Original Article

Comparisons of the Clinic-pathological Features, Risk of Metachronous Tumor and Survival among Colorectal Cancer Patients with Different Family History

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Key Words
Colorectal cancer;
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HNPCC;
FAP

Purpose. We investigate whether the family history (FH) of patients with colorectal cancer (CRC) affects their clinic-pathologic features, treatment outcomes, and post-operative follow-ups.
Patients and Methods. A total of 14082 CRC cases with complete data were identified. Clinicopathological features, treatment outcomes, and risk of developing metachronous CRC were compared across case groups with different FHs, using the multivariate Cox proportional hazard model.
Results. Among five patient groups with different FHs, patients with hereditary nonpolyposis colorectal cancer (HNPCC) displayed a lower frequency of rectal cancer than colon cancer (27.6%, $p < 0.0001$), presence of multiple tumors (27.9%, $p < 0.0001$), younger age, location predominance in the right side of the colon (49.5%), higher proportion of mucinous adenocarcinoma (15.0%), more poorly differentiated cancers, less lymph node metastases (61.1%, $p < 0.0001$), and reduced rate of distant metastases (11.2%), compared with other groups. Patients with positive FH had better OS (hazard ratios 0.873, $p < 0.0001$) and better RFS (hazard ratios 0.872, 95% CI 0.800-0.949, $p = 0.0016$) than those with sporadic CRC. The incidence of metachronous CRC occurrence among patients with sporadic, FAP, HNPCC, positive FH, and HNPCC-like diagnoses were 2.36, 1.44, 7.55, 2.94, and 5.71 per 1000 person-years, respectively ($p = 0.0005$). Risk ratios of metachronous CRC for HNPCC and HNPCC-like cancer were 4.185-fold ($p < 0.0001$) and 2.49-fold ($p = 0.003$) higher than patients with sporadic colon cancer, respectively.
Conclusions. There are different clinic-pathologic characteristics, risk of metachronous CRC, and treatment outcomes among patients with CRC with different FHs.
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Most incidences of colorectal cancer (CRC) are caused by both genetic and environment factors. A small minority of CRC cases, such as familial polyposis coli (FAP) and hereditary non-polyposis colorectal cancer (HNPCC), may arise through germline mutation of certain genes.[1-4] HNPCC is defined

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clinically as a family history that fulfills the Amsterdam II criteria (A-II C). Based on some minor variances of A-II C, namely lacking one of four items of A-II C (at least three relatives with a lynch associated cancer, one should be a first-degree relative of the other two, at least two successive generations affected, and at least one diagnosed before age 50), some cases were diagnosed as HNPCC-like. Recently clinically defined patients with HNPCC, who lacked a mismatch repair gene deficiency, were diagnosed with familial colorectal cancer syndrome type X (FCCTX),[5,6] and it remains unclear whether other more complex inheritance models exist.[7-9] Furthermore, certain environments modify the risks of genetic polymorphisms, and we hypothesize that CRC depends on family history.[10,11]

Family history is an important criteria for patients with cancer, because based on family history, clinicians can diagnose whether patients are likely to present hereditary cases. Distinct clinic-pathological features are also related to different groups of patients with colorectal cancers who present distinct classifications of family history. Compared to patients with sporadic colorectal cancer, which is defined as the absence of a family history of colorectal cancer, patients with HNPCC display clinically distinct characteristics, which include a younger age of onset, predominance for the right side of the colon, and poorly differentiated and mucinous adenocarcinomas.[12-15] FCCTX does not share the same clinical and histologic features as lynch syndrome.[5]

Family history serves as a guideline for patient surveillance and follow up and has the potential to improve outcome. Family history is an established risk factor for colorectal cancer, and while family history records can be inconsistent and infrequently reported, they have a clear impact on patient survival.[16-19] Furthermore, with advancements in the cancer field, family history records provide oncologist opportunities to reassess newly defined cancer susceptibility genes and guide advanced genetic testing.[20-24]

In this study, we retrospective analyzed 14479 patients with newly diagnosed colorectal cancers from January 1995 through December 2012. We compared clinic-pathological characteristics, treatment outcomes (overall survival and recurrence free survival), and risk of developing metachronous CRC among different family history groups of patients with colorectal cancer.

