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Original article

Early-onset Colorectal Cancer: A Study in a Colombian Population

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Abstract

Introduction: Colorectal cancer (CRC) is the third most common cancer in terms of incidence and the second cause of death secondary to cancer. Early-onset CRC accounts for about 10% of cases and carries a higher mortality than that seen in older patients. We analyze the association between age and the clinical, endoscopic, and histopathological characteristics of CRC at the time of diagnosis in a Latin American population. **Methods:** A cross-sectional study was conducted using the database of the Gastroenterology Service of Clínica Foscal and Clínica Foscal Internacional in Bucaramanga, Colombia. **Results:** Between July 2016 and June 2021, 521 cases of *de novo* adenocarcinoma-type CRC were diagnosed, of which 77 patients (14.7%) were under 50. In patients with early-onset CRC, the prevalence of CRC was higher in women. Family history of CRC was more common in patients younger than 50 years. Hereditary syndromes, particularly familial adenomatous polyposis and hereditary non-polyposis CRC, were also more frequent in the youth. Histopathologically, mucinous adenocarcinoma and signet ring cell adenocarcinoma were more common in young patients. **Conclusions:** The study showed an approach to the characteristics of early-onset CRC in a Latin American population. Increasing the prevention, control, and early detection of CRC in young people is necessary to improve diagnosis and treatment.

Keywords

Colorectal neoplasms, colon neoplasms, early onset, Colombia.

INTRODUCTION

Colorectal cancer (CRC) ranks as the third most prevalent cancer globally, accounting for approximately 1,931,590 new cases annually, and emerges as the second leading cause of cancer-related mortality, claiming 935,173 lives each year[(1)]. The incidence and mortality rates exhibit significant disparities across different nations. High-income countries report markedly high CRC-associated death rates; conversely, developing countries are witnessing a rise in both incidence and mortality rates linked to CRC[(2)]. According to the 2020 GLOBOCAN (Global Cancer Statistics) report, Colombia is experiencing an age-standardized incidence rate of 13.7 cases per 100,000 individuals, coupled with an age-standardized mortality rate of 6.3 cases per 100,000 individuals[(3)].

CRC, particularly the adenocarcinoma type, arises from the aberrant proliferation of glandular epithelial cells. These occurrences may be categorized as sporadic, hereditary, or

colitis-associated[2]. A blend of hereditary and environmental elements drives carcinogenesis, with microsatellite instability, chromosomal instability, and the CpG island methylator phenotype standing out as the most significant oncological genetic factors[4]. A comprehensive risk-modeling meta-analysis highlighted the association between inflammatory bowel disease, a history of CRC in first-degree relatives, and a substantially increased risk of CRC development. Furthermore, factors like obesity, consumption of red meat, smoking, reduced physical activity, and low intake of vegetables and fruits were linked to a moderately elevated risk[5].

Early-onset colorectal cancer (EOCRC) is identified in patients younger than 50 years[6]. Recent decades have observed a simultaneous global rise in EOCRC incidence alongside a decline in late-onset CRC cases and mortality, thereby lowering the average age at diagnosis from 72 in the early 2000s to 66 years presently[7]. This epidemiological trend has drawn significant attention from the scientific community, with a near 30% spike in the global incidence of EOCRC over the past 20 years, now constituting around 10% of all CRC cases[6,8].

Consequently, this study aims to explore the relationship between age and the clinical, endoscopic, and histopathological features of CRC at diagnosis within a Latin American population.

MATERIALS AND METHODS

Patient Selection

This study was a retrospective, descriptive cross-sectional analysis, utilizing the database from the Department of Gastroenterology at Clínica Foscal and Clínica Foscal Internacional, located in Bucaramanga, Colombia. Between July 1, 2016, and June 30, 2021, a total of 10,708 colonoscopies were performed for various medical indications, encompassing both inpatient and outpatient scenarios. Conducted in accordance with the Declaration of Helsinki's ethical standards, the study received approval from the institutional ethics committees.

Participants included in the study were individuals aged 18 and above with no prior diagnosis of CRC, who underwent colonoscopy based on recommendations from the emergency service, the hospital medical team, or through outpatient service. Exclusion criteria ruled out individuals previously diagnosed with CRC, those with CRC but with non-adenocarcinoma histology, individuals infected with the human immunodeficiency virus (HIV), recipients of solid organ or hematopoietic precursor transplants, and those under active treatment with immunosuppressive medications. The sample size calculation was influenced by the study conducted by Álvarez and colleagues[9], considering a significance level (alpha) of 0.05 and a statistical power of 80%. With a 33.4% prevalence in the exposed group and 48.6% in the unexposed group, alongside an exposed to unexposed ratio of 5 to 1, the calculation yielded a minimum sample size of 89 exposed and 446 non-exposed participants, totaling 534 individuals.

