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Advanced Stage Colorectal Cancer in Persons Younger Than 50 Years not Associated With Longer Duration of Symptoms or Time to Diagnosis

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Abstract

Background & Aims—The incidence of colorectal cancer (CRC) is increasing in the United States (US) among adults under the age of 50 years. Studies of young-onset CRC have focused on outcomes and treatment patterns. We examined patient presentation, provider evaluation, and time to diagnosis, which can affect stage and prognosis.

Methods—In a retrospective study, we collected data from patients with a diagnosis of colorectal adenocarcinoma, confirmed by pathologists, seen at the Stanford Cancer Institute from January 1, 2008 through December 31, 2014. We compared symptoms, clinical features, time to diagnosis, and cancer stage in patients with young-onset CRC (diagnosed at an age younger than 50 years, n=253) vs patients diagnosed with CRC at an age of 50 years or older (n=232).

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Results—A higher proportion of patients with young-onset CRC were diagnosed with advanced-stage tumors (72%) compared with older patients (63%) ($P=.03$). Larger proportions of patients with young-onset CRC also had a family history of CRC (25% vs 17% in older patients; $P=.03$), confirmed or probable hereditary cancer syndromes (7% vs 1% in older patients, $P<.01$), and left-sided disease (distal colon cancer in 41% vs 34% in older patients; $P=.01$ and rectal cancer in 40% vs 35% in older patients; $P=0.29$). Patients with young-onset CRC had a significantly longer median time to diagnosis (128 vs 79 days for older patients; $P<0.05$), symptom duration (60 vs 30 days for older patients; $P<.01$), and time of evaluation (31 vs 22 days; $P<.05$). In multivariable analyses, time to diagnosis was 1.4-fold longer for younger than for older patients ($P<.01$). Among younger patients, those with stage III or IV CRC had shorter durations of symptoms and evaluations than those with stage I or II CRC.

Conclusion—In a retrospective analysis of patients with CRC, we found that greater proportions of patients younger than 50 years were diagnosed with advanced stage tumors than older patients; this difference could not be explained simply by delays from symptom onset to diagnosis. Although tumor biology may be an important determinant of stage at diagnosis, clinicians should be aware of CRC alarm symptoms, family history, and genetic Syndromes, to speed evaluation and diagnosis of younger patients and potentially improve outcomes. It remains to be determined whether subgroups of persons at risk for young-onset CRC who benefit from early screening can be identified.

Keywords

colon cancer; detection; epidemiology; work-up

INTRODUCTION

Colorectal cancer (CRC) remains the third most common cancer and third most common cause of cancer death in the US in both men and women.¹ A decrease in overall CRC incidence in the US has been attributed in part to screening at ages 50 and over.² However, CRC incidence has increased in younger adults, for whom average-risk screening is not recommended.³ SEER data indicate that 15% of patients diagnosed with CRC are under the age of 50, with a mean age of 42.5 years.⁴ Based on current trends, colon and rectal cancer incidence rates are projected to increase, respectively, by 90.0% and 124.2% for patients ages 20–34, and by 27.7% and 46.0% for patients ages 35–49 years by 2030.⁵ The loss of loved ones to early-onset CRC has spurred advocacy supporting CRC screening and research.⁶

Initial studies of young-onset CRC focused on treatment patterns, genetics, and outcomes, noting a propensity to treat this population more aggressively, and reporting inconsistent results on disease-specific survival.^{4, 7–9} It has been postulated that this population tends to present late with respect to symptom development, which may explain the more advanced stage distribution observed at diagnosis.^{5, 10} Sporadic mutations in young persons may cause more biologically aggressive tumor phenotypes, with hereditary CRC syndromes only accounting for approximately 15% of young-onset CRCs.^{11–17} Some studies have explored features of CRC presentation in younger patients,^{18–21} including the potential influence of health insurance¹⁰ and racial background.²²

It is unclear whether more timely presentation by patients or more expeditious workup by physicians could improve the outcomes of young persons with CRC. This study highlights the patient perspective from initial symptom onset to diagnosis in an effort to identify factors affecting timely management and stage at diagnosis. We undertook a single-institution cohort study to 1) examine the type and duration of presenting symptoms and time to diagnosis in younger vs. older patients with CRC, and 2) identify factors associated with time to diagnosis and stage at diagnosis. We hypothesized that symptom duration and workup period would be longer in our younger cohort, and that these longer periods would be associated with more advanced stage at diagnosis.

