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Association of family history and survival in patients with colorectal cancer: a pooled analysis of eight epidemiologic studies

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Abstract

A family history of colorectal cancer (CRC) in first-degree relatives (FDRs) increases the risk of CRC. However, the influence of family history on survival among CRC patients remains unclear. We conducted a pooled analysis of survival in 5010 incident CRC cases. Cox proportional hazards models were used to estimate the association of family history with overall survival (OS) and CRC-specific survival (CSS). We also assessed the impact of the number of affected FDRs and age at CRC diagnosis in the affected FDRs on survival. Among CRC cases, 819 (16%) patients reported a family history of CRC. There were 1580 total deaths over a median follow-up of 4.6 years, of which 1046 (66%) deaths were due to CRC. Having a family history of CRC was not associated with OS [hazard ratio (HR), 1.03; 95% confidence interval (CI), 0.89–1.19] or CSS (HR, 1.13; 95% CI, 0.95–1.36)]. There were no associations between the number of affected relatives or age at CRC diagnosis of the affected relative with survival (all $P_{trend} > 0.05$). However, a family history of CRC did confer worse CSS in patients diagnosed with distal colon cancer (HR, 1.45, 95% CI, 1.03–2.04). A family history of CRC was generally not associated with survival after CRC diagnosis. However, having a family history of CRC was associated with worse CRC prognosis in individuals with distal colon cancer, suggesting a possible genetic predisposition with distinct pathogenic mechanism that may lead to worse survival in this group.

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Introduction

Colorectal cancer (CRC) is the third most common cancer diagnosed in both men and women in the United States. CRC is the second leading cause of cancer-related deaths in men and the third leading cause in women in the United States [1]. It is characterized by high heritability with approximately 10–15% of CRC patients having an affected first-degree relative (FDR), defined as the presence of CRC in a parent, sibling, or child [2–4]. Individuals with a family history of CRC in FDRs have a twofold to threefold increased risk of developing CRC [2, 5, 6]. This risk increases with a greater number of affected FDRs, the closer the degree of relation and younger age at diagnosis [2, 5–8].

Highly penetrant hereditary CRC syndromes, including familial adenomatous polyposis (FAP) and Lynch syndrome account for less than 5% of the familial risk [9, 10]. Beyond these rare CRC syndromes that have been associated with favorable prognosis [11, 12], the effect of general family history on CRC survival remains inconsistent [6, 13–25]. Several studies reported no association between having a family history of CRC and survival [16, 18, 24, 25]. Among 4284 CRC cases within the Colon Cancer Family Registry (CCFR), Phipps et al. [18] reported no association between family history and overall survival (OS) [hazard ratio (HR), 0.92; 95% confidence interval (CI), 0.79–1.08] or disease-specific survival (HR, 1.03; 95% CI, 0.85–1.24). Another study conducted among 2236 individuals within the Utah Population Database also revealed no impact of family history on survival [24]. In contrast, other studies reported either favorable or worse prognosis among patients with a family history of CRC [14, 15, 17, 19, 22]. In a large retrospective study of 10,782 CRC cases, Morris et al. [17] demonstrated that patients with a family history of CRC had a 11% lower risk of death compared to those with sporadic CRC (HR, 0.89; 95% CI, 0.81–0.98). Conversely, an analysis of 2090 incident CRC cases within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) showed an increased risk of CRC-specific mortality (HR, 1.31; 95% CI, 1.02–1.69) in individuals with a family history of CRC, compared to those without a family history [19]. The inconsistent evidence may be attributed to varied study designs (population-based cohort studies compared to case–control studies) or baseline differences in characteristics of the study population. Hence, we aim to address these inconsistencies by examining the influence of family history of CRC on OS and CRC-specific survival (CSS) after CRC diagnosis using individual patient data in eight observational epidemiologic studies in the International Survival Analysis in Colorectal Cancer Consortium (ISACC).