Data for the study were extracted from the electronic health records of both institutions. Variables of interest included sociodemographic details (age, sex), risk factors for CRC development (family history of CRC, inflammatory bowel disease, obesity, diabetes *mellitus*, tobacco and alcohol use, and hereditary syndromes linked to CRC). Diagnoses of hereditary non-polyposis colorectal cancer were established using the Amsterdam II criteria. In contrast, diagnoses of familial adenomatous polyposis were confirmed through the identification of either 100 or more adenomatous polyps in the colon and rectum or fewer than 100 polyps with a confirmed family history of familial adenomatous polyposis[10,11]. The study also considered clinical symptoms reported by patients during the colonoscopy, endoscopic macroscopic findings such as the anatomical lesion location and observed endoscopic patterns (e.g., protruding lesions, ulceration, annular stenosing), tumor staging according to the Eighth Edition of the American Joint Committee on Cancer's Staging Manual[12], and histopathological characteristics of the lesion, including histological subtype and tumor differentiation grade.

Statistical Analysis

A descriptive univariate analysis was performed for clinical, endoscopic, and histopathological variables. Quantitative variables were presented using central tendency and dispersion measures (median and interquartile range [IQR]), due to their non-normal distribution. Qualitative variables were characterized by absolute and relative frequencies. Furthermore, a bivariate analysis was undertaken, wherein each database variable was stratified and subjected to the appropriate statistical tests (χ^2 test or Fisher's exact test).

Age was employed as a dichotomous independent variable (categorized from 50 years of age) to calculate the prevalence ratio (PR) of CRC among patients younger than 50 years for each clinical, endoscopic, and histopathological feature, accompanied by its respective confidence interval. A significance level of $\alpha = 0.05$ was applied across all comparative analyses. The entire analytical process was executed using Stata 14 statistical software.

RESULTS

During the period from July 1, 2016, to June 30, 2021, a total of 538 *de novo* cases of CRC were identified. Seventeen

cases were excluded due to a non-adenocarcinoma histology (comprising 10 neuroendocrine carcinomas, 6 lymphomas, and 1 sarcoma), leaving 521 cases eligible for inclusion in the study. The median age at the time of diagnosis was established at 66 years, with an interquartile range (IQR) spanning from 57 to 76 years. Of these patients, 77 (14.7%) were younger than 50 years, while 444 (85.2%) were 50 years or older. Sex analysis revealed a slight female predominance in CRC diagnoses (55.28% compared to 44.72%), with similar proportions observed among both below and above 50-year-old patient groups. Statistically significant findings indicated a higher prevalence of family history of CRC and associated genetic syndromes in patients under 50 years old diagnosed *de novo* with CRC. Likewise, the incidence of clinical histories such as obesity, diabetes *mellitus*, and smoking was statistically more prevalent in the older patient cohort. The most commonly reported symptoms at the time of colonoscopy included gastrointestinal bleeding (69.29%), abdominal pain (59.5%), weight loss (57.01%), anemia (55.09%), and constipation (34.17%). Detailed patient clinical characteristics are further delineated in **Table 1**.

In the performance of colonoscopy, the anatomic sites where a higher incidence of tumor lesions was noted in the general population included the rectum (n = 166,

Table 1. Clinical Characteristics and Their Association with Colorectal Cancer Prevalence in Patients Under 50 Years of Age