METHODS

Study Design, Data Sources and Study Cohort

The Stanford University Institutional Review Board approved this study. We used the Stanford Cancer Institute Research Database (SCIRDB) (<http://med.stanford.edu/biostatistics/dcc/sccrdb.html>) to identify all patients with a diagnosis of colorectal adenocarcinoma, confirmed by Stanford pathologists, who were seen at the Stanford Cancer Institute between January 1, 2008 and December 31, 2014, including patients referred from inside or outside Stanford's primary care network. We excluded patients with adenocarcinoma in situ, appendiceal cancer, or recurrent cancer.

We conducted a retrospective chart review of all patients < 50 years of age at time of CRC diagnosis (young-onset), and of a random sample of a comparable number of patients 50 years of age at time of diagnosis who were not diagnosed with CRC as a result of age-appropriate screening.

We extracted initial symptoms, symptom duration, setting, and date of first medical visit, family history, history of inflammatory bowel disease (IBD), and number of subsequent clinic visits prior to diagnosis. For patients with multiple initial symptoms, we selected as chief presenting symptom the symptom that prompted the consultation, based on clinical notes. All abstracted data were maintained in a REDCap (<https://redcap.stanford.edu>) database. Patients with insufficient information regarding initial symptoms, symptom duration, or date of first medical visit were excluded from the analytic cohort. Date of birth, date of diagnosis, date of death (if applicable), demographic features, histology, tumor site, stage at diagnosis, marital status, diagnosis of hereditary cancer syndromes, and insurance status were obtained from compiled information in the SCIRDB.

Outcomes and Definitions

Our primary outcome was time to diagnosis, which was defined as the sum of symptom duration and workup duration. Symptom duration was defined as the patient's self-reported length of chief presenting symptom at the time of initial visit, as documented in the clinical record. For the patients who were identified incidentally (e.g. anemia or abnormal imaging), symptom duration was set to zero days. Workup duration was defined as the number of days from first medical visit to date of pathologic diagnosis.

Our secondary outcomes were symptom duration, workup duration and stage at diagnosis. Possible colorectal cancer symptoms were defined as hematochezia, melena, abdominal pain, fatigue, weight loss, constipation, diarrhea, and other changes in bowel habits. Non-specific symptoms were defined as nausea/emesis, bloating/gas, and other. Stages I and II were defined as non-advanced and Stages III and IV as advanced.

Right-sided colon cancers were identified as sites involving the cecum, ascending colon, hepatic flexure, and transverse colon. Left-sided colon cancers were identified as sites involving the splenic flexure, descending colon, sigmoid colon, and rectosigmoid. Family history of CRC was defined as the presence of a first-degree, second-degree, and/or third-degree relative with CRC.

Patients with suspected hereditary cancer syndromes based on abnormal tumor immunohistochemistry or clinical impression were classified as “confirmed,” “probable,” “possible” or “Lynch Syndrome excluded” as defined and shown in Table 1.

Statistical Analysis

We compared demographic and clinical features between younger and older patients using chi-square tests (or Fisher’s exact test for variables with small counts) for categorical variables. For time to diagnosis, symptom and workup duration, we calculated medians and interquartile ranges (IQR), and compared distributions by age group using the Wilcoxon rank-sum test. Spearman’s correlation coefficient was used to estimate the correlation between symptom and workup duration. We compared the proportion of hematochezia and abdominal pain by cancer site and age group using the Cochran-Mantel-Haenszel test. We conducted univariable analyses, using the Wilcoxon rank-sum test, for time to diagnosis for each variable listed below, separately for each age group, to determine if there was an association between time to diagnosis and the variable for each age group.

Our primary objective was to assess if there was a significant difference in time to diagnosis between younger and older patients. We fit a linear regression model using log-transformed time to diagnosis as the outcome, and age group, sex, ethnicity, family history of CRC, diagnosis of confirmed or probable genetic syndrome, IBD, setting of first medical visit, and symptom type (CRC, non-specific, incidental discovery) as predictors. For our secondary outcomes of symptom duration and workup duration, we fit a multivariate linear regression model using log-transformed symptom and workup durations as the outcomes, and the variables listed above as predictors. To enable ease of interpretation, we exponentiated the estimates of our models to present odds ratios and 95% confidence intervals.

