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ORIGINAL RESEARCH—CLINICAL

Surveillance Outcomes in Patients With a Family History of Colorectal Cancer in Both Parents

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BACKGROUND AND AIMS: A family history of colorectal cancer (CRC) in a first-degree relative is a well-established risk factor for CRC. When individuals have 2 parents with CRC, the impact on risk is uncertain, and there are no established guidelines for surveillance. We sought to define the surveillance practices and outcomes in individuals with a family history of CRC in both parents. **METHODS:** We identified probands with a family history of CRC in both parents from our Hereditary Gastrointestinal Cancer Database. Charts were retrospectively reviewed for colonoscopy surveillance patterns and incidence of adenomas and CRC. **RESULTS:** Sixty-six patients met the inclusion criteria. Forty-two patients (64%) had genetic testing, and no pathogenic germline mutations were identified. During a mean surveillance period of 144 ± 82.2 months and a mean surveillance interval of 33.4 ± 16.6 months, a total of 3.2 ± 8.9 adenomas were found per patient. These were small (median 6.5 mm), and 96% exhibited only low-grade dysplasia. Six patients (9%) were diagnosed with CRC at a mean age of 61.5 ± 11.3 years, corresponding to an incidence rate of 14 cases/10,000 person-years. Patients with CRC were older at first colonoscopy than those without cancer (59 vs 46 years, $P = .03$), and half of these cases were diagnosed at this first colonoscopy. **CONCLUSION:** Among patients with a family history of CRC in both parents, cases of CRC were seen primarily in those who significantly delayed their first colonoscopy. Initiation of colonoscopy at age 40 should be recommended to individuals with CRC in both parents, consistent with recommendations for those with 1 first-degree relative with CRC.

Keywords: Colorectal Cancer; First Degree Relatives; Colonoscopy; Multigene Panel

Introduction

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States.[1] Most CRCs are considered sporadic with a cumulative lifetime risk of 5%.[2] Up to 5% of CRC cases are associated with a well-defined hereditary syndrome. Approximately 20% of cases are associated with familial clustering of CRC in first- (FDR) or second-degree relatives (SDR), which may be a consequence of a low penetrance genetic alteration[3] and/or shared environmental factors such as vitamin D deficiency,[4] diabetes mellitus,[5] obesity,[6] alcohol consumption,[7] and smoking.[8]

Previous studies have demonstrated that the lifetime risk of CRC is increased approximately 2-fold compared to the general population in those with 1 FDR with CRC.[9,10] This risk increases with the number of FDRs affected and is inversely related to the age of the youngest FDR with CRC.[9,11,12] Current U.S. Multi-Society Task Force on Colorectal Cancer and American College of Gastroenterology guidelines recommend initiating colonoscopy at age 40 (or 10 years before the youngest affected relative) for those who have an FDR with CRC at an age younger than 60 years or at any age if there are 2 or more relatives, and exams should be repeated at intervals of every 5 years.[13,14] The NCCN guidelines are similar, but there is no restriction on the age of CRC diagnosis in the FDR.[15]

There is a unique subset of patients in whom both parents have been diagnosed with colon cancer. Technically, these individuals have 2 FDRs with CRC, but these FDRs are unrelated. The precise CRC risk to these individuals is uncertain, and there are limited data on this population. One retrospective study suggested a relative risk of 1.8 for developing advanced adenomas and a relative risk of 6.9 for CRC although only 2 cases of CRC were identified in this cohort.[16] A more extensive population-based study defined a familial relative risk (FRR) of 4.97 for CRC compared with the general population.[10] However, this was not significantly different from the FRR when both affected relatives were related.[10] Furthermore, there are no established surveillance guidelines for individuals with a family history of CRC in both parents, and it is uncertain whether surveillance should follow guidelines for 1 FDR with CRC or whether it should be more intensive.

Abbreviations used in this paper: **CRC, colorectal cancer; CT, computed tomography; FDR, first-degree relative; SDR, second-degree relative; TDR, third-degree relative.**

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We sought to describe the surveillance patterns and clinical outcomes of patients with 2 parents affected with CRC to better understand their CRC risk.

Methods

Study Population

The study population consisted of patients identified through the Hereditary Gastrointestinal Cancer Database at Massachusetts General Hospital. Patients aged 18 years or older were eligible if both parents were affected with CRC. Patients were excluded if they were younger than 18 years, had a history of inflammatory bowel disease, or a known CRC-associated germline mutation.

