)	0.599
I	131 (23.9%)	676 (21.8%)	
II	155 (28.2%)	891 (28.7%)	
III	199 (36.2%)	1,030 (33.2%)	
IV	65 (11.8%)	422 (13.6%)	

FCRC: Familial colorectal cancer; SCRC: sporadic colorectal cancer. Bold values indicate statistical significance.

underwent colorectal resection and were histologically diagnosed with CRC without preoperative adjuvant therapy, 549 patients had a family history of CRC in first- or/and second-degree relatives. We compared the clinicopathological factors between patients with CRC with a CRC family history (FCRC group) and sporadic CRC patients without a CRC family history (SCRC group).

Prior to propensity score matching, in the FCRC group, the age of onset was significantly younger (63.2 vs. 65.9;  $p < 0.001$ ), the proportion of women was significantly higher (54.3% vs. 49.7%;  $p = 0.042$ ), and symptomatic disease (bowel obstruction, obvious bloody or tarry stool, symptomatic anemia and abdominal mass) was significantly lower (76.9% vs. 80.8%;  $p = 0.008$ ) compared with the SCRC group. Among the SCRC group, the proportion of patients with rectal cancer was relatively high (31.4% vs. 28.2%) and that of patients with right-sided colon cancer was relatively low (26.1% vs. 27.5%) compared with the FCRC group; however, this was not statistically significant ( $p = 0.316$ ). In the SCRC group, distant metastasis including the liver (10.0% vs. 8.7%), lung (2.3% vs. 1.3%), and peritoneal metastasis (4.0% vs. 3.5%) was detected significantly more frequently compared with the FCRC group (14.9% vs. 11.3%;  $p = 0.023$ ). Therefore, tumor stage was more advanced in the SCRC group than in the FCRC group. Multiple CRCs, including metachronous or synchronous CRCs, were more frequently diagnosed in the FCRC group (10.2% vs. 7.8%;  $p = 0.037$ ). In this study, CRC in patients with a family history of CRC had a younger onset,

was more likely to occur in women, less symptomatic, more likely located in the right-sided colon, less likely to be rectal cancer, likely to be a multiple disease, and had less distant metastasis and non-advanced disease compared with that without a CRC family history.

*Survival analysis of patients with CRC before propensity score matching.* Cancer stage was not advanced in the FCRC group, as mentioned above. Prior to propensity score matching, CSS analysis showed that the 5-year CSS rate was 81.5% in the FCRC group and 77.8% in the SCRC group, and the CRC-specific prognosis of CRC was significantly better in the FCRC group compared with that in the SCRC group ( $p = 0.022$ ; Figure 1). This indicated that patients with CRC with a family history of CRC had a favorable prognosis in the unmatched analysis. However, it is clear that there were many confounding factors and biases, such as the differences in cancer stage, age, sex, presence of symptoms, tumor markers, and tumor location. To clarify the prognostic significance of CRC family history as a biological marker, we performed propensity score matching and analyzed the CRC prognosis.

*Propensity score matching for familial CRC patients.* After propensity score matching, we corrected for differences in patient characteristics between the two groups (age, sex, tumor location, presence of symptoms, tumor markers, pathological stage, and distant metastatic organs) (Table II). Multiple CRCs were also equivalent between the two groups.

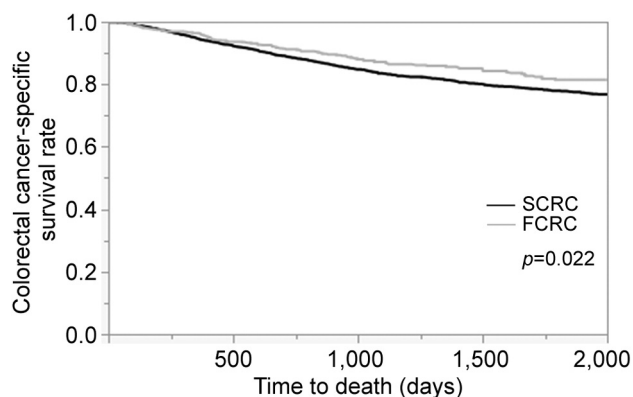


Figure 1. Colorectal cancer (CRC)-specific prognosis was significantly better in the FCRC group compared with that in the SCRC group ( $p=0.022$ ). FCRC group: Patients CRC with a CRC family history; SCRC group: sporadic CRC patients without a family history of CRC.