We assessed if there was a differential association between time to diagnosis, symptom or workup duration, and stage of disease (advanced or non-advanced) by age group. For time to diagnosis, we fit a linear regression model using log-transformed time to diagnosis as the outcome, and age group, stage of disease and the interaction between age group and stage of disease as predictors. For symptom and workup duration, we fit a multivariate linear regression model using a similar approach. For our secondary outcome of stage of disease, we ran a multinomial logit model²³ with stage of disease as the outcome, and age group, sex,

family history of CRC, diagnosis of confirmed or probable genetic syndrome, IBD, setting of first medical visit, and symptom type as predictors.

All statistical tests were two-tailed using a significance level of 0.05. Analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Cohort Demographics and Clinical Features

We identified 1,759 patients (382 patients age < 50 years and 1,377 patients age ≥ 50 years) with colorectal tumors from SCIRDB (Figure 1). After review of records and application of exclusion criteria (Figure 1), our analytic cohort consisted of 253 patients age < 50 years and 232 patients age ≥ 50 years.

Younger and older patients were similar with respect to sex, race/ethnicity, marital status, BMI, cancer site and pre-existing IBD (Table 1). Younger patients were more likely than older patients to have advanced stage at diagnosis (72% versus 63%, $p=0.03$), any family history of CRC (25% versus 17%, $p=0.03$), and confirmed or probable hereditary cancer syndromes (7% versus 1%, $p<0.01$) (Table 1). Younger patients were more likely than older patients to have rectal cancer (40% versus 35%), but the difference did not reach statistical significance ($p=0.29$). Colon cancer site differed by age ($p=0.01$); younger patients were more likely to have left-sided colon cancer (41% versus 34%) and older patients were more likely to have right-sided colon cancer (29% versus 16%) (Table 1).

Most patients were first seen by a primary care provider (PCP) (Table 2). On average, younger patients had 27% more visits than older patients until diagnosis after initial PCP visit ($p=0.05$, Appendix Table 1). Most patients presented with one symptom but approximately a third presented with two symptoms (Table 2). The chief presenting symptom type (CRC, non-specific, incidental discovery) differed by age group ($p=0.04$); more patients in the older age group were discovered through an incidental finding (10% versus 5%). In both age groups, the most common chief presenting symptom was hematochezia in rectal cancer, and abdominal pain in colon cancer; there was a strong association between symptom and cancer site after adjusting for age group (Cochran-Mantel-Haenszel test $p<0.01$, Table 2).

Time to Diagnosis, Symptom Duration and Workup Duration

Time to diagnosis was highly skewed (Appendix Figure 1). Median time to diagnosis was significantly longer in the younger versus older age group (128 days [IQR 60–265] versus 79 days [IQR 31–184], $p<0.05$, Table 3). Symptom and workup durations were also skewed (Appendix Figure 2). Symptom and workup duration were slightly correlated overall (Spearman correlation coefficient $\rho=0.24$, $p<0.01$); but a significant correlation was not observed within groups (< 50 years: $\rho=0.07$, $p=0.27$; ≥ 50 years: $\rho=0.12$, $p=0.07$, Appendix Figure 2). Symptom durations were longer than workup durations, and both were significantly longer in patients with young-onset CRC (Table 3).

Predictors of Time to Diagnosis

In univariable analyses within each age group, time to diagnosis was not significantly associated with sex, family history, confirmed or probable hereditary cancer syndromes, or pre-existing IBD, but it was significantly associated with symptom type ($p<0.01$) and provider seen at first medical visit ($p<0.01$ for <50 years; $p=0.02$ for ≥ 50 years). Among patients < 50 years, median (IQR) days to diagnosis were 144 (89–275) when first seen by a primary care provider, 66 (24–194) when first seen in the emergency department visit, and 48 (18–228) when first seen by a specialist. Among patients ≥ 50 years, the respective days were 113 (46–210), 28 (6–121) and 63 (18–155).

In multivariable analyses, age group, type of medical provider seen at first visit and symptom type (CRC vs. non-specific symptoms) were significantly associated with time to diagnosis (Table 4). Time to diagnosis was 1.4-fold longer in patients < 50 years old compared with patients ≥ 50 years old ($p<0.01$).