Patients and Methods

The registry and patients

From January 1995 through December 2012, a total of 14479 patients with newly diagnosed colorectal cancer at Chang Gung Memorial Hospital (CGMH), Taiwan, were recorded in the Colorectal Cancer Registry of CGMH. This registry was first established in 1985 by Chung Rong ChangChien, and a revised data record form was implemented in 1995 by Reiping Tang. Collected data covered fiver major categories, including detailed family histories, demographic variables, preoperative evaluations, operation records, and postoperative follow-ups. All data collected from patient interviews and clinical and pathological records were recorded by surgical nursing specialists on a standardized form, which was confirmed by either Reiping Tang, Jeng Fu You, or Hsin Yun Huang, before translation into numerical code and entry into computer records for later follow-ups. Pedigrees were traced backward and laterally, as far as possible. Patients were asked about the occurrences of malignancies among first- and second-degree relatives. Family history was classified into 5 categories: (1) sporadic, no family history, (2) familial adenomatous polyposis (FAP), (3) HNPCC defined by Amsterdam II criteria, (4) patients reported a history of any malignancy in a first degree relative but did not fulfill HNPCC criteria, and (5) HNPCC-like family, which was defined as patients who lacked one of four Amsterdam II criteria (at least three relatives with a lynch associated cancer, one should be a first-degree relative of the other two, at least two successive generations affected, and at least one diagnosed before age 50). Postoperative colonoscopic surveillance was performed one year after colectomy, after which colonoscopy was repeated every one to three years, depending on the results of previous colonoscopies. Follow-up data were added annually, by reviewing patients' records on medical

charts. Telephone interviews or mail questionnaires were performed if a patient's medical records were unavailable. This study was approved by the IRB of Chang Gung Memorial Hospital (IRB102-2284B).

Statistical analyses

The X^2 test, Fisher's exact test, and Wilcoxon ranked sum test were used to examine the distribution of patient characteristics between five family history groups. Survival curves were estimated by the Kaplan-Meier method. In univariate survival analysis, the association between patient characteristics, disease-free survival, and overall survival were evaluated by the log-rank test. The Cox proportional hazard model was used to investigate the effect of family history on survival, when adjusting for other factors. All *p*-values are two-sided. Statistical analyses were performed using SPSS 17 software (SPSS, Inc., Chicago, IL).

Results

Between January 1995 and December 2012, there were 14479 newly diagnosed patients with colorectal cancer in our hospital, and of them, 14082 (97.3%) presented complete data and were eligible for our study. Based on categories of family history, there were 8794 (62.4%) patients with sporadic colorectal cancer who lacked family history of CRC, 119 (0.8%) patients with FAP, 206 (1.5%) patients with HNPCC, 379 (2.7%) patients who were HNPCC-like, as described in patients and methods above, and 4584 (32.6%) patients who presented a family history of any malignancy that was not related to Lynch-associated tumors (Table 1).

We investigated clinic-pathological features, including age of onset, tumor size, tumor location, tumor differentiation, rate of mucinous adenocarcinoma, type of operations, ratio of staging and diagnosis, and disease free survival (DFS) and overall survival (OS) treatment outcomes by covariate analysis. We also analyzed the risk of developing metachronous colorectal cancers among patients with different family history categories of colorectal cancers.

