Family History of Colorectal Cancer in First-degree Relatives and Metachronous Colorectal Adenoma

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Running title: Family history of CRC and metachronous colorectal adenoma

Word count: 2383

Key words: colorectal cancer, family history, adenoma, neoplasia

Abstract

Introduction: Little is known about the relationship between having a first-degree relative (FDR) with colorectal cancer (CRC) and risk for metachronous colorectal adenoma (CRA) following polypectomy.

Methods: We pooled data from 7 prospective studies of 7697 patients with previously-resected CRAs to quantify the relationship between having a FDR with CRC and risk for metachronous adenoma.

Results: Compared to having no family history of CRC, a positive family history in any FDR was significantly associated with increased odds of developing any metachronous CRA (OR=1.14; 95% CI=1.01-1.29). Higher odds of CRA were observed among individuals with an affected mother (OR=1.27; 95% CI=1.05-1.53) or sibling (OR=1.34; 95% CI=1.11-1.62) as compared to those without, while no association was shown for individuals with an affected father. Odds of having a metachronous CRA increased with number of affected FDRs, with ORs (95% CIs) of 1.07 (0.93-1.23) for one relative and 1.39 (1.02-1.91) for two or more. Younger age of diagnosis of a sibling was associated with higher odds of metachronous CRA, with ORs (95% CIs) of 1.66 (1.08-2.56) for diagnosis at ≤ 54 years; 1.34 (0.89-2.03) for 55-64 years; and 1.10 (0.70-1.72) for ≥ 65 years (p-trend=0.008). Although limited by sample size, results for advanced metachronous CRA were similar to those for any metachronous CRA.

Conclusions: A family history of CRC is related to a modestly increased odds of metachronous CRA. Future research should explore whether having a FDR with CRC, particularly at a young age, should play a role in risk stratification for surveillance colonoscopy.

Introduction

It has been estimated that in 2017, there will be 95,520 new cases of colon cancer and 39,910 new cases of rectal cancer in the United States, with a combined 50,260 deaths from these malignancies(1). Worldwide, colorectal cancer (CRC) is the third leading cause of cancer deaths(2). Beyond well-characterized but comparatively rare genetic factors, such as Lynch Syndrome and Familial Adenomatous Polyposis (FAP), having a family history of CRC confers increased risk for CRC. Indeed, a family history of CRC informs guidelines for prevention strategies such as colonoscopy. In a recent review of the literature, it was noted that consensus regarding screening guidelines for those with a family history of CRC is critical to prevention efforts (3).

Prevention of CRC is attainable through screening and surveillance, including colonoscopic examination, during which neoplastic lesions can be found and removed during the procedure(4-13). Current colonoscopic screening guidelines in the United States recommend that individuals with a first-degree relative (FDR) who have had CRC or a colorectal adenoma (CRA) before the age of 60 years, or in two or more FDRs regardless of age, undergo colonoscopic screening every 5 years beginning either at 40 years of age, or at 10 years younger than the age of the index FDR (14). In contrast, among those lacking other risk factors and without a family history of CRC or CRA, colonoscopic screening is recommended to commence at age 50, with routine screening to follow once every ten years if the individual has a normal colonoscopy (14).

Guidelines for screening and surveillance among individuals with a family history of CRC or CRA are based largely on studies of adenoma incidence (15-28), some of which are limited by sample

size, lack of controls, lack of information regarding the relationship of the proband or index case to their relatives, or unavailable data for colorectal sub-site (distal vs. proximal). Further, there is a dearth of data on the role of family history and risk of metachronous CRA following polypectomy, which are critically important given the burden of colonoscopy on both patients and the healthcare system and for informing future screening and surveillance guidelines (29).

Prior work has investigated whether the type of FDR (parent, sibling) had an effect on risk of colorectal neoplasia (30, 31), and the number of affected relatives has been shown to be related to odds of colorectal adenoma in previously-published studies (14, 16, 32, 33). In addition, age of diagnosis of FDR has been studied in the past (23, 27, 33). However, none of the previously-published studies were able to investigate the association of these variables on metachronous lesions after polypectomy. We had the unique opportunity to investigate these hypotheses in our large study population.