Association Between Time to Diagnosis and Stage at Diagnosis

The longest time to diagnosis was observed among patients < 50 years old with non-advanced CRC at diagnosis (Stages I and II) followed by patients < 50 years old with advanced CRC at diagnosis (Stages III and IV) (median days: 174 versus 124, Figure 2). Both symptom duration and workup duration were shorter in those with advanced CRC compared to those with non-advanced CRC in the young-onset cohort (Figure 2). The association between symptom and workup duration by age group was not significantly different by stage at diagnosis (interaction p -value=0.54).

Predictors of Stage of Disease at Diagnosis

In multivariable analysis examining stage of disease, only age group was significantly associated with stage at diagnosis ($p=0.03$, Appendix Table 2). Younger patients with confirmed or probable Lynch syndrome tended to present with less advanced disease (Appendix Table 3).

DISCUSSION

Our study addresses timely questions related to CRC in younger patients. It explores in detail presenting symptoms, clinical features, time to diagnosis, and stage at diagnosis in a relatively large single-institution cohort.

Prior research has not traced in detail young patients' longitudinal experience from initial symptoms to first medical visit to CRC diagnosis. Two prior smaller studies examined time to diagnosis but did not capture workup period.^{18, 19} A larger retrospective study did not include an older comparison group or quantify time to diagnosis.²⁰ A separate study evaluated CRC patients under 65, but not specifically patients under age 50.²⁴

Our cohort's demographics reflect a typical academic cancer center, with an overall high proportion of patients with advanced cancer, as well as rectal cancer, which requires a multidisciplinary approach. Our results are consistent with previous reports of more advanced disease at time of diagnosis, and of a higher proportion of left-sided disease in

younger patients.^{4, 9, 10, 25} The mean age at diagnosis in our group of patients younger than 50 (41 years) was comparable to that reported in a recent study using SEER data (42.5 years).⁴ Our cohort is diverse, including representation of Hispanic (13%) and Asian (21%) patients, but includes few (2%) African-American patients.

In our study, 41% of the younger cohort presented with hematochezia as the chief presenting symptom, consistent with prior reports ranging from 26–51%.^{18, 19} Most younger and older patients (90% and 82%, respectively), presented with colorectal symptoms. However, these symptoms are not specific for neoplasia, and challenges remain in defining appropriate and timely workup. Patients with rectal cancer were more likely to present with hematochezia, while those with colon cancer were more likely to present with abdominal pain. In the appropriate context, it may be reasonable to consider a flexible sigmoidoscopy in younger patients with persistent hematochezia, particularly in resource-limited settings.

Our results confirm our first hypothesis that patients with young-onset CRC experience significantly longer symptom duration, longer workup duration, and thus longer total time to diagnosis. In our study, younger patients also had more advanced stage at diagnosis. Both symptom duration before seeking care and time from presentation to diagnosis are potentially modifiable.

However, contrary to our second hypothesis, younger patients with stage III or IV disease had shorter symptom and workup periods than those with stage I or II disease, suggesting that advanced stage at diagnosis is not explained simply by longer time to diagnosis. Nonetheless, it remains possible that more timely presentation by patients or more expeditious work up by clinicians could improve outcomes for young patients with CRC. A previous study found that in patients with possible CRC symptoms, workup duration < 5 weeks was associated with decreased mortality.²⁶

The overall mean total time to diagnosis was 200 days, longer than the range of 54 – 156 days reported in previous studies.^{18, 19} By age group, the periods that we observed were longer than those reported in Israel by Ben-Ishay et al, who also found that time to diagnosis was longer in younger patients.¹⁸ Our study extends the observations in prior studies^{18–20} by also capturing workup duration, in order to highlight the clinician's role in time to diagnosis.

Our finding that advanced stage at diagnosis does not seem to be explained simply by longer time to diagnosis suggests that biological factors may be important determinants of stage at diagnosis. Although we could not ascertain with confidence the symptom severity at presentation, it is possible that more severe symptoms in patients with more advanced disease could have led to more expeditious workup. It has been suggested that malignancies in young adults display a distinct biology.²⁷ Outcomes are affected by underlying biology as well as genetics.^{25, 28–30} Our findings suggest that greater patient and clinician awareness of CRC symptoms may not be enough to overcome underlying biological factors. Nonetheless, greater awareness of the rising incidence of young-onset CRC is warranted.