Methodology

Study population

We conducted a pooled analysis of 5010 incident CRC cases from six prospective cohort studies (Cancer

Prevention Study-II [CPS-II] [26], Health Professionals Follow-up Study [HPFS] [27], Nurses' Health Study [NHS] [28], Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial [PLCO] [29], VITamins And Lifestyle study [VITAL] [30], Women's Health Initiative [WHI] [31]), and two population-based case–control studies (Post-Menopausal Hormone Study within the Colorectal Cancer Family Registry [PMH-CCFR] [32], Diet, Activity, and Lifestyle Study [DALS] [33]) within ISACC. We included patients with incident CRC who provided information regarding family history of CRC in FDRs. We excluded individuals with a history of cancers other than nonmelanoma skin cancers. This study was approved by the Institutional Review Boards of the respective institutions. Informed consent was obtained from all participants.

Data collection

Demographic and epidemiologic data were obtained either at enrollment into the respective study (PMH-CCFR, CPS-II, DALS, PLCO, VITAL, WHI) or at subsequent follow-up at time of blood draw (HPFS, NHS). Family history of CRC, defined as either a parent, sibling, or child diagnosed with CRC was also collected as part of study questionnaire. All studies collected information on the number of FDRs with CRC. Several studies (PMH-CCFR, CPS-II, DALS, and PLCO) collected information regarding the age at diagnosis of CRC in the affected FDRs. Incident CRC was identified through self-report with medical record review (CPS-II, PLCO), self-report with medical and pathological records review (NHS, HPFS), central physician adjudication (WHI), or linkage to the Surveillance, Epidemiology, and End Results (SEER) cancer registry (PMH-CCFR, CPS-II, DALS, VITAL). Vital status was ascertained in all studies through follow-up and linkages to the National Death Index (NDI), except for VITAL, which was ascertained via linkage with the Washington State death records with censoring when a participant moved out of Washington State.

Statistical analyses

Missing data for smoking status, body mass index (BMI), regular use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), history of screening endoscopy and stage at diagnosis (all less than 6%) was accounted for by mean and mode imputation. Descriptive statistics were generated by standard methods. OS was defined as the time from diagnosis of CRC to the time of death from any cause. CSS was defined as the time from diagnosis of CRC to the time of death due to CRC. Cox proportional hazards (PH) models were used to estimate the HR and 95% CI for the association between family history of CRC with OS and CSS. PH assumption for the main effects was verified using Schoenfeld residuals. We stratified on the variables that violated the PH assumption, which include tumor location, stage at diagnosis (based on AJCC staging), and study site.

We fitted separate models for the associations of family history of CRC in FDR (yes/no), number of FDR with a history of CRC (0/1/≥2), youngest age at diagnosis of affected FDR (<60 years, ≥60 years), with OS and CSS. All analyses were adjusted for age at diagnosis (<60 years, 60–<70 years, ≥70 years), sex, BMI (<25 kg/m^2, 25-<30 kg/m^2, ≥30 kg/m^2), smoking status (never, former, current), regular use of aspirin or other NSAIDs [34], and history of screening endoscopy at baseline (yes/no), and stratified by study site. Additional analyses were adjusted for the covariates above, and stratified by stage at diagnosis (I, II/III, IV), and tumor location (proximal colon, distal colon, rectum, other), and study site. We performed prespecified subgroup analyses by age at diagnosis (<60 years, ≥60 years), sex, stage at diagnosis (I/II/III, IV), and tumor location (proximal colon, distal colon, rectum). Tests of interactions between family history of CRC and potentially modifying covariates were assessed by entering the cross-product term for FDR and the covariate of interest in the multivariate models. Two-tailed P-value of <0.05 was considered statistically significant. All analyses were performed using R version 3.2.2 and SAS version 9.4 (SAS Institute, Inc, Cary, NC).