Comparisons of clinic-pathological characteristics

Of all patients summarized in Table 1, patients with HNPCC displayed a significantly lower frequency of rectal cancer (27.6%, $p < 0.0001$), more frequent presence of multiple synchronous or metachronous tumors (27.9%, $p < 0.0001$), and younger age at diagnosis (mean 50.5 years) compared with other patients with family histories of colorectal cancer. The mean age of patients with HNPCC was 13, 12, or 9.1 years younger than patients with sporadic, positive family history (FH), or HNPCC-like CRC, respectively ($p < 0.0001$). As shown in Fig. 1, patients with ages younger than 40 years included 20.9% of patients with HNPCC, 10.3% of patients with HNPCC-like CRC, 4.95% of patients with sporadic CRC, and 5.28% of patients with positive FH. Patients with a past history of CRC were more frequently represented in patients with HNPCC and patients with HNPCC-like CRC categories (9.7% and 5.8%, respectively), and less frequently among patients with sporadic CRC (2.0%) and among patients classified as family history-positive (1.8%) ($p < 0.0001$). Tumors presented the strongest predominance for right colon localization in patients with HNPCC (49.5%), whereas patients who were classified as sporadic (21.1%), positive FH (22.9%), and HNPCC-like (25.6%) displayed reduced right colon predominance. Mucinous/signet type adenocarcinoma (15.0%) was higher for patients with HNPCC, compared to patients with sporadic (8.0%), positive FH (7.2%) and HNPCC-like (8.4%) CRC ($p = 0.0013$). Poorly differentiated cancers were more frequently observed in patients with HNPCC (17%), compared to patients who displayed sporadic (8.6%), positive FH (8.7%), and HNPCC-like CRC (10.6%) ($p < 0.0001$). Comparisons of TNM stage ratios among patients from different family history groups revealed that there were significantly less lymph node metastases and more patients classified as N0 among the group of patients with HNPCC (61.1%, $p < 0.0001$), when compared to patients in HNPCC-like CRC (51.7%), positive family history (51.1%), and sporadic CRC (49.6%) groups. Patients with HNPCC also presented a reduced rate of distant metastases

Table 1. Clinic-pathologic characteristics of colorectal cancer patients with different family history