As might be expected, younger patients were more likely to have a family history of CRC, or a confirmed or probable diagnosis of a hereditary cancer syndrome, but confirmation of a genetic syndrome was rare, and in almost all cases it followed the diagnosis of CRC in the

young patient. Few young patients with CRC had inflammatory bowel disease. Thus, most young patients in our study did not have an identified indication for early screening. Having a first-degree relative with CRC approximately doubles a patient's risk of developing CRC.³¹ The Family History Task Group of the National Colon Cancer Roundtable (NCCRT) has recently recommended strategies for persons with familial risk, including improving the collection and utilization of family history.³² Additional strategies will be needed to address the problem of young-onset CRC in those without a family history of CRC, recognized cancer genetic syndromes, or inflammatory bowel disease.

Patients first seen by a primary care provider took longest to get diagnosed, but this does not necessarily reflect inappropriate care. One would expect shorter times to lower endoscopy after presentation to the emergency department (ED) or directly to a subspecialist. A greater proportion of older patients presented to the ED, consistent with data on utilization of ED services for gastrointestinal complaints by older patients.³³ Younger people may ascribe lower urgency to similar symptoms. We found a positive association between symptom duration and workup duration in our younger cohort. Although the available data did not allow a detailed analysis of symptom patterns, we observed that numerous young-onset CRC patients presented with acute on chronic symptoms, which may have contributed to longer workup duration if patients, clinicians or both did not initially appreciate the change in symptoms as significant.

Our study must be interpreted with caution given that our study was a single-institution, retrospective study, in a referral center setting. It is not clear if our single-institution results are representative of the population at large, or if the spectrum of disease could reflect a referral bias. Some patients were excluded because data on symptoms and presentation were not always complete. The chart notes regarding symptom durations may reflect recall bias by patients, and could be affected by the subjective nature of providers' history-taking and charting. Not all tumors underwent screening and not all patients underwent genetic testing, and thus some patients with inherited cancer syndromes might have been missed. CRCs in patients with Lynch syndrome have a faster progression from adenoma to CRC but tend to be diagnosed at earlier stages than sporadic CRCs. Thus, it is difficult to know how our observed symptom and workup durations are affected by the relatively small number of patients with confirmed Lynch Syndrome or those in whom an inherited cancer syndrome might have been missed. We acknowledge that this study's aims did not include discovery of novel genetic markers of risk, and that we could only examine clinical predictors that were available for data extraction.

Our cohort of patients with young-onset CRC experienced longer times to diagnosis, symptom duration, and workup duration than patients diagnosed with CRC at 50 years of age. Patients diagnosed with more advanced-stage CRC had shorter symptom duration and workup periods, which suggests that delay in diagnosis may not be a primary determinant of stage at diagnosis. It remains to be determined whether risk-stratification strategies can be developed to identify persons at risk for young-onset CRC, beyond those with a family history of CRC, a genetic cancer syndrome, or inflammatory bowel disease, who might benefit from earlier screening.

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Abbreviations

CRC	Colorectal cancer
SCIRDB	Stanford Cancer Institute Research Database
BMI	body mass index
IBD	inflammatory bowel disease
IQR	interquartile range
PCP	primary care provider
FDR	first degree relative
SDR	second degree relative
TDR	third degree relative

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APPENDIX

Appendix Figure 1: Distribution of log total time to diagnosis by age group.

Depicted as box and whisker plot in log days; shows right-skew distribution of data.

Appendix Figure 2: Distribution of log symptom duration and log workup duration.

Scatterplot with log symptom duration on x-axis and log workup duration on y-axis. Non-advanced stage (stage I or II) cases are shown in red circles and advanced stage (stage III or IV) cases are shown in blue circles. Spearman correlation coefficient for < 50 years age group for symptom duration and workup duration=0.07, p=0.27; for ≥ 50 years age group 0.12, p-value=0.07.