Results

Of the 5010 eligible participants, 819 (16.3%) individuals reported a family history of CRC in one or more FDRs at the baseline interview. The median follow-up period was 4.6 years (interquartile range 2.2–7.3 years) after CRC diagnosis. Among the 1580 (31.5%) total deaths, 1046 (66.2%) deaths were attributed to CRC. Individuals who reported a first-degree family history of CRC were more likely to have undergone screening endoscopy ($P < 0.001$) and have proximal colon tumors ($P = 0.04$) and non-metastatic CRC ($P = 0.003$; Table 1). Overall, having a family history of CRC was not associated with OS (HR, 1.03; 95% CI, 0.89–1.19) or CSS (HR, 1.13; 95% CI, 0.95–1.36) after adjusting for age at diagnosis, sex, BMI, smoking status, regular use of aspirin or NSAIDs, history of endoscopy screening, and stratified by tumor location, stage at diagnosis, and study site (Table 2).

There was no evidence of an association between the number of affected FDRs on survival. Compared to patients without a family history of CRC, the multivariate HRs for OS were 1.00 (95% CI, 0.85–1.18) for individuals with 1 affected FDR and 0.92 (95% CI, 0.59–1.43) for

individuals with ≥2 affected FDRs. The corresponding HRs for CSS were 1.11 (95% CI, 0.91–1.37) with 1 affected FDR and 0.98 (95% CI, 0.55–1.76) for ≥2 affected FDRs (Table 2). There was also no relationship between the age at CRC diagnosis of the affected FDR with OS or CSS. Compared to patients without a family history of CRC, the HRs for OS were 0.84 (95% CI, 0.57–1.24) for individuals with an affected FDR diagnosed at age <60 years, and 1.02 (95% CI, 0.81–1.29) for those with an affected FDR diagnosed at age ≥60 years. The corresponding HRs for CSS were 1.09 (95% CI, 0.69–1.74) and 1.19 (95% CI, 0.89–1.61), respectively (Table 2).

In subgroup analyses, the effect of family history appeared to vary according to tumor location (Table 3). Among patients with distal colon cancer, having a family history of CRC was associated with lower CSS (HR, 1.45; 95% CI, 1.03–2.04), compared to individuals without a family history of CRC. In contrast, there was no statistically significant association between family history of CRC and CSS among individuals with proximal colon cancer (HR, 1.04; 95% CI, 0.82–1.33) or rectal cancer (HR, 1.34; 95% CI, 0.80–2.23).

Table 1. Baseline characteristics of study participants according to family history of colorectal cancer.

Characteristic	No family history of CRC (*n* = 4191) *N* (%)	Positive family history of CRC (*n* = 819) *N* (%)
Age at diagnosis, year		
<40	22 (1)	6 (1)
40–<50	67 (2)	23 (3)
50–<60	461 (11)	80 (10)
60–<70	1612 (39)	286 (35)
≥70	2029 (48)	424 (52)
Median age at diagnosis, year (Interquartile range)	71 (65,76)	70 (65,75)
Sex		
Male	1534 (37)	281 (34)
Female	2657 (63)	538 (66)
Smoking status		
Never	1842 (44)	344 (42)
Former	1928 (46)	399 (49)
Current	398 (10)	71 (9)
Unknown	23 (1)	5 (1)
Body mass index, kg/m^2		
<25.0	1441 (34)	283 (35)
25.0–29.9	1629 (39)	324 (40)
≥30.0	1067 (26)	205 (25)
Unknown	54 (1)	7 (1)
Regular Aspirin/NSAIDS use		
Yes	1496 (36)	294 (36)
No	2571 (61)	508 (62)
Unknown	124 (3)	17 (2)
History of prior screening endoscopy		
Yes	1514 (36)	359 (44)
No	2430 (58)	418 (51)
Unknown	247 (6)	42 (5)
Tumor site		
Proximal colon	2107 (50)	437 (53)
Distal colon	1360 (33)	240 (29)
Rectum	632 (15)	114 (14)
Others	92 (2)	28 (3)
Stage of CRC		
I	1415 (34)	306 (37)
II/III	2036 (49)	398 (49)
IV	512 (12)	67 (8)
Unknown	228 (5)	48 (6)
Study site		
CPS-II	529	82
HPFS	131	36
NHS	250	46
PLCO	853	148
VITAL	233	40
WHI	1011	257
CCFR-PMH	259	20
DALS	925	190

CRC, colorectal cancer; NSAIDs, nonsteroidal anti-inflammatory drugs.

