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ORIGINAL ARTICLE – COLORECTAL CANCER

Impact of Family History on Prognosis of Patients with Sporadic Colorectal Cancer

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ABSTRACT

Purpose. A family history (FH) of colorectal cancer (CRC) increases the risk for development of CRC, but the impact of FH of CRC on survival from sporadic CRC is unclear. This study investigated the prognostic impact of FH of CRC on the recurrence and survival of patients with sporadic CRC.

Methods. We reviewed the records of patients with sporadic CRC from two tertiary referral hospitals in Korea who underwent surgical resection between May 2007 and September 2013. The clinicopathologic features and oncologic outcomes of those with and without FHs of CRC were compared.

Results. We examined the records of 2960 eligible patients, 163 (5.5%) of whom had first-degree relatives with CRC. Patients with and without FHs of CRC had similar baseline characteristics. Multivariable analysis indicated that a FH of CRC was not significantly associated with disease-free survival but was significantly associated with better overall survival (OS) [adjusted hazard ratio = 0.539, 95% confidence interval (CI) 0.330–0.881, $P = 0.014$]. Subgroup analysis indicated that females and rectal cancer patients with FHs of CRC had significantly better prognoses. Microsatellite status did not affect the improved survival rate associated with FH.

Conclusions. This study of patients with sporadic CRC indicated that those who had FHs of CRC had better OS but similar cancer recurrence as those who had no FH of CRC. The effect of FH of CRC on OS was independent of microsatellite status. Further studies are needed to identify underlying mechanisms and determine the optimal clinical management of CRC according to FH.

Lynch syndrome is the most common hereditary form of colorectal cancer (CRC), and it accounts for approximately 3% of all newly diagnosed cases.[1,2] Lynch syndrome is caused by a germline mutation in one of several genes that have roles in DNA mismatch repair. Patients with Lynch syndrome have better survival rates than those with sporadic CRC.[2] In addition, CRC with microsatellite instability (MSI), in which there is a change in length of tandemly repeated DNA sequences caused by loss of DNA mismatch repair activity, also is associated with better prognosis than CRC without MSI.[3,4] However, the prognosis of CRC patients with family histories (FHs) of CRC who do not have the well-defined germline mutations remains uncertain. Relative to patients with no FH of CRC, previous studies reported that a FH of CRC was associated with better outcome, had no effect on outcome, and was associated with poorer prognosis.[5–13] One reason for these discrepant findings may be that these studies used different inclusion criteria regarding sex, tumor location, and

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stage.[5–13] A FH of CRC is easy to determine from self-reported history, and it is clearly important to better understand the relationship of FH of CRC with survival. Thus, we investigated the association between FH of CRC and recurrence and survival in patients diagnosed with sporadic CRC using a large, prospective cohort.

METHODS

Study Population

A prospective database was reviewed, and patients diagnosed with sporadic CRC who provided information about FH of CRC were included. A patient with sporadic CRC was defined as one who may have had a FH of CRC but had no well-defined germline defect (Lynch Syndrome or familial adenomatous polyposis [FAP]). All patients underwent surgery between May 2007 and September 2013 at one of two tertiary referral hospitals (Seoul National University Bundang Hospital and Chonnam National University Hwasun Hospital). Patients with recurrent CRC, FAP, or Lynch syndrome with germline mutation results or hereditary nonpolyposis colorectal cancer (HNPCC) diagnosed by Amsterdam criteria were excluded. The study protocol was approved by the institutional review board of each institution.