Family history subgroup	Sporadic	FAP	HNPCC	FH positive	HNPCC-like	*p* values
Patient no. (%)	8794 (62.4)	119 (0.8)	206 (1.5)	4584 (32.6)	379 (2.7)	
Organ involved						< 0.0001
Colon	4528 (51.5)	41 (34.5)	149 (72.3)	2439 (53.2)	222 (58.6)	
Rectum	4022 (45.7)	27 (22.7)	39 (18.9)	1997 (43.6)	137 (36.1)	
Both	244 (2.8)	51 (20.9)	18 (8.7)	148 (3.2)	20 (5.3)	
Multiplicity						< 0.0001
Single	7650 (87.0)	83 (69.8)	149 (72.3)	3940 (85.9)	303 (79.9)	
Synchronous	455 (5.2)	25 (21.0)	13 (6.3)	251 (5.5)	31 (8.2)	
Metachronous	689 (7.8)	11 (9.2)	44 (21.6)	293 (8.6)	45 (11.9)	
Age, y/o						
Mean (SD)	63.5 (13.3)	37.4 (14.1)	50.5 (13.3)	62.5 (12.9)	59.6 (14.1)	< 0.0001*
Median (range)	65 (15-101)	35 (15-82)	49 (26-88)	63 (15-99)	61 (25-98)	
SEX						0.1513
Female	3968 (45.1)	57 (47.9)	104 (50.5)	1988 (43.4)	161 (42.5)	
Male	4826 (54.9)	62 (52.1)	102 (49.5)	2596 (56.6)	218 (57.5)	
Past history						
(CRC)						< 0.0001
No	8619 (98.0)	114 (95.8)	186 (90.3)	4501 (98.2)	357 (94.2)	
Yes	175 (2.0)	5 (4.2)	20 (9.7)	83 (1.8)	22 (5.8)	
(Non-CRC)						0.1416
No	8445 (96.0)	115 (96.6)	195 (94.7)	4364 (95.2)	357 (94.2)	
Yes	349 (4.0)	4 (3.4)	11 (5.3)	220 (4.8)	22 (5.8)	
Tumor location†						N/A†
R't colon	1856 (21.1)	55 (46.2)	102 (49.5)	1051 (22.9)	97 (25.6)	
L't colon	2766 (31.5)	27 (22.7)	57 (27.7)	1457 (31.8)	134 (35.4)	
Rectum	4118 (46.8)	37 (31.1)	47 (22.8)	2044 (44.6)	148 (39.1)	
TMN_T stage						< 0.0001
Tis/T1	835 (9.5)	47 (39.5)	17 (8.3)	499 (10.9)	52 (13.7)	
T2	957 (10.9)	6 (5.0)	17 (8.3)	514 (11.2)	32 (8.4)	
T3	3517 (40.0)	26 (21.9)	93 (45.2)	1957 (42.7)	129 (34.0)	
T4	3188 (36.3)	31 (26.1)	75 (36.4)	1482 (32.3)	158 (41.7)	
Unknown	297 (3.4)	9 (7.6)	4 (1.9)	132 (2.9)	8 (2.1)	
TMN_N stage						< 0.0001
N0	4360 (49.6)	77 (64.7)	126 (61.1)	2340 (51.1)	196 (51.7)	
N1	2102 (23.9)	15 (12.6)	45 (21.8)	1112 (24.3)	86 (22.7)	
N2	1551 (17.6)	17 (14.3)	21 (10.2)	790 (17.2)	74 (19.5)	
N3	395 (4.5)	8 (6.7)	7 (3.4)	171 (3.7)	11 (2.9)	
Unknown	386 (4.4)	2 (1.7)	7 (3.4)	171 (3.7)	12 (3.2)	
TMN_M stage						N/A†
M0	7107 (80.8)	103 (86.6)	183 (88.8)	3776 (82.4)	305 (80.5)	
M1	1651 (18.8)	14 (11.8)	23 (11.2)	793 (17.3)	74 (19.5)	
Unknown	36 (0.4)	2 (1.7)	0 (0.0)	15 (0.3)	0 (0.0)	
Operation type						< 0.0001
Segmental	8507(96.74)	22 (18.49)	154 (74.76)	4441 (96.88)	347 (91.56)	
Extensive	287(3.3)	97 (81.5)	52 (25.2)	143 (3.1)	32 (8.4)	
Tumor histology						0.0013
Adenocarcinoma	8088(92.0)	114 (95.8)	175 (85.0)	4252 (92.8)	347 (91.6)	
Mucinous/signet	706(8.0)	5 (4.2)	31 (15.0)	332 (7.2)	32 (8.4)	
Tumor differentiation						< 0.0001
Well/moderate	7745 (88.07)	74 (62.18)	165 (80.10)	4041 (88.15)	327 (86.28)	
Poor	754 (8.6)	3 (2.5)	35 (17.0)	397 (8.7)	40 (10.6)	
Others	295 (3.35)	42 (35.3)	6 (2.91)	146 (3.18)	12 (3.2)	
Tumor size cm^2 (width x length)						< 0.0001*
Mean (SD)	19.4 (21.5)	17.2 (18.1)	24.5 (18.7)	18.9 (21.5)	19.7 (26.9)	
Median (range)	14.0 (0.1-480.0)	12.2 (0.4-90.0)	20.0 (0.3-100.0)	13.6 (0.6-510.0)	13.7 (0.9-408.0)	

* Wilcoxon rank sum test. † Sporadic colorectal cancer patients had 0.6% anal cancer not listed.

(11.2%), when compared with patients assigned to either HNPCC-like CRC (19.5%), positive family history (17.6%), or sporadic CRC (19.2%) groups. However, we observed an increased tumor size (24.5 cm^2, $p < 0.0001$) and less T1/T2 tumors (16.6%, $p < 0.0001$) in patients with HNPCC, compared to other types of CRCs.

Comparison of treatment outcomes in terms of disease-free survival (DFS) and overall survival (OS)

Subtotal or total colectomies, compared with segmental resections such as anterior resections and hemicolectomies, were significantly elevated among patients who were diagnosed with FAP (81.5%) or HNPCC (25.2%), in comparison with patients from sporadic CRC (3.3%), positive family history (3.1%), and HNPCC-like CRC (8.4%) groups ($p < 0.0001$) (Table 1).