Discussion

In this large pooled analysis of 5010 CRC cases, having a family history of CRC in FDRs was not associated with CRC survival in the overall population. There were also no significant associations between the number of affected FDRs or age at CRC diagnosis of the affected FDRs and CRC survival. Compared to patients without a family history of CRC, having a family history of CRC in FDRs among individuals with distal colon conferred worse CSS.

Having a family history of CRC is a known risk factor for the development of CRC [2, 5, 6, 19]. However, the prognostic significance of family history of CRC remains uncertain [13–20, 22–25]. Similar to previous studies, we found that individuals with a family history of CRC were more likely to have proximal colon cancer [18], earlier stage at diagnosis [6, 13], and underwent screening endoscopy [13, 19]. However, this did not lead to differences in CSS and OS in our adjusted analyses. Our finding of no association between family history of CRC and survival in patients with CRC is consistent with reports from five previous studies conducted in population-based cohorts or within a clinical trial [16, 18, 23–25]. The most robust study was conducted within the CCFR which reported no association between family history of CRC and OS, after adjusting for microsatellite instability (MSI) status or tumor site [18]. Although we are unable to account for MSI and other mutation status, for example, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) due to lack of information, several studies suggested that adjustment for MSI or mismatch repair (MMR) status and mutation status had minimal impact on the null associations [18, 25]. Among stage III resected colon cancer

Table 2. Family history of colorectal cancer in first-degree relatives and overall and colorectal cancer-specific survival after colorectal cancer diagnosis.

	Overall survival			Colorectal cancer-specific survival		
	No. of deaths/ no. at risk	Model 1 HR (95% CI)[1]	Model 2 HR (95% CI)[2]	No. of deaths/ no. at risk	Model 1 HR (95% CI)[1]	Model 2 HR (95% CI)[2]
Family history in FDR						
No	1337/4191	1.0 (ref)	1.0 (ref)	885/4190	1.0 (ref)	1.0 (ref)
Yes	243/819	0.90 (0.78–1.03)	1.03 (0.89–1.19)	161/819	0.91 (0.77–1.07)	1.13 (0.95–1.36)
No. of affected FDR						
0	1337/4191	1.0 (ref)	1.0 (ref)	885/4191	1.0 (ref)	1.0 (ref)
1	180/627	0.92 (0.78–1.07)	1.00 (0.85–1.18)	122/627	0.95 (0.79–1.15)	1.11 (0.91–1.37)
≥2	21/83	0.73 (0.47–1.13)	0.92 (0.59–1.43)	12/83	0.68 (0.38–1.21)	0.98 (0.55–1.76)
Age at CRC diagnosis of affected FDR[3]						
No family history	754/2566	1.0 (ref)	1.0 (ref)	476/2566	1.0 (ref)	1.0 (ref)
<60 years	28/118	0.73 (0.50–1.07)	0.84 (0.57–1.24)	20/118	0.85 (0.54–1.33)	1.09 (0.69–1.74)
≥60 years	91/289	1.01 (0.82–1.26)	1.02 (0.81–1.29)	58/289	1.08 (0.82–1.42)	1.19 (0.89–1.61)

CRC, colorectal cancer; FDR, first-degree relative; HR, hazard ratio; CI, confidence interval.

[1]Adjusted for age at diagnosis, sex, body mass index, smoking, regular use of aspirin or nonsteroidal anti-inflammatory drugs, history of endoscopy screening and stratified by study site.

[2]Adjusted for age at diagnosis, sex, body mass index, smoking, regular use of aspirin or nonsteroidal anti-inflammatory drugs, history of endoscopy screening, and stratified by tumor location, stage at diagnosis, and study site.