Perioperative Management

Demographic and clinical data were obtained by retrospective review of the prospective database. The preoperative clinical evaluation consisted of physical examination, colonoscopy, abdominopelvic and chest computed tomography (CT), endorectal ultrasonography (US), or pelvic magnetic resonance imaging (MRI) for rectal cancer and laboratory test results. The basic surgery procedures and neoadjuvant/adjuvant therapies were similar at the two institutions. Neoadjuvant chemoradiation (45.0–50.4 Gy plus 5-fluorouracil/leucovorin or capecitabine) was administered to patients with clinical T3-4 or N1-2 mid-to-low rectal cancers, followed by curative surgery after 6–8 weeks. Most patients underwent standardized radical surgeries using conventional surgical oncologic principles.[14,15] Postoperative adjuvant treatment was determined by the attending physician based on the pathologic stage and the general condition and with the agreement of the patient. For patients with stage II CRC and a high risk for systemic recurrence or stage III CRC, 5-fluorouracil-based postoperative adjuvant treatment was recommended. For patients with metastatic CRC, cetuximab or bevacizumab was considered. All cases were restaged retrospectively according to the 7th Edition of the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system.[16]

Family History Assessment

A detailed FH was taken by well-trained research assistants, attending residents, or nurses at the initial outpatient clinic and/or at the time of hospital admission. According to the NCCN guideline, we assessed comprehensive FH, including current age and age at diagnosis of cancer, the age and cause of death, and the type of cancer of every relative in at least three generations.[17] The interviewer obtained this information by using the structured questionnaire, and every interview took approximately 20–30 min or more. Based on this information, high-risk patients who need further genetic studies are screened. In the present study, a FH of CRC was defined as having at least one first-degree relative (FDR) with CRC.

Microsatellite Instability Analysis

MSI testing was conducted on specimens after surgery. For each patients, DNA was extracted from paraffin-embedded tumor and surrounding normal tissues. To determine microsatellite status, five microsatellite markers (BAT-25, BAT-26, D2S123, D5S346, D17S250) were utilized. After polymerase chain reaction analyses, tumors with two or more of the five microsatellite markers exhibiting shifted alleles were classified as MSI-high (MSI-H), whereas tumors with only one marker displaying a shifted allele were classified as MSI-low (MSI-L). The others were classified as microsatellite stable. For MSI-H, patients who were highly suspicious of Lynch syndrome, for example, in young patients or patients with a FH who did not meet Amsterdam criteria, we selectively conducted germline mutation tests, and excluded those with Lynch syndrome in the present study.

Follow-Up

Patients were monitored at regular intervals according to the National Comprehensive Cancer Network guidelines.[18,19] Disease-free survival (DFS) was defined as the date of surgery to the date of recurrence or death, with censoring of patients lost to follow-up. Overall survival (OS) was defined as the date of surgery to the date of death from any cause, with censoring as above. Recurrence was determined by clinical and radiological examinations or histological confirmation.

Statistical Analyses

Categorical variables were compared using the χ^2 test or Fisher's exact test, and continuous variables were compared using Student's *t* test. Survival rates were estimated and compared using the Kaplan–Meier method and the log-rank test. Cox regression analysis was utilized for the multivariate survival analysis. The assumption of proportional hazards was verified by examination of log cumulative hazard plots, which were parallel. We utilized multiple imputation to account for missing data, under the assumption of missing at random.[20] All clinicopathologic variables in Table 1 were included in the imputation procedure, and we performed five iterations of the dataset with the missing values replaced by imputed values. Overall estimated associations averaging different estimated associations in each of the imputed datasets were obtained. All results were considered clinically significant for a P value <0.05. Statistical analyses used SPSS software version 22.0 (IBM Inc., Armonk, NY).

RESULTS

We examined the records of 2960 patients with sporadic CRC (Table 1). A total of 163 patients (5.5%) had at least 1 FDR with CRC, and 10 (0.3%) had 2 family members with CRC. Only 12 patients (0.4%) had FDRs with diagnoses of CRC when younger than age 50 years. The potential prognostic clinicopathologic factors, including TNM stage, were similar in those with and without FHs of CRC. However, patients with FHs of CRC had a higher incidence of MSI-H than those without FHs of CRC (17.5% vs. 5.9%, $P < 0.001$).