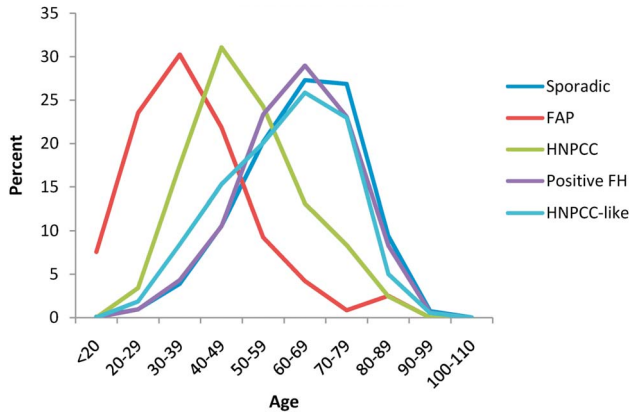

Fig. 1. Distribution of age of diagnosis related to different family history colorectal cancer patients.

We also analyzed treatment outcomes, in terms of disease-free survival (DFS) and overall survival (OS), among patients from different family history groups. As shown in Table 2, significant differences were observed among different family history groups. Four significant factors affect treatment outcomes, including tumor location (rectum or colon), age, sex, and presence of metachronous tumors (Table 2). The multivariate Cox proportional hazard model demonstrates that patients with positive FH or with HNPCC-like CRC have better OS than patients with sporadic CRC (hazard ratios 0.873, $p < 0.0001$ and 0.769, $p = 0.0012$, respectively), upon adjusting for other risk factors (Table 2).

Upon excluding patients with stage IV CRCs, a total 11532 patients were included in our DFS analysis. Table 2 shows the differences of DFS observed for patients with different family histories. The multivariate model shown in Table 2 reveals that patients with positive FH have significantly better DFS than those with sporadic CRC (DFS: HR:0.872, $p = 0.0016$). Patients with other colon cancers and female patients showed significantly better DFS and OS than patients diagnosed with metachronous CRC.

Risk of metachronous colorectal cancer occurrence

Metachronous colorectal cancer is defined as the occurrence of a second colorectal cancer, diagnosed

Table 2. Treatment outcome comparisons related to different clinical subgroups

Clinical subgroups	Overall survival		Disease free survival	
	p value	Adjusted hazard ratio (95% C.I.)	*p* value	Adjusted hazard ratio (95% C.I.)
FAP vs. sporadic	0.6184	0.914 (0.643-1.301)	0.3970	0.815 (0.507-1.309)
HNPCC vs. sporadic	0.1778	0.830 (0.633-1.088)	0.5197	0.891 (0.627-1.266)
Positive FH vs. sporadic	< 0.0001	0.873 (0.825-0.924)	0.0016	0.872 (0.800-0.949)
HNPCC-like vs. sporadic	0.0012	0.769 (0.655-0.902)	0.2278	0.858 (0.668-1.101)
Synchronous vs. solitary	0.2998	1.077 (0.936-1.239)	0.3418	0.892 (0.706-1.128)
Metachronous vs. solitary	0.0054	0.780 (0.655-0.929)	< 0.0001	0.495 (0.363-0.676)
Rectum vs. colon	< 0.0001	1.186 (1.121-1.254)	< 0.0001	1.535 (1.412-1.668)
Age, per 10 increase	< 0.0001	1.325 (1.297-1.353)	0.0202	1.036 (1.006-1.067)
Sex, male vs. female	< 0.0001	1.166 (1.108-1.228)	< 0.0001	1.166 (1.079-1.260)

during a follow up at least one year after tumor treatment recorded in our colorectal cancer registry. During an average post-operative follow-up period of 4.8 years (range 2-15 years), 192 patients with metachronous CRCs were identified.

The frequencies of metachronous colorectal cancer for patients with either sporadic, FAP, HNPCC, positive FH, or HNPCC-like CRC are 2.36, 1.44, 7.55, 2.94 and 5.71 per 1000 person-years, respectively (Table 3). Occurrences of metachronous CRCs were significantly fewer in female patients than in males (p = 0.0005). Significantly different cumulative incidences were also observed (Fig. 2), and patients with HNPCC displayed the greatest risk (10.3%, 54.1%, 73.5% for 10, 20, 30 years, respectively), followed by patients with HNPCC-like CRC (5.2%, 47.2%, 51.8% for 10, 20, 30 years, respectively), and the lowest risk was observed for patients with sporadic CRC (2.3%, 31.1%, 42.2% for 10, 20, 30 years, respectively).