[3]Age at CRC diagnosis of the youngest affected FDR.

patients treated with adjuvant chemotherapy in a randomized controlled trial (N0147), having a family history of CRC did not impact disease free survival and OS, after adjustment for other predictors of mortality including *KRAS* or *BRAF* mutations and MMR status [25].

Our results contradict two large studies conducted within the PLCO which reported a 31% increase risk of mortality, and a population-based registry in the United Kingdom which reported a modest 11% reduction in the risk of death in individuals with a family history of CRC compared to those with sporadic CRC [17, 19]. The PLCO study included individuals aged 55–74 years, whereas our study included patients beyond this age range, hence selection bias could account for some of the observed differences. In addition, the PLCO study did not adjust for stage and smoking which are important predictors of mortality [35, 36]. Similar to the PLCO study and another study conducted within the NHS, younger age at diagnosis in the affected FDR (<60 years) was not associated with differential increase risk of CRC mortality compared to individuals with FDRs diagnosed at older ages in our study [13, 19]. In the retrospective study conducted by Morris et al. [17] within the National Study of CRC Genetics (NSCCG), individuals with familial CRC had improved survival compared to those with sporadic CRC, with survival correlating with the number of affected FDRs. The observed differences may be attributed to different population characteristics and study design. The NSCCG was a retrospective observational study with inherent recall bias, whereas most of the studies included in our study are prospective cohort studies. Compared to our study, the patients within the NSCCG were younger and had a higher proportion of rectal cancer. It is also unknown whether there were differences in other predictors of mortality such as smoking, BMI, prior endoscopy, use of aspirin/NSAIDs between individuals with and without a family history of CRC within the NSCCG, and these confounders were not accounted for in their analyses. Although the authors suggested that the improved survival may be due to a higher proportion of cases with right-sided tumors among those with a family history of CRC, which are associated with a deficient MMR pathway linked to better prognosis [37, 38], the MMR status in the CRC cases were not available for analyses. In contrast, we did not see improved survival in our cohort despite having a higher proportion of right-sided tumors in those with family history of CRC, which was consistent with the study conducted within CCFR [18]. Furthermore, there remains a conundrum regarding the prognosis of right-sided tumors as they are also commonly associated with BRAF mutations which confer a poor prognosis [39, 40]. Family history of CRC has been shown to confer an improved OS in stage III colon cancer patients with deficient MMR expressing tumors compared to proficient MMR tumors [25]. The impact of MSI and mutational status on the prognostic significance of family history certainly warrants further validation.

In our study, having a family history of CRC in FDRs was associated with increased CRC-specific mortality in individuals with distal colon cancer, but not proximal or rectal cancers. For individuals with rectal cancers, there

Table 3. Subgroup analyses of overall and colorectal cancer-specific survival by family history of colorectal cancer.

		Overall survival			Colorectal cancer-specific survival		
		No family history of CRC	Positive family history of CRC	P_{int}	No family history of CRC	Positive family history of CRC	P_{int}
Age at diagnosis							
<60 years	No. of deaths/no. at risk	134/462	19/90	0.13	110/462	17/90	0.46
	MV HR (95% CI)	1.0 (ref)	0.62 (0.33–1.14)		1.0 (ref)	0.64 (0.33–1.25)	
≥60 years	No. of deaths/no. at risk	1203/3729	224/729		775/3729	144/729	
	MV HR (95% CI)	1.0 (ref)	1.07 (0.92–1.24)		1.0 (ref)	1.18 (0.98–1.43)	
Sex							
Male	No. of deaths/no. at risk	519/1534	88/281	0.55	305/1534	57/281	0.38
	MV HR (95% CI)	1.0 (ref)	0.94 (0.74–1.21)		1.0 (ref)	1.25 (0.91–1.71)	
Female	No. of deaths/no. at risk	818/2657	155/538		580/2657	104/538	
	MV HR (95% CI)	1.0 (ref)	1.08 (0.90–1.30)		1.0 (ref)	1.10 (0.88–1.37)	
Stage							
I/II/III	No. of deaths/no. at risk	810/3451	169/704	0.21	416/3451	100/704	0.77
	MV HR (95% CI)	1.0 (ref)	0.97 (0.83–1.14)		1.0 (ref)	1.07 (0.87–1.33)	
IV	No. of deaths/no. at risk	437/512	58/67		412/512	53/67	
	MV HR (95% CI)	1.0 (ref)	1.28 (0.94–1.73)		1.0 (ref)	1.25 (0.91–1.73)	
Tumor site							
Proximal colon	No. of deaths/no. at risk	716/2107	132/437	0.67	482/2107	83/437	0.34
	MV HR (95% CI)	1.0 (ref)	1.01 (0.83–1.22)		1.0 (ref)	1.04 (0.82–1.33)	
Distal colon	No. of deaths/no. at risk	381/1360	67/240		235/1360	47/240	
	MV HR (95% CI)	1.0 (ref)	1.15 (0.87–1.51)		1.0 (ref)	1.45 (1.03–2.04)	
Rectum	No. of deaths/no. at risk	194/632	31/114		138/632	21/114	
	MV HR (95% CI)	1.0 (ref)	1.29 (0.85–1.96)		1.0 (ref)	1.34 (0.80–2.23)	