The median follow-up time was 41 (range: 1–92) months. The 3-year DFS was 85.4%, and the 5-year OS was 78.6%. Kaplan–Meier survival analysis showed that patients with FHs of CRC had better OS than those without FHs of CRC (5-year OS: 85.9% vs. 78.2%, $P = 0.024$; Fig. 1a). Multivariable Cox regression analysis, with exclusion of cases that had missing values, indicated that a FH of CRC was an independent prognostic factor for OS (adjusted hazard ratio [aHR] = 0.444, 95% confidence interval [CI] 0.255–0.775, $P = 0.004$). Similarly, after multiple imputation, a FH of CRC also was an independent prognostic factor for OS (aHR = 0.539, 95% CI 0.330–0.881, $P = 0.014$; Table 2).

We also analyzed DFS as a secondary endpoint to determine the influence of a FH of CRC on cancer recurrence. Kaplan–Meier survival analysis showed that a FH of CRC was not associated with DFS (3-year DFS: 83.4% vs. 85.5%, $P = 0.753$; Fig. 1b). Multivariable Cox regression analyses also showed no significant association between FH of CRC and DFS in all complete cases (aHR = 1.135, 95% CI 0.729–1.768, $P = 0.575$) and after multiple imputation (aHR = 1.146, 95% CI 0.738–1.781, $P = 0.543$; Table 2; Supplemental 1).

We performed survival analysis to determine the effect of the number and age of family members with CRC (Fig. 2a). The results indicate a tendency for longer OS in patients who had more family members with CRC (2 family members: 100.0%; 1 family member: 85.0%; no family member: 78.2%; $P = 0.054$). The age of the FDR with CRC also did not affect the OS of the patients with sporadic CRC (Fig. 2b; Supplemental 2).

We performed subgroup analysis to identify the effect of different clinicopathologic variables on the prognostic impact of a FH of CRC in patients with sporadic CRC (Table 3). The results indicate that a FH of CRC improved the prognosis of females (aHR = 0.246, 95% CI 0.088–0.683, $P = 0.007$) rather than males and of patients with rectal cancer (aHR = 0.434, 95% CI 0.201–0.935, $P = 0.033$) rather than colon cancer. Microsatellite status had no effect on the prognostic impact of FH of CRC (Table 3). Because of the small number of MSI-L patients ($n = 110$) and MSI-H patients ($n = 70$), multivariable survival analysis was not possible in these subgroups.

DISCUSSION

Several previous studies reported that a FH of CRC was associated with an increased incidence of CRC.[21–25] However, it is uncertain whether a FH of CRC affects the prognosis of patients with sporadic CRC. Several studies reported better survival in patients with FHs of CRC; however, most of these previous studies used certain exclusion criteria.[5–11] In particular, some of them only examined patients with stage III CRC.[5,9] Others reported results from subgroup analyses according to tumor location.[6,9,11] One study examined the effect of the number of affected FDRs.[10] Several of these studies reported no significant survival differences when all CRC patients were included.[9–11] In contrast, other studies reported poor cancer-specific survival and OS in CRC patients with FHs of CRC.[12,13] In other words, there are discrepant results regarding the prognostic impact of a FH of CRC in patients with sporadic CRC (Table 4). The results of the present, large, multicenter study, which indicate improved OS in patients with FHs of CRC, are important because of its use of broad inclusion criteria—all CRC patients except those with FAP or HNPCC.

The reason for the better survival in patients with FHs of CRC is uncertain. It is possible that individuals with FHs of CRC tend to have more frequent CRC surveillance and that this improved their survival. In other words, more regular screening may cause lead time and length time bias, and

TABLE 1 Baseline characteristics of patients who did and did not have family histories of colorectal cancer