We used data from a large pooled dataset from 7 prospective studies to determine variation in risk for metachronous CRA among individuals with a family history of CRC as compared to those without such history. We hypothesized that odds of any metachronous CRA and advanced CRA would differ by family history of CRC, as would the location of the lesions in the colorectum. We further hypothesized that these associations would vary depending on the specific FDR affected (mother, father, sibling), by number of affected relatives, and by age at CRC diagnosis of FDRs.

Methods

Study Participants and Data Sources

Individual-level data were pooled from individuals who were participants in six chemoprevention trials and one cohort study conducted in North America (34-40). Each study obtained approval from their respective institutional review boards for the pooling protocol, the design of which has been described in detail previously (41). Briefly, studies selected for inclusion in the pooling study were prospective investigations that had reported results in the literature by June 2005 and had met the following criteria: 1) at least 800 participants included in the original study who had undergone a baseline colonoscopy with at least one adenoma detected and removed; 2) at least one follow-up colonoscopy was conducted during the trial as specified by a predetermined surveillance schedule; 3) data for adenoma characteristics detected during follow-up were available, including size, number, and histopathology. Data regarding family history were self-reported on questionnaires administered by each study at baseline. Participants indicated whether they had a family history of CRC, the number of relatives with CRC, and in which relative the cancer occurred (mother, father, sibling). In addition, data were available for the age at which relatives were diagnosed with CRC. Information regarding participant characteristics such as age, sex, smoking history, and history of colorectal polyps preceding the baseline colonoscopy were also available via questionnaires.

Study Endpoints

Adenomas or cancers detected via colonoscopy after at least 6 months of follow-up were classified as metachronous colorectal neoplasia. Endoscopy and pathology reports were reviewed by personnel at each study site and data regarding size, histology, number, and degree of dysplasia were extracted. Next, central pathology review was conducted at each study site. Endoscopy reports were used to ascertain size of adenomas, with pathology reports employed if data were not

available from the former. Metachronous CRA were classified as non-advanced if they were <10 mm in size, had tubular histology, and had no high-grade dysplasia. Advanced lesions were categorized as such if they met at least one of the following criteria: 1) ≥ 10 mm in size; 2) tubulovillous or villous histology; 3) presence of high-grade dysplasia; or 4) invasive CRC. For colonic location, CRAs were classified as proximal only or distal only. A CRA at or proximal to the splenic flexure was categorized as “proximal” and those distal to the splenic flexure were designated as “distal”. For the analyses of colorectal sub-site, we excluded those who had CRAs at both locations.

Statistical Analyses

Logistic regression analyses were employed to investigate the relationship between having a family history of CRC and odds of metachronous CRA. The outcome categories for the primary analyses of the association between family history of CRC and metachronous CRA were: 1) CRA vs. no CRA; and 2) advanced CRA vs. no CRA. Variables assessed for confounding included age at baseline (in tertiles), sex, race, study, history of polyps prior to baseline study colonoscopy, NSAID and aspirin use, number of colonoscopies during follow-up, and baseline adenoma characteristics. Of these, age, sex, history of polyps prior to baseline, number of colonoscopies during follow-up, baseline adenoma location (distal, proximal, both), and baseline adenoma size changed the point estimate by 10% or greater (42) and were included in the final models. Similar analyses were employed for the investigation of associations by colorectal sub-site. Location was classified as “distal” if only distal lesions were present, with no proximal lesions; while for the analysis of proximal lesions, participants having only proximal lesions were included. All *P* values

for this work were two-sided, and all analyses were conducted with STATA v. 13.1 [College Station, TX].

Results

Among 7697 participants, 3719 (48.3%) had at least one CRA detected during follow-up, and a total of 949 (12.3%) participants had an advanced CRA. Relative to participants with no family history of CRC, those with a family history were statistically significantly younger and more likely to be female (Table 1). There was a significantly greater proportion of participants who reported white race in the group with a family history of CRC compared to those without, and more participants who had never smoked. There were no notable differences between the two groups for BMI, although there was a higher proportion of individuals reporting presence of polyps prior to the baseline qualifying colonoscopy in the group with a family history of CRC.