Data Collection

Patient records from the Epic electronic health records were reviewed. We retrospectively collected data, including demographics (age, gender, race, ethnicity), tobacco and alcohol use (self-reported in charts), relevant comorbidities (obesity, diabetes mellitus, metabolic syndrome), and medication usage (as documented at the time of genetic counseling) associated with possible chemoprevention effect (aspirin, statins, and metformin). Genetic data and relevant family history were collected from genetic consultation reports and included the date and age at the time of consultation, type of genetic testing, number of genes examined, DNA sequencing findings in terms pathogenicity, and family history of polyps and malignancy up to third degree relatives (age at presentation, type of malignancy).

Endoscopic surveillance data from colonoscopies and sigmoidoscopies, including the indication, quality of preparation, presence of polyps (location, size, number, and histology), and other significant findings, were also recorded. All corresponding histopathology reports were also reviewed.

Colonic and extracolonic malignancies (age of presentation, date of malignancy, location), mortality events, and causes of death were also recorded. Person years for calculation of the incidence proportion rate of CRC were deduced from the last clinical office visit date.

Data were stored on a REDCAP platform (a secure, password-protected database) and later exported as Excel files (saved on encrypted drives) for data analysis.

Data Analysis

Categorical variables were described as frequencies and percentages. Pearson Chi-square test (or Fisher's exact test if >20% of cells had an expected count <5) was used to test correlations of dichotomous and categorical variables. Continuous variables such as patient age or adenoma burden were described as a mean ± standard deviation, median, and range. All statistical tests were 2-sided, and $P < .05$ was considered statistically significant. Comparison of incidence proportion was done using the confidence interval of sample size proportion formula ("p hat"). Microsoft Excel software Data analysis tool and SPSS software (IBM SPSS Statistics for Windows, ver. 28.0.1.0[142]) were used for all statistical analyses.

This study was approved by the institutional review board, and it was carried out in accordance with the ethical principles described in the Helsinki Declaration.

Results

Patient Demographics

Sixty-six patients with a family history of CRC in both parents were identified and comprised our cohort. Forty-six patients (69.7%) were female, predominantly white non-Hispanic (95.5%) represented by Irish, English, and Italian ancestry (complete list in Table A1). Data concerning lifestyle risk factors for CRC were available for 63 patients. Twenty-one patients (33.3%) reported any smoking history, with a mean burden of 25.3 ± 5.7 (range 2–75, median 15) pack-years. Six patients (9.5%) were identified as current smokers. Forty-one patients (65%) reported any history of alcohol usage. Nineteen (30.1%) were identified as active drinkers who consumed 1–7 drinks/wk regularly, 3 patients (4.7%) consumed more than 1 drink per day regularly, and 2 patients (3.17%) were reported as having a history of alcohol abuse. Seventeen patients (26.9%) consumed less than 1 drink per day. Twenty-one patients (32.3%) had any metabolic comorbidity (diabetes mellitus or obesity). Thirty-two patients (48.4%) were identified as chronic users of medications with a potential effect on colonic neoplasia (aspirin/nonsteroidal anti-inflammatory drugs, metformin, or statins), and most were using aspirin (20 patients, 20.3%) for cardiovascular primary and secondary prevention (Table 1).

Familial Malignancy Burden

A total of 139 cases of CRC in an FDR were reported. One hundred thirty-two of these cases represented the patient's parents, and there were also 7 siblings with CRC. The median ages of paternal and maternal CRC diagnosis were 65 (range 35–90) and 67 years (36–94), respectively. Nine patients (13.6%) had a parent with early-onset colorectal cancer (early-onset CRC < 50 years). Overall, individuals in the cohort had a mean of 2.8 ± 0.1 (range 2–7, median 3) FDRs with any malignancy. There were 104 cases of non-CRC malignancy in an FDR reported in 46 patients (69.6%). Of these, the most common were breast (25%), lung (10%), and bladder (6.7%) (Table A2).

Twenty-eight patients (42.4%) had a second-degree relative (SDR) with CRC, and 13 patients (19.6%) had more than 1 SDR with CRC. Fifty-six patients (84.8%) had an SDR with any malignancy (mean 3.1 ± 0.2, range 1–10, median 3). Breast (33.3%), lung (18.2%), and prostate (18.2%) cancer were most commonly reported. Eight patients (12.1%) were reported to have a third-degree relative (TDR) with CRC, including 7 with 1 TDR and 1 with 2 TDR. Twenty-eight patients (42.4%) had a TDR with any malignancy, and breast (24.2%), gastric (6.1%), and prostate (6.1%) cancer were most commonly reported (Table A2).