	Without family history (n = 2797)	With family history (n = 163)	P
Sex			
Male	1744 (62.4%)	99 (60.7%)	0.679
Female	1053 (37.6%)	64 (39.3%)	
Age (yr), mean ± SD	64.2 ± 10.9	62.0 ± 12.5	0.013
BMI (kg/m^2), mean ± SD	23.5 ± 3.6	23.5 ± 2.9	0.898
ASA			
1, 2	2626 (94.1%)	149 (92.5%)	0.434
3, 4	166 (5.9%)	12 (7.5%)	
Location			
Colon	1640 (58.6%)	98 (60.1%)	0.708
Rectum	1157 (41.4%)	65 (39.9%)	
Operative time (min), mean ± SD	173.7 ± 77.8	174.2 ± 94.5	0.935
EBL (mL), mean ± SD	183.8 ± 231.5	158.9 ± 194.0	0.193
T stage			
0, 1, 2	843 (30.1%)	53 (32.5%)	0.521
3, 4	1954 (69.9%)	110 (67.5%)	
N stage			
0	1660 (59.3%)	104 (63.8%)	0.260
1, 2	1137 (40.7%)	59 (36.2%)	
M stage			
0	2520 (90.1%)	147 (90.2%)	0.971
1	277 (9.9%)	16 (9.8%)	
TNM stage			
0	42 (1.5%)	5 (3.1%)	0.435
I	699 (25.0%)	41 (25.2%)	
II	862 (30.8%)	55 (33.7%)	
III	917 (32.8%)	46 (28.2%)	
IV	277 (9.9%)	16 (9.8%)	
Lymphovascular invasion			
Negative	2243 (82.2%)	131 (82.9%)	0.811
Positive	487 (17.8%)	27 (17.1%)	
Perineural invasion			
Negative	1883 (68.4%)	104 (65.4%)	0.435
Positive	871 (31.6%)	55 (34.6%)	
Differentiation			
w/d, m/d	2471 (92.0%)	142 (88.8%)	0.151
p/d, mucinous	216 (8.0%)	18 (11.3%)	
Tumor size (cm), mean ± SD	4.2 ± 2.2	4.4 ± 2.8	0.227
Preoperative CEA (ng/mL)			
< 5	1875 (71.6%)	112 (72.3%)	0.852
≥ 5	745 (28.4%)	43 (27.7%)	
Adjuvant chemotherapy			
Performed	1736 (62.1%)	94 (57.7%)	0.261
Not performed	1061 (37.9%)	69 (42.3%)	
Microsatellite status			
MSS	1016 (85.7%)	56 (70.0%)	<0.001

TABLE 1 continued

	Without family history (n = 2797)	With family history (n = 163)	P
MSI-L	100 (8.4%)	10 (12.5%)	
MSI-H	70 (5.9%)	14 (17.5%)	

SD standard deviation; *BMI* body mass index; *ASA* American Society of Anesthesiologists; *EBL* estimated blood loss; *w/d* well differentiated; *m/d* moderately differentiated; *p/d* poorly differentiated; *CEA* carcinoembryonic antigen; *MSS* microsatellite stable; *MSI-L* microsatellite instability-low; *MSI-H* microsatellite instability-high

thereby a "biased" better survival.[26] However, we found no differences in the clinicopathologic characteristics, including tumor stage, of groups with and without FHs of CRC, so early detection of tumors or favorable tumor characteristics do not explain our results. Furthermore, a FH of CRC remained a prognostic factor after adjusting for confounders by multivariable survival analysis. Therefore, increased screening does not explain the improved OS of patients with FHs of CRC.

Another possible reason for the better OS in those with FHs of CRC may be that these subjects modified their lifestyles after seeing a family member develop cancer. Previous studies have reported favorable lifestyle modifications, such as increased physical activity, quitting smoking, and positive dietary changes, in family members of cancer patients.[27,28] Physical activity and smoking are associated with recurrence and OS in CRC patients.[29–31] Although we could not assess the association between smoking, alcohol consumption, or physical activity with a FH of CRC due to the retrospective design of this study, these could partly explain the better survival of patients with FHs of CRC.