*Prognostic analysis of patients with CRC after propensity score matching.* After propensity score matching, we repeated the survival analysis and generated a survival curve by Kaplan–Meier analysis. The curves overlapped and there was no significant difference between the two groups ( $p=0.915$ ; Figure 2). The 5-year CSS rate was 83.8% in the FCRC group and 84.6% in the SCRC group. Cox proportional hazards model showed that the CRC-specific prognosis of CRC was significantly better in the FCRC group compared with the SCRC group [hazard ratio (HR)=0.794, 95% confidence intervals (CI)=0.646-0.976,  $p=0.022$ ] prior to propensity score matching. However, it was equivalent between the two groups (HR=1.011, 95%CI=0.740-1.383,  $p=0.915$ ) after matching, indicating that CRC family history itself was not prognostic marker of CRC patients.

## Discussion

The current study of 3,655 patients with CRC who underwent colorectal resection demonstrated that CRC with a family history had several features before correction of the cohort using propensity score matching: younger onset, female propensity, was more likely to occur in the proximal colon, less likely to be rectal cancer, less symptomatic, had a smaller number of distant metastasis, and was earlier stage. Several studies of patients with CRC found that CRC family history was associated with earlier stage and younger age at diagnosis, as well as location in the proximal colon (10, 15). This study also demonstrated that the clinicopathological data of familial CRC patients before propensity score matching were consistent with previous reports and reflected the real world situation. After propensity score matching, we

also revealed that family history of CRC itself is not a prognostic marker among patients with CRC.

FAP and Lynch syndrome are early-onset diseases; hence, the onset age of patients with CRC with a family history was younger than that of those without a family history in previous reports. This study excluded patients with FAP or Lynch syndrome, unlike previous studies, and demonstrated the significance of younger onset of CRC in the FCRC group compared with the SCRC group. In the near future, universal genetic screening of hereditary CRC, which has recently been initiated in many high-volume medical institutes, will detect more gene alterations involved in the onset of hereditary CRC and result in fewer familial CRC patients without evidence of specific gene mutations. This may increase the age of diagnosis in familial CRC except for hereditary CRC because of the early onset of hereditary CRC, such as FAP and Lynch syndrome.

In this cohort, the SCRC group had more advanced disease compared with the FCRC group for several potential reasons. First, familial CRC patients may have a more favorable biological background than other CRC patients do. A previous study showed that patients with familial breast cancer without *BRCA* mutations had a favorable prognosis compared with those with *BRCA* mutations and sporadic breast cancer (16). Second, multiple adenomas and CRCs are frequently observed in patients with familial CRC. These patients can be diagnosed at an early stage because patients with familial CRC often undergo colonoscopy for follow-up (17, 18). Third, patients with familial CRC are more likely to undergo fecal occult blood tests and colonoscopy for screening because CRC frequently occurs in relatives at an earlier age (19). Fourth, there is a possibility that CRC with a family history has a biological behavior to prevent distant metastasis (20). Prior to matching, previous studies, including our study, indicated that familial CRC has a good prognosis among patients with CRC because of differences in clinicopathological factors (10). To elucidate the prognostic value of a family history of CRC, we performed propensity score matching. After matching, we extracted two groups that were equivalent in terms of clinicopathological factors except for CRC family history. In this study, the survival curve almost overlapped after matching, indicating that CRC family history itself had no survival impact in this cohort.

*Study limitations.* Although we performed propensity score matching to reduce bias as much as possible, there were unmeasured confounders and large selection biases because the study was retrospective. Moreover, we excluded patients with hereditary CRC, such as those with FAP or Lynch syndrome. However, this study included patients from the 1970s onwards. Although most CRC cases associated with colonic polyposis, such as FAP, can be clinically diagnosed using colonic endoscopy, we could not diagnose hereditary CRC, especially Lynch syndrome, because genetic testing was

Table II. Clinicopathological factors after propensity score matching.