As shown in Table 2, individuals with any affected FDR had significantly increased odds for any metachronous CRA as compared with those without family history, with an adjusted odds ratio (OR) and 95% confidence interval (95% CI) of 1.14 (1.01-1.29). The OR for metachronous advanced CRA was almost identical but imprecise due to a lower number of events (OR 1.15; 95% CI 0.96-1.37). When considering the association by specific relative, those with an affected mother [OR 1.27; 95% CI (1.05-1.53)] or sibling [OR 1.34; 95% CI (1.11-1.62)] had significantly increased odds for metachronous CRA; while those with an affected father did not [OR 0.91; 95% CI (0.75-1.10)]. Similar, but imprecise ORs for advanced CRA were observed. A significantly higher odds of metachronous CRA was observed among individuals with 2 or more affected

relatives compared to those with no family history (OR=1.39; 95% CI, 1.02-1.91). When examining age at diagnosis of the affected relative (treated as tertiles) and odds for CRA, no difference was observed for age of affected mother or father (data not shown). For affected siblings, the ORs (95% CIs) for any metachronous CRA were 1.66 (1.08-2.56) for at least one sibling diagnosed at age ≤ 54 years; 1.34 (0.89-2.03) for ages 55-64 years; and 1.10 (0.70-1.72) for ages 65 years or greater (p-trend=0.008). A higher, non-significant OR for advanced CRA was shown having an affected sibling diagnosed <54 years of age (OR=1.24; 95% CI, 0.66-2.33) but not for older age groups.

Table 3 presents the relationship between family history of CRC and metachronous CRA by colorectal sub-site. Although the point estimates lacked precision, generally higher odds ratios were observed for proximal than for distal metachronous CRA. No statistically significant associations were observed for any family history variable and odds of distal lesions, while for proximal metachronous CRA, having a sibling who was diagnosed with CRC was associated with a significantly increased odds for a metachronous adenoma [OR 1.41; 95% CI (1.13-1.75)]. In addition, a modest direct association was observed for proximal lesions and number of affected relatives (p-trend=0.05), while there was an inverse association between age of sibling diagnosis and proximal lesions (p-trend=0.04).

Discussion

CRC screening guidelines recommend FDRs of CRC patients begin screening colonoscopy earlier than unaffected individuals, and that they receive more frequent repeat screening colonoscopies (i.e., every 5 years instead of 10 years for unaffected), even if the exam is normal(14). In contrast,

surveillance guidelines have no special considerations for individuals with family history (32). Our results show that having a family history of CRC in FDRs is associated with a modestly increased odds of metachronous CRA. We also observed that increasing number of affected relatives, and younger age of siblings at diagnosis, were significantly associated with odds of having a metachronous CRA. With the exception of sibling age, results for metachronous advanced CRA were similar to those for any metachronous CRA, but the risk estimates were imprecise.

A recent state-of-the-science review recommended several strategies for reducing CRC risk, including establishing clear screening guidelines among those with a family history of CRC (3). With some exceptions (33), prior work indicates that having a single FDR with CRC is associated with a higher risk of developing an adenoma (15, 17, 20, 23, 25-28, 31) and a higher risk of advanced CRA or features that make up advanced neoplasms (i.e., large size, villous histology, or dysplasia(22-25, 27)). Lacking in the literature, however, are reports on the association of family history and metachronous CRA, including advanced neoplasia, which could inform surveillance guidelines. Thus, a key feature of our study is that we ascertained the role of family history following polypectomy in the development of metachronous lesions. Although we previously reported on the association of any family history and metachronous colorectal neoplasia (41), the current work extends this by reporting on the characteristics of the affected family members. These results suggest that family history could have a role in risk stratification and surveillance recommendations, given that our risk estimates are in the same order of magnitude as those for villous adenoma features (41, 43) and high grade dysplasia (43), two characteristics for which their presence calls for surveillance colonoscopy to occur in 3 years (32). However, conclusive

evidence would need to derive from prospective studies with a larger number of metachronous advanced neoplasms than those in our study.

We further investigated whether there was variation in the odds of metachronous CRA based upon the specific affected FDR, a topic of importance for informing screening and surveillance guidelines but with limited published data (30, 31). We found that having an affected mother or sibling was significantly associated with increased odds of metachronous CRA, but having an affected father was not. Wong et al. reported no difference in the association whether the relative was a mother, father, or sibling (31); however, their study was of prevalent and not metachronous CRAs, which could explain the difference in their results from ours. It is possible that our results stratified by affected relative were influenced by a reduced number of endpoints, and as such may represent a potentially spurious finding.