Genetic differences (such as MSI status) of those with and without FHs of CRC could possibly explain the differences in OS. Previous studies reported that a FH of CRC was associated with MSI-H status and can possibly improve the prognosis of patients with FHs of CRC.[5,11,32,33] However, some previous studies demonstrated that MSI status had little effect on survival according to FH of CRC, although a FH of CRC was associated with MSI-H status.[5,11] Similarly, we found that FH of CRC was associated with MSI-H status (Table 1). However, we also found that a FH of CRC was an independent prognostic factor after adjusting for the confounding effect of MSI status by multivariable analysis (Table 2). In addition, our subgroup analysis indicated that MSI status had little effect on the improved OS associated with a FH of CRC (Table 3). We conclude that the favorable prognostic impact of a FH of CRC was independent of MSI status. Nevertheless, we cannot exclude the possibility that the prognostic impact of a FH of CRC arises from other specific genetic or environmental factors.

It is interesting that the prognostic impact of FH of CRC was significant for females but not males and for those with rectal tumors but not colon tumors (Table 3). Some previous studies of female CRC patients also reported that a FH of CRC affected survival.[10,13] In contrast, other studies of CRC reported reduced cancer recurrence or improved OS in males but not females.[5,6] This result may be attributed to gender-specific differences in competing risks.[6] For example, behavioral changes in individuals with FHs of CRC may be different in males and females. In addition, the difference of technical difficulty, particularly in rectal cancer surgery, between male and female patients may be another possible reason. However, a definitive explanation for the difference between males and females is not possible at this time because of the conflicting results of previous studies. Regarding tumor location, some previous studies reported improved survival was associated with a FH of CRC only in colon cancer patients.[6,7,9] Other studies (in agreement with the present study) reported improved survival only in rectal cancer patients.[11] Actually, genetic and environmental factors are different according to tumor location. More specifically, right-sided colon cancers have a higher frequency of MSI and are more strongly associated with fatty diets and increased bile acid exposure.[6] However, there are no consistent results regarding the association between tumor location and prognostic impact of a FH of CRC.

A FH of CRC can be easily ascertained, and therefore, it can be a cost-effective clinical tool to predict survival if prognosis for those with FHs of CRC is different.[10] The present study confirmed that patients with a FH of CRC may have better survival compared with those without a FH. Hence, the importance of FH assessment is not only to distinguish hereditary CRC but also to provide additional information about the prognosis of the CRC patients.[7] Actually, the specific mechanism of the relationship between a FH and survival of CRC is uncertain because of the different results and settings of the previous studies (Table 4). We think that the results of the present study provide important clue to encourage future studies about underlying mechanisms of better survival in those with a FH of CRC, which may contribute to individualized tailored treatment in the era of precision medicine.