Risk differences among patients in different family history groups were estimated using multivariate Cox proportional hazard models, and we adjusted for sex, age, and confounding factors. Significantly different metachronous CRC risk ratios were observed among patients from different family history groups. As shown in Table 4, patients with either HNPCC or HNPCC-like CRC displayed 4.185-fold (p < 0.0001) or 2.49-fold (p = 0.003) higher risk ratios, respectively, than patients with sporadic CRC, while we did not observe significant differences between patients in sporadic CRC and positive groups.

Table 3. Rate of metachronous colorectal cancer among different family groups

Characteristics	Event no.	Person year	Event/ per 1,000 person-year	p value
Family history group				0.0093
Sporadic	100	42267.45	2.36	
FAP	1	689.88	1.44	
HNPCC	9	1190.77	7.55	
Positive FH	66	22422.18	2.94	
HNPCC-like	12	2098.51	5.71	
Unclassified	4	1516.75	2.63	
Sex				0.0005
Female	65	32447.90	2.00	
Male	127	37737.66	3.36	

By univariate Poisson regression.

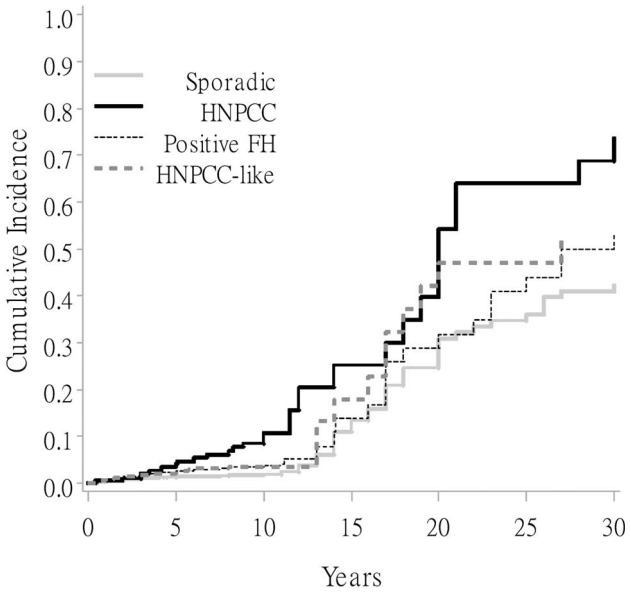

Fig. 2. Cumulative incidences of colorectal cancer patients with different family history.

Table 4. Comparisons of risk of metachronous colorectal cancer

Type of colorectal cancer comparisons	p value	Adjusted hazard ratio (95% C.I.)
FAP vs. sporadic	0.9666	1.044 (0.139-7.861)
HNPCC vs. sporadic	< 0.0001	4.185 (2.049-8.548)
Positive FH vs. sporadic	0.1395	1.265 (0.926-1.728)
HNPCC-like vs. sporadic	0.0030	2.490 (1.362-4.554)
Unclassified vs. sporadic	0.8711	0.920 (0.338-2.506)
Age, per 10 increase	< 0.0001	1.278 (1.132-1.442)
Sex, 1 vs. 0	0.0006	1.692 (1.251-2.287)

By multivariate Cox proportional hazard model*.

* Cause-specific model: considering completing risk of death (death without second cancer was treated as censored case).

Discussion

To our knowledge, this is the largest study in a single institute to date that has investigated clinic-pathological characteristics related to different family history groups of patients with colorectal cancers. In addition to previous reported findings, we have achieved new findings, which we reported in this study.