Table 1. Cohort Characteristics (N = 66)

Parameter	Number (%)
Female gender	46 (69.7)
Ethnicity	
White (non-Hispanic)	63 (95.5)
Black or African American	2 (3)
Asian	1 (1.5)
Paternal origin[a]	
Irish	19 (21.1)
Italian	10 (11.1)
English	10 (11.1)
Ashkenazi Jewish	6 (9)
Maternal origin[a]	
Irish	26 (28.2)
English	12 (13)
Italian	10 (10.8)
Ashkenazi Jewish	5 (7.5)
Habits[b]	
Any smoking history	21 (33.3)
Current smokers	6 (9.5)
Pack years	25.3 ± 5.7 (range 2–75, median 15)
Any alcohol consumption	41 (65)
Active—between 1–7 drinks per wk regularly	19 (30.1)
Metabolic comorbidities[cd]	21 (32.3)
Usage of potential chemopreventive medication[e]	32 (48.4)

[a]Leading 3 paternal and maternal origin.
[b]Data were available for 63 patients.
[c]Diabetes mellitus and/or obesity.
[d]Data were available for 65 patients.
[e]Chronic usage of statins and/or nonsteroidal anti-inflammatory drugs and/or metformin.

Table 2. CRC-Related Genes Included in Genetic Testing Panels and the Number of Patients who Underwent Testing

CRC-related genes	N	%
MLH1	35	83.33
MSH2	35	83.33
MSH6	32	76.19
EPCAM	31	73.81
PMS2	31	73.81
APC	29	69.05
CHEK2	29	69.05
TP53	29	69.05
BMPR1A	27	64.29
MUTYH	27	64.29
PTEN	27	64.29
STK11	27	64.29
ATM	26	61.90
SMAD4	25	59.52
POLD1	24	57.14
POLE	24	57.14
GREM1	23	54.76
AXIN2	18	42.86
NTHL1	15	35.71
MSH3	12	28.57
BLM	6	14.29
GALNT12	3	7.14
RPS20	3	7.14
MUTYH (Y179C and G396D mutations only)	2	4.76

Genetic Testing

All patients had genetic counseling at a mean age of 58.8 years (range 41–81, median 59). The indications for genetic testing included family history of malignancy (93.9%), personal history of non-CRC malignancy (40.9%), suspected familial syndrome (15.2%), personal history of CRC (7.6%), and personal history of more than 10 adenomas (3%).

Forty-two patients (64%) pursued germline genetic testing. A mean of 27 ± 3.7 genes were analyzed (range 2–90 genes, median 24), and the number of genes analyzed was individualized after genetic counseling. Ten patients declined genetic testing, genetic testing was not recommended in 11 cases, and 3 patients were lost to follow-up. The spectrum of CRC-related genes analyzed is described in Table 2 (complete list in Table A3).

No pathogenic germline mutations were identified. Eleven different variants of unknown significance were found in 11 patients (26.1%) (Table A4).

Colonoscopy Findings and CRC Burden

Two hundred thirty-eight colonoscopy reports from 58 patients (87.8%) with at least 1 colonoscopy performed (range 1–18, median 4 colonoscopies per patient) were reviewed. The main indications were surveillance (50.8%) and screening (45.3%), followed by evaluation of abnormal computed tomography (CT) findings (1.6%), fecal immunochemical test (1.3%), evaluation of symptoms (0.4%), and precolectomy colonic clearance (0.4% each). The mean age of patients at the first colonoscopy was 47.5 ± 1.1 years (range 35–68, median 47). A total of 163 adenomatous polyps were reported, mostly small (range 2–25 mm, median 6.5 mm) with tubular adenoma with low-grade dysplasia representing the predominant histology (87.3%), followed by tubulovillous adenoma with low-grade dysplasia (8.4%), tubular adenoma with high-grade dysplasia (2.8%), and tubulovillous adenoma with high-grade dysplasia (1.4%). Forty-nine patients were documented to have had 2 or more colonoscopies. Over a mean surveillance period of 144 ± 82.2 months (range 18–381 months, median 140), 229 colonoscopies were performed, which translates to a mean of 4.6 ± 3 (range 2–18, median 4) colonoscopies per patient at a mean interval of 33.4 ± 16.6 months (range 9–90.5, median 33.5) and a mean total adenomatous polyp burden of 3.2 ± 8.9 (range 0–62, median 1) per patient.