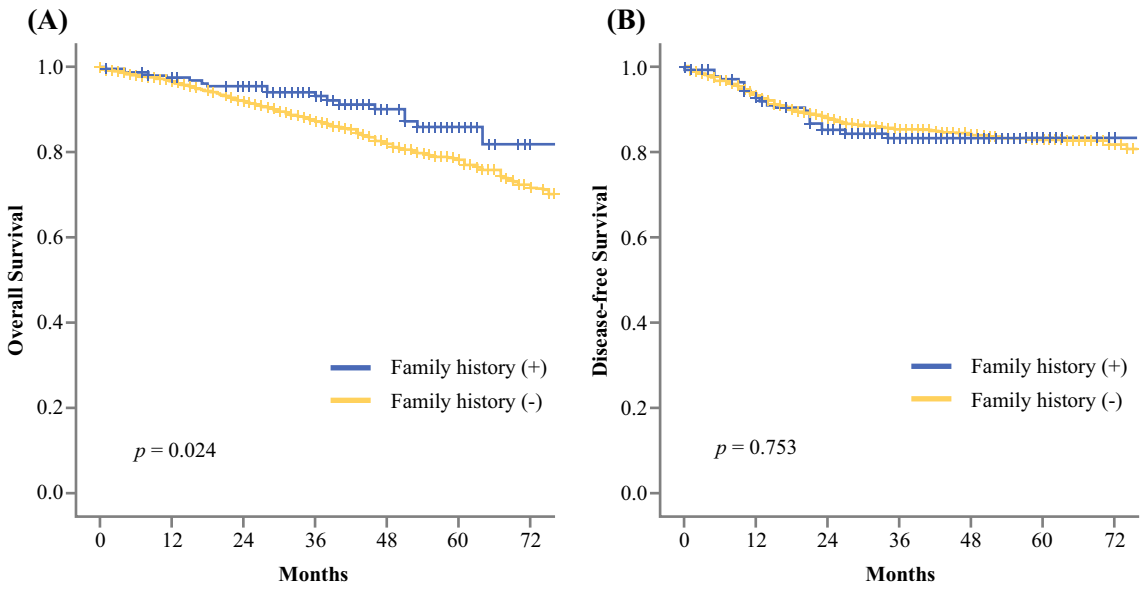

FIG. 1 Kaplan–Meier curves for overall survival (**a**) and disease-free survival (**b**) in patients who did and did not have family histories of colorectal cancer

TABLE 2 Multivariable analysis of factors associated with disease-free survival and overall survival after multiple imputation

Variable	Disease-free survival		Overall survival	
	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Male sex	1.206 (0.968–1.503)	0.096	1.181 (0.976–1.428)	0.087
Age ≥ 70 years	1.120 (0.898–1.398)	0.315	1.942 (1.607–2.347)	<0.001
BMI ≥ 25 kg/m^2	0.911 (0.720–1.154)	0.442	0.870 (0.700–1.081)	0.209
ASA ≥ 3	1.292 (0.864–1.930)	0.212	1.493 (1.118–1.995)	0.007
Rectal cancer	2.022 (1.638–2.497)	<0.001	1.481 (1.234–1.778)	<0.001
T stage ≥ 3	2.442 (1.658–3.597)	<0.001	1.650 (1.178–2.310)	0.004
N stage ≥ 1	1.945 (1.532–2.469)	<0.001	1.343 (1.077–1.677)	0.009
Distant metastasis	–	–	2.777 (2.206–3.495)	<0.001
Lymphovascular invasion	1.030 (0.797–1.332)	0.820	1.170 (0.934–1.466)	0.172
Perineural invasion	1.796 (1.440–2.241)	<0.001	1.840 (1.478–2.291)	<0.001
High-grade differentiation	1.347 (0.940–1.931)	0.105	1.356 (1.017–1.807)	0.038
Tumor size ≥ 5 cm	0.837 (0.670–1.045)	0.116	1.110 (0.914–1.349)	0.293
Preoperative CEA ≥ 5 ng/mL	1.518 (1.223–1.885)	<0.001	1.590 (1.304–1.939)	<0.001
Adjuvant chemotherapy	1.220 (0.902–1.650)	0.196	0.729 (0.581–0.915)	0.006
Microsatellite status (vs. MSS)				
MSI-L	1.117 (0.557–2.241)	0.730	1.159 (0.799–1.683)	0.430
MSI-H	0.721 (0.334–1.557)	0.384	0.803 (0.424–1.521)	0.486
Family history	1.146 (0.738–1.781)	0.543	0.539 (0.330–0.881)	0.014

HR hazard ratio; *CI* confidence interval; *BMI* body mass index; *ASA* American Society of Anesthesiologists; *CEA* carcinoembryonic antigen; *MSS* microsatellite stable; *MSI-L* microsatellite instability-low; *MSI-H* microsatellite instability-high

The present study has several limitations. First and foremost, there were many missing values, and particularly, only 42.8% of patients (1266/2960) had data on MSI. Previous studies seemed to have similar limitations. In a large-scale previous study, the results of MSI tests were available only in 68.0% of patients, and the main result was analyzed without MSI and the results of adjusting MSI results were presented in addition.[5] Analyzing only patients with MSI results might be a simple and easy way, but it might result in crucial selection bias, because the