It is unclear why age of affected sibling, but not of an affected mother, would be related to odds of metachronous lesions. Dong and Hemminki reported that having a sibling with colon cancer is associated with a higher risk of this cancer in an index case than having an affected parent, with a Standardized Incidence Ratio (SIR) and 95% Confidence Interval (CI) of 4.05 (2.62-5.99) for siblings and 1.89 (1.60-2.20) for parents, though they did not address the impact of age of affected relative in this study (44). We speculate that siblings might be more likely to share influential risk exposures than mother/child and might account for differences in sibling vs. mother/child risks. For example, in work by Pachucki et al., having a brother or sister who is obese was more likely to be associated with obesity in a sibling than having a parent who is obese (45).

We also found that having two or more affected relatives was related to higher risk for metachronous CRA than for those with one or none. We observed a trend for higher odds for metachronous CRA and lower age of affected sibling, indicating that metachronous CRAs are more common when sibling is younger a diagnosis. However, we did not observe an age gradient for either parent. These findings suggest that surveillance guidelines might also need to consider number of affected FDRs and possible age of affected sibling. Furthermore, understanding the role of younger age at diagnosis of a relative as a risk factor for new or metachronous neoplasia is particularly important given the increasing incidence in young onset CRC in the United States(46).

Because colorectal neoplasia of the distal colorectum may arise through different mechanistic pathways than proximal neoplasms (47), we evaluated whether there were differences by colorectal sub-site in our study. Our stratified analysis showed a suggestion of higher odds of proximal vs. distal metachronous CRA, particularly if a sibling were the affected relative. While our findings mirror those of Armeleo et al. (25), and in contrast to those of a large cross-sectional study of adenoma prevalence (27), our results are limited by the small number of endpoints. Furthermore, as with our other results, it must be stressed that the present work was focused on metachronous CRA, which does not permit a direct comparison with published work on prevalent CRAs.

Strengths of our study include the large sample size, prospective design, and detail regarding family history of CRC, including identification of probands and age at diagnosis. Nonetheless, limitations to the study must also be considered. Our data for family history of CRC were self-reported and as such were susceptible to misclassification. However, the work of Aitken et al. (22)

demonstrated that the sensitivity of self-reported family history of CRC ranges from 0.82-0.87, with a specificity of 0.97, accuracy high enough to suggest only a limited potential for serious bias. Data on sibling gender were not available, precluding analyses of whether sibling-associated risk differed by sibling gender. Finally, the primary endpoint of this study was metachronous CRA, with a range of follow-up from 3-5 years. This may limit the comparability of these results as the timing of colonoscopies was different from what would be observed using current standards of clinical practice for screening or surveillance programs. The definition of metachronous CRA for the pooling project was set *a priori* at any adenoma detected at least 6 months after baseline colonoscopy. These lesions may represent adenomas that were missed at the baseline examination; however, only 54 participants of 7697 (0.7%) had a single colonoscopy at less than one year of follow-up, and exclusion of these individuals from the analysis did not alter the results.

In conclusion, results of our large prospective study show that having a family history of CRC, including an affected mother or sibling, and younger age of diagnosis for affected sibling, are significantly associated with odds for metachronous CRA. Larger studies than ours are needed to confirm our findings related to metachronous advanced CRAs, which will inform future surveillance guidelines.

Study Highlights

1. WHAT IS CURRENT KNOWLEDGE

- Having a FDR with CRC is associated with increased risk for prevalent adenoma.
- Limited data exist regarding the association between family history of CRC and metachronous adenoma.
- Individuals with a family history of CRC are recommended for earlier and more frequent screening colonoscopy.

2. WHAT IS NEW HERE

- Having a FDR with CRC is associated with increased risk of metachronous colorectal adenoma.
- Having a mother or sibling affected with CRC is related to a higher risk for metachronous colorectal adenoma.
- Family history of CRC may need to be considered for risk stratification and surveillance of individuals following polypectomy.

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Table 1. Baseline characteristics of participants by family history of CRC.