Factors	FCRC (n=493)	SCRC (n=493)	p-Value
Sex (Male)	242 (49.1%)	225 (45.6%)	0.278
Age (range)	64.2 (63.2-65.2)	64.2 (63.2-65.2)	0.982
Symptomatic disease	373 (75.7%)	386 (78.3%)	0.325
CEA >5 ng/ml	176 (35.7%)	178 (36.1%)	0.894
CA19-9 >37 ng/ml	61 (12.4%)	55 (11.2%)	0.553
Multiple CRC	52 (10.6%)	36 (7.3%)	0.073
Primary lesion			0.206
Right side	140 (28.4%)	146 (29.6%)	
Left side	218 (44.2%)	181 (39.0%)	
Rectum	135 (27.4%)	155 (31.4%)	
Distant and/or peritoneal metastasis	53 (10.8%)	54 (10.9%)	0.918
Peritoneal metastasis	15 (3.0%)	16 (3.3%)	0.855
Liver metastasis	40 (8.1%)	35 (7.1%)	0.548
Lung metastasis	7 (1.4%)	7 (1.4%)	1
TNM classification			0.91
0	18 (3.7%)	18 (3.7%)	
I	119 (24.1%)	112 (22.7%)	
II	143 (29.0%)	157 (31.9%)	
III	156 (31.6%)	152 (30.8%)	
IV	57 (11.6%)	54 (11.0%)	

FCRC: Familial colorectal cancer; SCRC: sporadic colorectal cancer.

not performed at that time. Moreover, even during the recent study period, only a limited number of patients underwent genetic testing for Lynch syndrome. Therefore, a considerable number of patients with Lynch syndrome were included in this study. The presence of malignancies can alter the prognosis of patients with CRC. Therefore, in this study, we excluded patients with other malignancies. Patients with multiple metachronous or synchronous CRC were included in this study. After correcting for matching, the propensity score matching minimized the prognostic influence of multiple CRCs. However, unmeasured confounders cannot be ruled out. Above all, the duration of the patients' enrollment in the present study was long. We did not consider the duration of the surgery for each patient. Advances in medical technology, including the development of imaging modalities, cancer therapeutic drugs (such as chemotherapy and molecular target drugs) and radiation therapy (such as heavy-ion radiotherapy), have improved treatment outcomes for both groups. The frequency of familial CRC does not change with time; however, bias can exist. Among the total cohort in this study, the disease stage of the FCRC group was less advanced than that of the SCRC group. Therefore, the result showing that the prognosis was equivalent regardless of the presence of CRC family history using propensity score matching is limited.

Patients with familial CRC showed less advanced disease, but CRC family history itself had no prognostic impact at a Japanese single tertiary hospital. To validate these results, a large-scale population-based prospective cohort study is required.

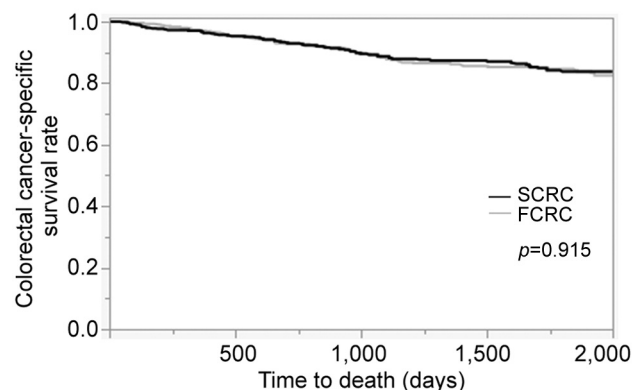


Figure 2. Kaplan–Meier analysis indicated that survival curves overlapped and there was no significant difference between the FCRC and SCRC groups after propensity score matching ( $p=0.915$ ; Figure 2). FCRC group: Patients with CRC with a CRC family history; SCRC group: sporadic CRC patients without a family history of CRC.

## Conflicts of Interest

The Authors declare no competing interests in relation to this study.

## Authors' Contributions

All Authors contributed to the study conception and design. Yusuke Mizuuchi: Writing – Original Draft, Funding acquisition and project

administration, Yoshitaka Tanabe: Writing – Review & Editing, Koji Tamura and Kenoki Ohuchida: Formal analysis, Software, Shuntaro Nagai, Kyoko Hisano and Jinghui Zhang: Visualization, Takaaki Fujimoto and Kinuko Nagayoshi: Investigation, Resources, Kohei Nakata: Data Curation, Validation, Masafumi Nakamura: Supervised the project. All Authors read and approved the final manuscript.

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