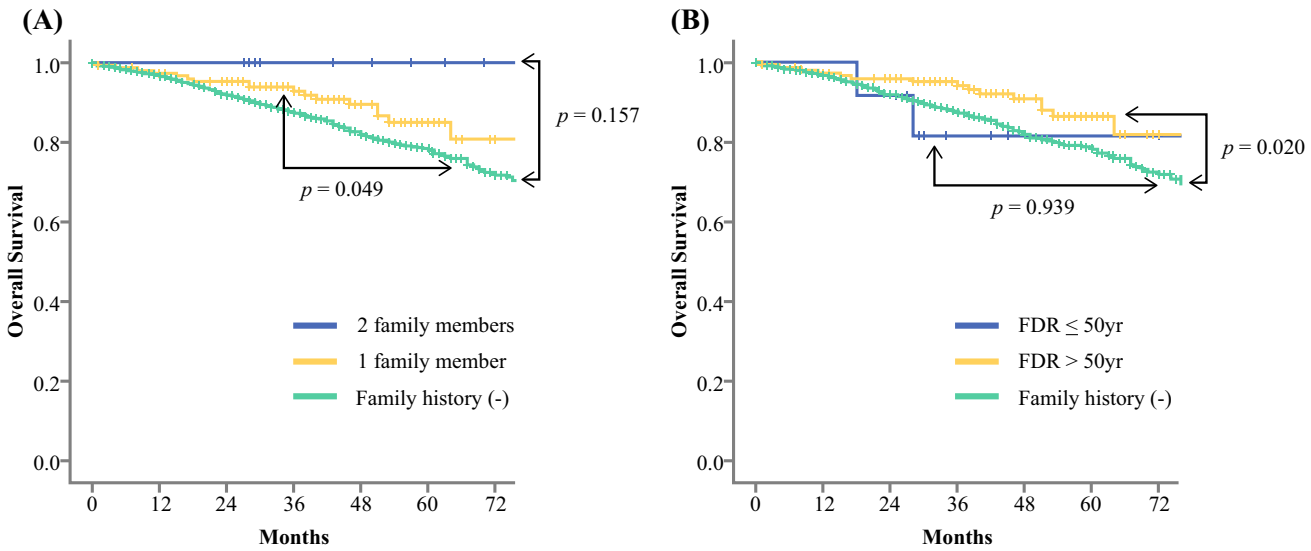

FIG. 2 Kaplan–Meier curves for overall survival according to the number (**a**) and age (**b**) of family members who had colorectal cancer

TABLE 3 Subgroup analysis of overall survival according to family history

Variable	Univariable analysis		Multivariable analysis[b]	
	HR (95% CI)[a]	*P*	Adjusted HR (95% CI)[a]	*P*
Sex				
Male	0.724 (0.416–1.261)	0.254	0.755 (0.427–1.333)	0.333
Female	0.355 (0.132–0.958)	0.041	0.246 (0.088–0.683)	0.007
Age (yr)				
< 70	0.491 (0.243–0.992)	0.048	0.513 (0.251–1.049)	0.067
≥ 70	0.736 (0.378–1.433)	0.367	0.613 (0.309–1.213)	0.160
Tumor location				
Colon	0.699 (0.371–1.316)	0.267	0.674 (0.352–1.293)	0.235
Rectum	0.460 (0.217–0.976)	0.043	0.434 (0.201–0.935)	0.033
Stage				
0, I	0.356 (0.049–2.578)	0.306	0.377 (0.047–3.044)	0.360
II	0.490 (0.180–1.332)	0.162	0.464 (0.167–1.292)	0.142
III	0.865 (0.426–1.756)	0.688	0.739 (0.263–2.076)	0.565
IV	0.461 (0.170–1.245)	0.127	0.412 (0.148–1.149)	0.090
Microsatellite status				
MSS	0.658 (0.352–1.227)	0.185	0.623 (0.341–1.136)	0.122
MSI-L	0.341 (0.005–23.866)	0.591	NA[c]	NA[c]
MSI-H	0.222 (0.005–9.699)	0.419	NA[c]	NA[c]