MV HR, multivariate hazard ratio; CI, confidence interval.

Multivariate model adjusted for age at diagnosis, sex, body mass index, smoking, regular use of aspirin or nonsteroidal anti-inflammatory drugs, history of endoscopy screening, study site, tumor location, and stage at diagnosis, with the omission of the stratification variable in the model.

was a trend toward worse CSS although not significant, possibly due to limited statistical power. Our finding differs from the result of the NHS study which showed an increased risk of CRC mortality among those with proximal colon cancer (HR 1.69; 95% CI, 1.03–2.77) [13]. The NHS cohort comprises of females only and this may limit its comparability to our study that included both males and females. The increased mortality observed in patients with distal colon cancer with a family history of CRC in our study may suggest a biologically more aggressive disease due to differences in molecular and genetic features or shared environmental factors among FDRs. These possibilities warrant further investigation.

Our study has several strengths. First, this analysis included a large study population of CRC cases (n = 5010) with detailed demographic and epidemiologic information. Second, most of the included studies are prospective cohort studies, which minimized the possibility of recall bias attributed to differential reporting of family history of CRC with varying cancer stages. Third, we had information on the number of affected FDRs and age at diagnosis of CRC in affected FDRs in a subset of the population. This allowed us to explore the influence of the number of affected FDRs and age at CRC diagnosis of the affected FDR on survival.

There are some limitations in this study. First, family history information was obtained by self-report. This may result in a potential for misclassification of family history status. However, self-report family history has been shown to be reliable when compared to death certificates, medical records, or registry data [41, 42]. Second, we could not exclude cases with familial cancer syndromes (FAP and Lynch syndrome) from all studies as most of the studies did not elicit this information. However, this is unlikely to alter our results significantly as familial CRC syndromes account for less than 5% of CRC cases [10]. Third, although we were unable to account for the effect of CpG island methylator phenotype (CIMP), MSI status, and mutations such as *BRAF* due to lack of available information, which are known to affect CRC prognosis, studies have suggested that adjustment of these factors had little impact on the associations [18, 25]. Last, the limited availability of treatment data precludes adjustment for treatment in the multivariate models. However, treatment was generally uniform according to stage at diagnosis. Thus, our adjustment for stage at diagnosis should largely minimize any different effect of treatment on survival.

In conclusion, we found that having a family history of CRC in FDRs was generally not associated with OS

and CSS, after adjusting for other predictors of mortality including stage at diagnosis. However, our data indicate that family history of CRC may be associated with worse CRC prognosis in patients with distal colon cancer, suggesting a possible genetic predisposition with distinct pathogenic mechanism that confers a poor prognosis. Additional studies are needed to validate our findings and fully elucidate the potential pathways by which family history may affect survival.

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Conflict of Interest

None declared.

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