Symptom duration by work up duration, both age groups

Appendix Table 1

Number of subsequent medical visits

	Age < 50 years		Age ≥ 50 years		p-value
	N=253		N=232		
	N	%	N	%	
First medical visit type					
Emergency department	50	19.8	63	27.2	
Number of subsequent visits					
Mean (SD)	0.66 (0.87)		0.73 (1.0)		0.7
0	28		34		
1	13		18		
2	7		7		
3	2		2		
4	0		2		

	Age < 50 years		Age ≥ 50 years		p-value
	N=253		N=232		
	N	%	N	%	
Primary care provider	180	71.2	140	60.3	
Number of subsequent visits					
Mean (SD)	1.4 (1.3)		1.1 (1.0)		0.05
0	44		29		
1	61		80		
2	21		51		
3	14		4		
4	2		3		
5	1		0		
7	1		0		
8	2		1		
Unknown	4		2		
Non-primary care provider	23	9.1	26	11.2	
Number of subsequent visits					
Mean (SD)	0.8 (1.2)		1.1 (1.4)		0.43
0	13		11		
1	3		8		
2	4		3		
3	1		2		
4	1		1		
5	0		1		
Unknown	1		0		
Unknown	0	0	3	1.3	
Number of subsequent visits					
0	0		1		
1	0		2		

SD, standard deviation

Appendix Table 2

Multivariable multinomial logit analysis of predictors of stage of disease at diagnosis

	Stage of disease at diagnosis			
	IV vs. I	III vs. I	II vs. I	p-value
Age <50 years vs. ≥ 50 years	2.68 (1.38, 5.18)	2.47 (1.26, 4.84)	1.95 (0.96, 3.95)	0.03
Female vs. male	0.76 (0.41, 1.42)	0.81 (0.43, 1.52)	0.68 (0.35, 1.33)	0.72
Had CRC family history	0.82 (0.40, 1.69)	0.43 (0.20, 0.93)	0.50 (0.22, 1.13)	0.06
Had confirmed or probable hereditary cancer syndrome	1.39 (0.14, 14.09)	3.11 (0.32, 30.10)	6.16 (0.66, 57.59)	0.11
Had inflammatory bowel disease	0.13 (0.02, 0.81)	Not applicable	0.37 (0.07, 1.86)	0.18

	Stage of disease at diagnosis			p-value
	IV vs. I	III vs. I	II vs. I	
Setting of first encounter				0.14
ED v. non-PCP	3.24 (1.03, 10.18)	2.90 (0.85, 9.86)	1.57 (0.46, 5.32)	
PCP v. non-PCP	1.57 (0.59, 4.17)	2.31 (0.81, 6.59)	1.42 (0.51, 3.91)	
Chief presenting symptom type				0.49
CRC v. non-specific	1.24 (0.40, 3.82)	1.39 (0.43, 4.48)	4.88 (0.88, 27.13)	
Incidental discovery v. non-specific	0.72 (0.17, 3.09)	0.67 (0.14, 3.09)	3.60 (0.51, 25.33)	

Cancer genetic syndrome defined as confirmed or probable before or after CRC diagnosis.

ED, emergency department; PCP, primary care provider; CRC, colorectal cancer; SD, standard deviation.

Appendix Table 3

Relationship between stage of disease, family history and genetic syndromes in persons diagnosed with colorectal cancer before age 50.

	Non-advanced stage	Advanced stage	p-value
	N=72	N=181	
	N (%)	N (%)	
Any family history of CRC	19 (26)	44 (24)	0.75
Confirmed or probable hereditary cancer syndrome	7 (10)	10 (5)	0.27
Confirmed or probable Lynch Syndrome	6 (8)	5 (3)	0.08

Figure 1.
Study cohort.

Figure 2.
Median symptom and workup durations by age and stage.

Table 1

Demographic and clinical characteristics of patients with colorectal cancer

	Age < 50 years		Age ≥ 50 years		p-value
	N=253		N=232		
Age (years)					
Mean (SD)	41 (7.1)		68 (11)		< 0.001
Median (IQR)	43 (38–47)		67 (59–75)		
	N	%	N	%	
Sex					0.21
Female	119	47	96	41.4	
Male	134	53	136	58.6	
Race/Ethnicity					0.48
Hispanic	35	13.8	27	11.6	
NH Asian	51	20.2	49	21.1	
African American	4	1.6	7	3	
NH Other	27	10.7	15	6.5	
NH Unknown	6	2.4	5	2.2	
NH Caucasian	130	51.4	129	55.6	
Marital Status					0.19
Married/Partner	176	69.6	147	63.4	
Unmarried	77	30.4	83	35.8	
Unknown	0	0	2	0.9	
Body-Mass Index (BMI)					