Six patients were diagnosed with CRC at a mean age of 61.5 ± 11.3 years (median 64.5). This corresponds to an incidence proportion of 9.1% and an incidence rate of 14 cases/10,000 person-years. Four of these patients had

genetic testing performed, and all were negative (Table A5). CRC was diagnosed in 1 patient during his first colonoscopy at the age of 70 years for a 2.6-cm polypoid mass seen on a CT scan; in the second patient, during his first screening colonoscopy at the age of 67 years; and in the third patient, during his first colonoscopy at the age of 51 years for evaluation of a positive fecal immunochemical test test. In the fourth patient, CRC was diagnosed at his fourth surveillance colonoscopy at the age of 62 years. This patient had 4 colonoscopies over a period of 193 months (mean interval of 48.5 months) before his CRC was diagnosed. The fifth patient was diagnosed during his second colonoscopy at the age of 74 years for evaluation of change in bowel habits and a right colon mass on CT scan, 9 months after his previous colonoscopy that identified only a 3-mm sessile polyp in the sigmoid colon. The sixth patient was diagnosed at the age of 45 years, and colonoscopy data were unavailable. (Complete list of colonoscopy indications for CRC cases is listed in Table A6).

Two patients had mismatch-repair-proficient CRC, and 1 met the criteria for familial CRC syndrome X. Three had mismatch-repair-deficient CRC, all with loss of MLH1-PMS2 on immunohistochemistry, and 2 of these cases exhibited a BRAF mutation and MLH1 promotor methylation. The third case was negative for a BRAF mutation and MLH1 methylation, and genetic testing was declined by the patient. Of note, Amsterdam criteria were not met in this patient. Four patients had only both parents as relatives with CRC, and the other 2 patients also had an SDR with CRC. (Table 3).

Patients diagnosed with CRC had their first colonoscopy at a median age of 59 years (range 46–68). This was significantly older than the median age of first colonoscopy for the 60 patients who were not diagnosed with CRC (46 years, range 35–57, $P = .03$). Although the non-CRC group was characterized by a higher maximal number of colonoscopies performed (18 vs 5), no statistically significant difference was found in terms of the median number of colonoscopies (4 in both groups. $P = .56$) or the median adenoma burden (1 in both groups, $P = .83$). In addition, no difference was found with respect to the age of presentation of CRC in parents, proportions of early-onset colorectal cancer in parents, or familial CRC burden, as described in Table 4.

In terms of malignancies other than CRC, 37 patients (54.5%) were diagnosed with at least 1 extracolonic malignancy. There were a total of 51 extracolonic malignancies diagnosed at a mean age of 57.9 ± 1.7 years (range 40–81, median 60), with the highest frequencies for breast cancer (29.4%) and nonmelanoma skin cancer (17.6%). (complete list in Table A7)

Table 3. Clinical Features of CRCs Diagnosed in the Cohort

Patient ID	Age at 1st colon.	Age CRC	CRC location (surgical procedure)	MMR status	CRC stage	Surv. interval (mo) to CRC[c]	Adenoma burden	Total surv. interval (mo)	CRC age father	CRC age mother	No. of SDR with CRC	Age CRC SDR [d]
2	68	68	Rt. (RHC)	MMR-P	1	0	Multi.	45	60	78	0	NA
14	67	67	Rt.[a] (RHC)	MMR-D	3A	0	7	129	75	72	3	60
18	51	51	Rec.[c] (LAR)	MMR-P	2A	0	0	27	48	62	4	45
31	46	62	Rec.[b] (LAR)	MMR-D	3C	56	9	193	85	64	0	NA
47	No data	74	Rt.[a] (RHC)	MMR-D	3B	8	1	52	57	90	0	NA
49	No data	45	No data	No data	No data	No data	No data	No data	55	45	0	NA

Colon., colonoscopy; Inter., interval; LAR, left anterior resection; MMR-P, mismatch repair genes proficient; MMR-D, mismatch repair genes deficient; Multi, multiple; Rec., rectum; RHC, right hemicolectomy; Rt., right colon; SDR, second-degree relative; Surv., surveillance.
[a]MMR deficient (MLH1 and PMS2) and MSI-high CRC positive for MLH1 promotor methylation and BRAF mutation.
[b]MMR deficient (MLH1 and PMS2) and MSI-high CRC negative for MLH1 promotor methylation and BRAF mutation.
[c]Surveillance interval from the last documented colonoscopy to CRC diagnosis.
[d]Youngest age of CRC, presentation in an SDR.