Heredity has been an uncontrolled risk factor that affects both the incidence of CRC and age of diagnosis. While we have known that age of diagnosis significantly varies among patients with different family histories, the large sample size of this analysis further demonstrates that the mean age at diagnosis (Fig. 1 and Table 1) for patients with HNPCC are 12 or 13 years younger than patients with either positive family or sporadic CRC, respectively (mean age of 50.5 years vs. 62.5 or 63.5 years, respectively). The age of diagnosis for patients from different family history groups are shown in Fig. 1. Sporadic colorectal cancer diagnoses increase progressively after the age of 40 years, rise sharply after age 50,[25] and drop after the age of 80. In contrast, incidences of patients with HNPCC increase from age 30 and drop after age 70. In this study, more than 95% of colorectal cancer cases occur in individuals aged 40 or older for sporadic CRC or positive FH cases.[25] The incidence rate is more than 50 times higher in persons aged 60 to 79 years than in those younger than 40 years.[25,26] Patients with HNPCC-like CRC, who lack of only one item of the Amsterdam II criteria, are an average of 9.1 years older than patients with HNPCC who were investigated this study. While we do not know the mutation status of patients with HNPCC-like CRC, we suspected that mutations in MSH6 occur at a later age of onset than MLH1 and MSH2 mutations.[27]

Pertaining to clinicopathological variables related to patients with CRC with different family histories, it has been documented previously that HNPCC patients often display characteristic phenotypes such as poorly differentiated features, mucinous features, and signet-ring cells (SEER cancer statistics review, 1975-2005. Bethesda, MD: 2008.).[25,28] In addition, microsatellite instable colorectal cancer is associated with localization to the right side of the colon and improved overall survival.[29-31] In this large retrospective study, the rates of mucinous (15%), poorly differentiated (17%), and right colon (49.5%) carcinomas were similar to previous reports and associated with incidences of HNPCC.

Whether patients with CRC with family histories of the disease have improved overall survival compared to cases of sporadic CRC remains controversial. Some studies have suggested that family history of CRC is associated with better survival after CRC diagnosis. For example, the survival of patients with familial CRC was significantly better than those with sporadic CRC (HR 0.89, 95%CI: 0.81-0.98, $p = 0.02$).[17] ML Slattery et al. discovered that family history of colon cancer has a favorable impact on patient survival after diagnosis with colon cancer.[32] Furthermore, patients with CRC that have a family history of the disease have improved overall survival, compared to patients with sporadic CRC, and the improved survival was found to be independent of other clinically relevant factors.[33] However, AI Phipps et al. observed that family history of CRC is not associated with patient survival, regardless of microsatellite instability (MSI) status,[34] in terms of overall survival [hazard ratio (HR), 0.92; 95% CI, 0.79-1.08] or disease-specific survival (HR, 1.03; 95% CI, 0.85-1.24) for all cases combined, after adjustment for MSI status or tumor site. Such inconsistencies may result from various factors, such as tumor location (colon vs. rectum), sex, age, and specific family history subgroup.

Some studies have included clinically defined cases of HNPCC only, while have exclusively included cases with a positive family history of CRC. In this study, we combined factors of sex, age, and tumor location and grouped family history into five categories. We observed no evidence that cases of HNPCC are associated with better colorectal cancer survival, in agreement with AI Phipps et al. However, patients with HNPCC-like CRC have a better OS (RFS: HR: 0.872, 95% CI 0.800-0.949, $p = 0.0016$), and patients with positive FH have significantly better RFS and OS, than patients with sporadic CRC, as shown in Table 2 and Figs. 1 and 2 (hazard ratios 0.873 $p < 0.0001$ and 0.769 $p = 0.0012$, respectively). These findings are in agreement with others who have reported better sur-

vival for patients with a family history of CRC.[17,33] However, the specific mechanisms that underlie family history and may have a prognostic impact remain unclear and merit further study. It is possible that patients display different responses to chemotherapy, at the levels of intracellular signaling, apoptosis, cell cycle checkpoints, loss of mismatch repair-dependent toxicity, and induction of an antitumor immune response of oxaliplatin.[35,36]