	Age < 50 years	Age 50 years	p-value
	N=253	N=232	
Normal	25	49	0.14
Obese	14	13	5.6
Overweight	9	31	13.4
Underweight	3	1	0.4
Unknown	202	138	59.5
Stage at diagnosis			0.03
Not advanced	72	87	37.5
Stage I	20	38	16.4
Stage II	52	49	21.1
Advanced	181	145	62.5
Stage III	86	70	30.2
Stage IV	95	75	32.3
Cancer Site			0.29*
Colon	153	151	65.1
Right	41	66	28.5
Left	103	78	33.6
NOS	9	7	3.0
Rectal	100	81	34.9
Any Family History of CRC	63	39	16.8
1 FDR	17	22	9.5

**

0.01

	Age < 50 years	Age 50 years	p-value
	N=253	N=232	
0 FDR, 1 SDR	40	13	5.6
0 FDR, 0 SDR, 1 TDR	6	4	1.7
Suspected hereditary cancer syndrome	18	6	0.02
Confirmed Syndrome [^] FAP (APC gene)	3	0	
Lynch Syndrome (MLH1, MSH2, MSH6, PMS2, or EPCAM gene)	6	2	
MYH-associated Polyposis (MYH gene)	1	0	
Li-Fraumeni Syndrome (p53 gene)	1	0	
Probable Lynch Syndrome ^o /FAP ^o	5 / 1	0 / 0	
Possible Lynch Syndrome ^{oo}	0	3	
Ruled Out Lynch Syndrome ^{ooo}	1	1	
Confirmed or probable hereditary cancer syndrome	17	2	0.0009
Diagnosed prior to cancer diagnosis	1	0	
Diagnosed after cancer diagnosis	16	2	
Had pre-existing IBD	6	3	0.51
Year of Diagnosis			0.14
2008	22	23	9.9
2009	22	31	13.4

	Age < 50 years	Age 50 years	p-value
	N=253	N=232	
2010	46	35	15.1
2011	42	30	12.9
2012	50	36	15.5
2013	36	50	21.6
2014	35	27	11.6
Deceased	74	78	33.6
Insurance Type			0.3
EPO	36	9	3.9
Government	48	128	55.2
HMO	25	21	9.1
PPO	131	48	20.7
Other	13	26	11.2

* Comparing colon versus rectal

** Comparing cancer location (left, right, NOS, rectal)

[^] Confirmed hereditary syndrome based on available evidence of pathogenic germline mutation

^o Probable Lynch Syndrome based on abnormal IHC and pedigree suggestive of Lynch Syndrome, or secondary records referencing a germline mutation

^o Probable FAP based on polyposis phenotype without an identified mutation, or secondary records referencing a germline mutation

^{oo} Possible Lynch Syndrome based on abnormal IHC but pedigree not suggestive of Lynch syndrome

^{ooo} Ruled out Lynch Syndrome based on abnormal IHC but germline testing normal and pedigree not suggestive of Lynch Syndrome

CRC, colorectal cancer; FDR, first-degree relative; SDR, second-degree relative; TDR, third-degree relative; IBD, inflammatory bowel disease; IHC, immunohistochemistry; FAP, Familial Adenomatous Polyposis; EPO, exclusive provider organization; HMO, health maintenance organization; PPO, preferred provider organization.

Table 2

Presentation and clinical features by age group and cancer type

	Age < 50 years		Age 50 years		p-value
	N=253		N=232		
	N	%	N	%	
First Medical Visit Type					
Emergency department	50	19.8	63	27.2	0.06
Primary care provider	180	71.2	140	60.3	
Non-primary care provider	23	9.1	26	11.2	
Unknown	0	0	3	1.3	
Total Number of Symptoms					0.68
1	134	53.0	134	57.8	
2	80	31.6	63	27.2	
3	29	11.5	26	11.2	
4	10	4.0	9	3.9	
Chief Presenting Symptom/Factor					<0.01 *
Colon cancer (n=304)					
Hematochezia	44	28.8	35	23.2	
Abdominal pain	63	41.2	41	27.2	
Other					
Melena	2	1.3	5	3.3	
Fatigue	8	5.2	10	6.6	
Weight loss	3	2.0	2	1.3	
Constipation	6	3.9	11	7.3	
Diarrhea	9	5.9	7	4.6	
Other changes in bowel habits	0	0	4	2.7	
Nausea/Emesis	2	1.3	3	2.0	
Bloating/Gas	5	3.3	3	2.0	