Characteristic	No family history (n=5818)	Family history (n=1879)	p-value
Age (years, mean $\pm$ sd)	62.5 $\pm$ 9.2	60.9 $\pm$ 9.8	<0.001
Male (n, %)	4268 (73.4)	1198 (63.8)	<0.001
Race (n, %)			
White	5129 (88.2)	1734 (92.3)	
Black	340 (5.8)	72 (3.8)	
Other	349 (6.0)	73 (3.9)	<0.001
Cigarette smoking status (n, %)			
Never	1891 (32.5)	746 (39.7)	
Former	2944 (50.6)	891 (47.4)	
Current	965 (16.6)	237 (12.6)	
Unknown	18 (0.30)	5 (0.30)	<0.001
BMI in kg/m ² (n, %)			
<25	1658 (28.5)	519 (27.6)	
25 to <30	2633 (45.3)	902 (48.0)	
$\geq$ 30	1516 (26.0)	455 (24.2)	
Missing or unknown	11 (0.2)	3 (0.2)	0.10
Previous polyp (yes, n, %) ¹	1398 (24.0)	498 (26.5)	0.04

¹Self-reported polyp prior to qualifying colonoscopy for entry to study; data missing for 160 participants.

Table 2. Adjusted Odds Ratios (95% Confidence Intervals) for any metachronous CRA or advanced metachronous CRA compared to no CRA according to CRC family history characteristics.

	Any metachronous adenoma		Advanced metachronous adenoma	
Family history	CRA/total	Adjusted OR	CRA/total	Adjusted OR
characteristic		(95% CI) ¹		(95% CI) ¹
No family history	2777/5818	1.00 (Referent)	710/5818	1.00 (Referent)
Any first degree relative	942/1879	1.14 (1.01-1.29)	239/1879	1.15 (0.96-1.37)
Specific relative ²				
Mother	318/616	1.27 (1.05-1.53)	74/616	1.24 (0.94-1.65)
Father	275/613	0.91 (0.75-1.10)	65/613	0.92 (0.69-1.24)
Sibling	360/643	1.34 (1.11-1.62)	96/643	1.24 (0.95-1.62)
Number of relatives ²				
1	655/1357	1.07 (0.93-1.23)	167/1357	1.14 (0.93-1.40)
2+	117/212	1.39 (1.02-1.91)	29/212	1.32 (0.83-2.07)
p-trend		0.05		0.11
Youngest age of sibling				
CRC diagnosis				
≤ 54 years	65/107	1.66 (1.08-2.56)	15/107	1.24 (0.66-2.33)
55-64 years	66/116	1.34 (0.89-2.03)	14/116	0.99 (0.53-1.85)
≥ 65 years	49/97	1.10 (0.70-1.72)	11/97	0.71 (0.35-1.43)
p-trend		0.008		0.79

¹Models adjusted for age, sex, history of polyps prior to baseline, number of colonoscopies during follow-up; and baseline adenoma location (distal, proximal, both) and baseline adenoma size.

²Data are missing or could not be definitively ascertained for specific relative (n=7) and number of relatives (n=310).

Table 3. Adjusted Odds Ratios (95% Confidence Intervals) for proximal or distal metachronous CRA compared to no metachronous CRA.

	Distal-only metachronous		Proximal-only metachronous	
	CRA		CRA	
Family history characteristic	CRA/total	Adjusted OR (95% CI) ¹	CRA/total	Adjusted OR (95% CI) ¹
No family history	728/3769	1.00 (Referent)	1287/4328	1.00 (Referent)
Any first degree relative	213/1150	1.02 (0.86-1.23)	442/1379	1.14 (0.99-1.31)
Specific relative				
Mother	76/374	1.14 (0.87-1.51)	148/446	1.25 (1.00-1.56)
Father	68/406	0.89 (0.67-1.18)	132/470	0.92 (0.74-1.16)
Sibling	70/353	1.06 (0.80-1.42)	170/453	1.41 (1.13-1.75)
Number of relatives				
1	148/850	0.92 (0.75-1.14)	308/1010	1.11 (0.94-1.30)
2+	28/123	1.38 (0.88-2.15)	56/151	1.43 (1.00-2.04)
p-trend		0.83		0.05
Youngest age of sibling				
CRC diagnosis				
≤ 54 years	15/57	1.53 (0.83-2.83)	30/72	1.58 (0.96-2.60)
54-64 years	15/65	1.21 (0.67-2.21)	31/81	1.26 (0.78-2.06)
≥ 65 years	7/55	0.63 (0.28-1.44)	24/72	1.12 (0.67-1.87)
p-trend		0.24		0.04

¹Models adjusted for age, sex, history of polyps prior to baseline, number of colonoscopies during follow-up; baseline adenoma location and baseline adenoma size.