The high reported risk of metachronous colon cancer in patients with HNPCC has led some authors to recommend total colectomy as the preferred operation for primary colon cancers, and we reflect this concept in our clinical practice. We found that 25.2% of patients with HNPCC undergo total or subtotal colectomies, compared with 3.1 to 8.4% for other types of patients with a family history of CRC (Table 1). Previous reports have shown that segmental resection reduces metachronous CRC risk by 31% (95% CI 12-46%; $p = 0.002$) for every 10 cm of bowel removed.[37] Therefore, the risk of metachronous CRC for patients with carcinomas who underwent a segmental resection was evident, despite that the majority underwent regular surveillance, because in our hospital post-operative annular colonoscopies take place every 3 years and later at intervals of 3-5 years. In this study, patient follow-up was performed using this guideline, and we found that patients with HNPCC displayed a 4.185 fold higher ($p < 0.0001$) frequency of second CRC incidence than patients with sporadic and HNPCC-like CRC (2.49 fold higher, $p = 0.003$). We also discovered that the incidences of patients with sporadic CRC, HNPCC, and HNPCC-like CRC are 2.36, 7.55, and 5.71 per 1000 person-years, respectively. However, the true incidence of metachronous CRC requires further clarification because one fourth of patients with HNPCC underwent extensive colectomy, while less than 5 percent of patients with sporadic CRC underwent extensive colectomies. Furthermore, patients in this study are not always undergoing "first time" operations, and specifically, some patients underwent colectomies due to metachronous colorectal cancer. Such cases are either missing or not clearly defined in previous studies. In our study, 1.8% to 9.7% cases underwent colectomies due to metachronous CRC (Table 1).

While we performed a large retrospective study, limitations pertaining to patient recall bias, with respect to family history, may affect our results. Some patients with sporadic CRC may also have relatives who developed CRC at a later time and were not recorded in our registry. Further studies that include molecular biomarkers and prospective studies are still needed.

Conclusions

Different clinic-pathologic characteristics exist among five distinct family history categories of patients with CRC (sporadic, FAP, HNPCC, other positive family history, and HNPCC-like) in terms of age of diagnosis, mucinous histology, tumor differentiation, tumor location, risk of metachronous CRC, and treatment outcomes. Specifically, patients with HNPCC are less likely to display lymph node or distant metastases than patients in other family history groups.

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Conflict of Interest Statement

All the authors do not accept any financial or other interest that is relevant to the subject matter under consideration in this article.

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原　著

比較不同家族史對於結直腸癌病人之臨床病理特徵，異時性結直腸癌的風險及術後存活之影響

江支銘 [1,2]　蔣昇甫 [1,2]　謝寶秀 [1,2]　葉建裕 [1,2]　游正府 [1,2]
洪欣園 [1,2]　蔡文司 [1,2]　陳進勛 [1,2]　游耀東 [1,2]　唐瑞平 [1,2]

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目的　本研究探討家族史對於結直腸癌 (CRC) 患者是否影響臨床病理特徵，治療結果和術後追蹤。

方法　包括 14082 例的 CRC 病人。利用多變量 Cox 比例風險模型，比較不同家族史的病人，對於臨床病理特徵，治療結果　和異時性 CRC 的風險。

結果　在五個不同家族史患者組中，遺傳性非息肉性結腸直腸癌 (HNPCC) 患者，除了年齡較小；較多位於右結腸 (49.5%)；粘液型腺癌 (15.0%)；及分化較差之外；直腸癌 (vs. 結腸) 頻率較低 (27.6%, $p < 0.0001$)；多發性腫瘤較高 (27.9%, $p < 0.0001$)；較少淋巴結轉移 (61.1%, $p < 0.0001$)；而遠處轉移率較低 (11.2%)。有家族史病人 OS 明顯高於偶發性 CRC (風險比 0.873；$p < 0.0001$)，且 RFS 明顯優於偶發性 CRC (HR: 0.872, $p = 0.0016$)。偶發性 CRC，FAP，HNPCC，陽性 FH 及 HNPCC-like 五組病人中，異時性 CRC 發生率分別為 2.36、1.44、7.55、2.94 和 5.71/1000 人 ($p = 0.0005$)。HNPCC 及 HNPCC-like 病人之異時性 CRC 的風險分別顯著高出偶發性 CRC4.185 倍 ($p < 0.0001$)，及 2.49 倍 ($p = 0.003$)。

結論　不同家族史的 CRC 患者存在不同的臨床病理特徵，異時性 CRC 的風險和治療結果。

關鍵詞　遺傳性非息肉性結腸直腸癌、偶發性結直腸癌、家族史、異時性結直腸癌。