Discussion

A family history of CRC in an FDR is a well-established risk factor for CRC. This risk increases as the number of affected FDRs relatives increases, and this may reflect the

Table 4. Comparisons Between Individuals With CRC and Those Without CRC in the Cohort

A. Categorical variables

Parameter	CRC (N = 6)	No CRC (N = 60)	Fisher's exact test sig. (2-sided)
Gender (F)	4 (66.7%)	42 (70%)	1
Amsterdam+	3 (50%)	9 (15%)	0.068
EOCRC in parent	4 (66.7%)	7 (11.7%)	0.18
CRC in SDR	2 (33.3%)	26 (43.3%)	1
CRC in TDR	1 (16.7%)	7 (11.7%)	0.55
Smoking Hx.	4 (66.7%)	17 (29.8%)	0.08
Alcohol use	2 (33.3%)	39 (68.4%)	0.17

B. Scaled variables

Parameter	Patients with CRC	Patients without CRC	Mann-Whitney U value	Test sig. (2-sided)
Age at first colonoscopy (y)[c]	59 (46–68)	46 (35–57)	115	0.03
Total number of colonoscopies	4[a] (2–5)	4[b] (2–18)	88.5	0.56
Adenoma burden	1 (0–7)	1 (0–62)	111	0.83
Earliest age of CRC in parent (y)	60 (48–72)	62.5 (35–84)	98	0.8

Data available for 35 patients. All data are presented as median and range.
EOCRC, early-onset colorectal cancer; Hx, history; Sig., significance level.
[a]Data available for 5 patients.
[b]Data available for 42 patients with at least 2 colonoscopies documented.
[c]Data available for 4 patients.

presence of an underlying genetic susceptibility. A previously published meta-analysis reported a pooled relative risk of CRC of up to 1.92 for those with 1 FDR with CRC and up to 2.81 for those with at least 2 FDRs.[17]

However, the precise risk when there are 2 unrelated FDRs (ie, parents) is not well-defined as data are limited. In an Australian cohort of 96 patients, 2 patients were diagnosed with CRC (2%), and a relative risk of 6.9 of CRC was calculated compared to a North American average-risk population historical control.[16] In a large population-based study comprising more than 2 million individuals, a FRR of 1.96 was calculated when at least 1 FDR was diagnosed with CRC, but a higher FRR (4.97) was calculated when the mother and father were both affected.[10]

In our cohort, CRC was diagnosed in 6 patients (9%) at an average age of 61.5 years. This corresponds to an incidence proportion of 9.1% and an incidence rate of 14 cases/10,000 person-years. While these rates are substantial, they are comparable to rates seen among individuals with 1 FDR with CRC as measured in the The Prostate, Lung, Colorectal, and Ovarian cancer-screening trial in the United States. Two hundred thirty-eight patients with 1 FDR were diagnosed with CRC during 151,995 person-years of follow-up, reflecting an incidence rate of 15.7 cases per 10,000 person-years. Patients who had at least 2 FDRs with CRC had a much higher incidence rate of 26.8 cases per 10,000 person-years, but it is uncertain how many of these cases were in individuals who had 2 parents with CRC.[18]

Current guidelines recommend surveillance exams for individuals with 1 FDR with CRC to start at age 40 or 10 years earlier than the age of CRC in the FDR and to repeat exams every 5 years.[13,15,19] In our cohort, most patients repeated exams at 3-year intervals, a possible reflection of a concern that they were at higher risk than those with 1 FDR. The number and histology of the polyps identified would not have warranted more frequent surveillance. However, most did not initiate surveillance at the recommended age. In fact, those who developed CRC significantly delayed their first colonoscopy until the age of 59 years compared to those who did not develop cancer (46 years), and half of these cancers were diagnosed at the first colonoscopic exam.

Our study has some limitations. Our cohort comprised patients referred for genetic counseling, leading to a potential selection bias toward families with a more substantial family history of cancer. The cohort primarily comprised Caucasian females of European descent, and thus may not represent the broader population. Although high proportions of our cohort had appropriate genetic testing, not all the patients in the cohort were tested, so a hereditary syndrome cannot be excluded in the entire cohort. Due to the retrospective nature of the study, endoscopy and pathology reports may not be complete.

In conclusion, we found that patients with a history of CRC in both parents developed CRC at an incidence rate similar to historical populations with 1 FDR with CRC.

Individuals who developed CRC significantly delayed their initial colonoscopy compared to those who did not develop CRC. Adherence to existing guidelines to initiate colonoscopy at age 40 for a family history of CRC would be appropriate for these individuals.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2022.07.018.

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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

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Data are unavailable due to patient privacy restrictions and the absence of consent for public sharing.