	Age < 50 years N=253		Age ≥ 50 years N=232		p-value
	N	%	N	%	
Other non-specific symptoms	3	2.0	8	5.3	
Incidental discovery	8	5.2	22	14.6	
Rectal cancer (n=181)					
Hematochezia	60	60.0	48	59.3	
Abdominal pain	15	15.0	6	7.4	
Other					
Melena	0	0	0	0	
Fatigue	0	0	1	1.0	
Weight loss	3	2.3	1	1.0	
Constipation	6	6.0	5	6.2	
Diarrhea	6	6.0	10	12.4	
Other changes in bowel habits	3	2.3	5	6.2	
Nausea/Emesis	0	0	0	0	
Bloating/Gas	0	0	1	1.0	
Other non-specific symptoms	2	1.5	3	3.7	
Incidental discovery	5	5.0	1	1.0	

* Cochran-Mantel-Haenszel test $p < 0.01$ comparing hematochezia, abdominal pain and other by cancer type, adjusting for age group

Table 3

Time to diagnosis, symptom and workup duration by age group

	Age < 50 years	Age ≥ 50 years
	N=253	N=232
Total Time to Diagnosis (days) *		
Mean (SD)	243 (465.2)	154 (236.8)
Median (IQR)	128 (60–265)	79 (31–184)
Symptom Duration (days) **		
Mean (SD)	152 (334.2)	87 (151.3)
Median (IQR)	60 (30–180)	30 (7–120)
Workup Duration (days) *		
Mean (SD)	91 (232.4)	67 (183.2)
Median (IQR)	31 (10–79)	22 (6–62)

** Wilcoxon rank sum test two-sided $p < 0.01$

* Wilcoxon rank sum test two-sided $p < 0.05$

Workup duration was the days from first medical visit to diagnosis

Table 4

Multivariable regression results by time to diagnosis, symptom duration and workup duration

	Time to diagnosis [^]	Symptom duration ^{^^}	Work-up duration ^{^^}
	Estimate (95% confidence interval)		
Age < 50 years vs. 50 years	1.4 (1.1–1.8) [*]	1.4 (1.1–1.8) ^{***}	1.3 (1.0–1.7)
Female vs. male	1.2 (1–1.5)	1.2 (0.9–1.5)	1.5 (1.1–2.0) ^{***}
Hispanic vs. White	1.2 (0.8–1.7)	1.1 (0.8–1.7)	1.2 (0.8–2.0)
Asian vs. White	0.9 (0.7–1.2)	0.9 (0.7–1.3)	0.9 (0.6–1.4)
African American vs. White	0.9 (0.4–2.1)	0.5 (0.2–1.1)	2.4 (0.9–6.6)
Other vs. White	1.1 (0.8–1.7)	0.9 (0.6–1.4)	2.1 (1.3–3.6) [*]
Had CRC family history	1.0 (0.7–1.3)	1.0 (0.8–1.4)	1.0 (0.7–1.5)
Had confirmed or probable hereditary cancer syndrome	0.7 (0.4–1.3)	0.8 (0.4–1.6)	0.4 (0.2–0.9) ^{****}
Had inflammatory bowel disease	1.0 (0.4–2.3)	0.4 (0.2–1.1)	1.4 (0.5–4.0)
First visit ED vs. non-PCP	0.5 (0.3–0.8) [*]	0.3 (0.2–0.6) [*]	0.5 (0.3–0.9) ^{****}
First visit PCP vs. non-PCP	1.8 (1.2–2.7) [*]	1.4 (0.9–2.3)	2.1 (1.2–3.5) ^{***}
CRC symptoms vs. non-specific symptoms	1.7 (1.1–2.9) ^{****}	1.9 (1.1–3.1) ^{****}	1.3 (0.7–2.4)
Incidental discovery vs. non-specific symptoms	0.8 (0.4–1.5)	0.04 (0.02–0.09) [*]	2.4 (1.1–5.4) ^{**}
R ² [‡]	22%	44%	17%

[^] Multivariable linear regression model^{^^} Multivariate, multivariable linear regression model^{*} p<0.01^{**} p=0.03^{***} p=0.01^{****} p=0.02[‡] Amount of variation explained by the model

Results presented after transforming back to original scale

CRC, colorectal cancer; ED, emergency department; PCP, primary care provider