HR hazard ratio; *CI* confidence interval; *MSS* microsatellite stable; *MSI-L* microsatellite instability-low; *MSI-H* microsatellite instability-high

[a]Comparing patients with family history with those without family history

[b]Included covariables were sex, age, body mass index, American Society of Anesthesiologists score, tumor location, TNM stage, lymphovascular invasion, perineural invasion, differentiation, tumor size, preoperative carcinoembryonic antigen, adjuvant chemotherapy, and microsatellite status

[c]Cannot be assessed because of the small number of patients in the subgroup

proportion of those with MSI results was too low. To compensate for this limitation, we utilized multiple imputation, under the assumption of missing at random. In addition, when we stratified patients by MSI status, there was improved OS in all subgroups (Table 3). This suggests that the missing values did not significantly affect the

TABLE 4 Association between family history (FH) and survival of colorectal cancer (CRC): comparison of the present study with previous studies

References	Country	No. of patients	With FH, *n* (%)	Inclusion criteria	Oncologic outcomes[a]		
					OS	DFS/ CSS	Subgroup
Present study	Korea	2960	163 (5.5%)	All CRC	Better	Similar	Female, rectum: better OS
Bass[13]	USA	1001	163 (16.3%)	Female CRC	Poorer	Poorer	Stage IV, colon: poorer CSS
Chan[5]	USA	1087	195 (17.9%)	Stage III CC	Better	Better	≥ 2 FDR, male, age ≥ 50, right colon: better DFS
Kirchhoff[10]	USA	1391	262 (18.8%)	Female CRC	Similar	–	≥ 2 FDR: better OS
Zell[6]	USA	1154	208 (18.0%)	All CRC	–	–	Colon: better OS
Birgisson[7]	Sweden	318	31 (9.7%)	All CRC	Better	Better	Colon: better OS
Kao[8]	Taiwan	3383	297 (8.8%)	All CRC	Better	Better	–
Lee et al.[9]	Korea	971	63 (6.5%)	Stage III CRC	Similar	Similar	Colon: better OS
Phipps[11]	USA	4284	744 (17.4%)	All CRC	Similar	Similar	Rectum: better OS

FH family history; *OS* overall survival; *DFS* disease-free survival; *CSS* cancer-specific survival; *CRC* colorectal cancer; *CC* colon cancer; *FDR* first-degree relative

[a]Comparison of patients with a FH of CRC with those without a FH

results. Nevertheless, low proportion of patients with MSI results and the statistical correction of these missing values are still major limitations of the present study. Large-scale studies, which will be available from detailed FH and the results of MSI and MMR gene tests, will eliminate the influence of MSI and fully identify the impact of FH on prognosis. Second, we could not obtain data on lifestyle, such as diet, smoking, alcohol intake, and exercise, because of the retrospective design of the study. Third, the possibility of misclassification or underestimation of FH of CRC remained. Actually, the validity of patient-reported FH of cancer was reported to be different according to the type of cancers, and a previous study showed that self-reported FH for FDR was accurate and valuable for CRC risk assessment.[34,35] In addition, we tried our best to minimize the misclassification of FH by meticulous interview. Therefore, we still believe that our pedigree database is trustworthy and FH is reasonable to be used as a prognostic factor in sporadic CRC, despite its risk of underestimation. Lastly, a number of patients were censored during the follow-up period, and this could have affected survival outcomes. Nevertheless, the present study is one of the largest to analyze the prognostic significance of a FH of CRC and to report improved OS of patients with sporadic CRC who had FHs of CRC.

CONCLUSIONS

This study of patients with sporadic CRC indicates that a FH of CRC in a FDR was associated with better OS but had no effect on DFS. The prognostic impact of FH of CRC was unrelated to MSI status. Further studies are needed to determine whether a FH of CRC can be used to better guide the clinical management of patients with sporadic CRC and to identify the specific genetic or environmental factors that are responsible for the differences in prognosis.

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