Characteristics	Total n = 521 (100%)	< 50 Years n = 77 (14.7%)	≥ 50 Years n = 444 (85.2%)	p-Value	Prevalence Ratio (95% CI)	p-Value
Sex						
Female	288 (55.28)	44 (57.14)	244 (54.95)	0.409	Reference	
Male	233 (44.72)	33 (42.86)	200 (45.05)		0.92 (0.61-1.40)	0.722
Background						
Family History of CRC	46 (8.83)	22 (28.57)	24 (5.41)	**< 0.001**	4.13 (2.79-6.10)	**< 0.001**
Familial Adenomatous Polyposis	6 (1.15)	3 (3.90)	3 (0.68)	**< 0.001**	3.64 (1.58-8.34)	0.002
Non-Polyposis Hereditary CRC	5 (0.96)	4 (5.19)	1 (0.23)		5.82 (3.57-9.50)	**< 0.001**
Crohn's Disease	1 (0.19)	-	1 (0.23)	0.770	-	-
Ulcerative Colitis	2 (0.38)	-	2 (0.45)			
Obesity	201 (38.58)	13 (16.88)	188 (42.34)	**< 0.001**	0.32 (0.18-0.57)	**< 0.001**
Diabetes *mellitus*	98 (18.81)	4 (5.19)	94 (21.17)	**< 0.001**	0.23 (0.08-0.63)	**0.004**
Smoking	130 (24.95)	11 (14.29)	119 (26.80)	**0.01**	0.50 (0.27-0.91)	**0.026**
Alcoholism	68 (13.05)	12 (15.58)	56 (12.61)	0.290	1.22 (0.70-2.15)	0.469
Signs and Symptoms						
Constipation	178 (34.17)	35 (45.45)	143 (32.21)	**0.044**	1.48 (0.96-2.26)	0.071
Diarrhea	72 (13.82)	6 (7.79)	66 (14.86)		0.62 (0.27-1.43)	0.268
Abdominal Pain	310 (59.50)	51 (66.23)	259 (58.33)	0.119	1.33 (0.86-2.07)	0.197
Rectal Pain	108 (20.73)	22 (28.57)	86 (19.37)	**0.049**	1.52 (0.97-2.39)	0.062
Gastrointestinal Bleeding	361 (69.29)	54 (70.13)	307 (69.14)	0.498	1.04 (0.66-1.63)	0.863
Anemia	287 (55.09)	47 (61.04)	240 (54.05)	0.155	1.27 (0.83-1.95)	0.258
Narrow Stools	80 (15.06)	17 (22.08)	63 (14.19)	0.059	1.56 (0.96-2.53)	0.070
Weight Loss	297 (57.01)	43 (55.84)	254 (57.21)	0.459	0.95 (0.62-1.44)	0.823
Palpable Abdominal Mass	49 (9.40)	10 (12.99)	39 (8.78)	0.168	1.43 (0.79-2.60)	0.232
Intestinal Obstruction	48 (9.21)	6 (7.79)	42 (9.46)	0.415	0.83 (0.38-1.81)	0.645
Ascites	17 (3.26)	1 (1.30)	16 (3.60)	0.256	0.60 (0.15-2.30)	0.335

CRC: colorectal cancer; CI: confidence interval. Author's own research

31.86%), the sigmoid colon (n = 108, 20.73%), and the ascending colon (n = 103, 19.77%). This study observed a predominance of exophytic tumor lesions (n = 362, 69.48%) as compared to constricting annular lesions (n = 159, 30.52%). Tumor staging was conducted according to the Eighth Edition of the American Joint Committee on Cancer's Staging Manual, with a majority of patients classified as stage III (n = 177, 33.97%), followed by stages IV (n = 163, 31.29%) and II (n = 128, 24.57%). No statistical difference was found regarding tumor location, endoscopic pattern of the lesion, or tumor staging between patients under and over the age of 50.

The study population was limited to patients diagnosed with adenocarcinoma-type CRC. The conventional adenocarcinoma subtype was the most prevalent in both age groups, being significantly more common in the group aged over 50 (84.91% vs. 51.95%, $p < 0.001$). The younger group more frequently exhibited histological subtypes such as mucinous adenocarcinoma (27.27% vs. 13.29%; $p < 0.001$) and signet ring cell adenocarcinoma (20.78% vs. 1.8%; $p < 0.001$). Additionally, moderately differentiated adenocarcinomas were more predominant among patients aged 50 or older (69.98% vs. 64.94%), followed by well-differentiated adenocarcinomas (23.93% vs. 18.18%). In contrast, poorly differentiated adenocarcinomas were more commonly reported in patients younger than 50 years (16.88% vs. 6.09%; $p = 0.004$). Complementary information detailing endoscopic, neoplastic, and histological features is outlined in **Table 2**.

Table 2. Endoscopic, Neoplastic, and Histological Features in Conjunction with the Prevalence Ratio for Colorectal Cancer in Patients up to 50 Years of Age

Characteristics	Total n = 521 (100%)	< 50 Years n = 77 (14.7%)	≥ 50 Years n = 444 (85.2%)	p-Value	Prevalence Ratio (95% CI)	p-Value
Endoscopic Localization						
Cecum	46 (8.83)	3 (3.90)	43 (9.68)	0.396	Reference	
Ascending Colon	103 (19.77)	14 (18.18)	89 (20.05)		2.08 (0.62-6.90)	0.229
Transverse Colon	32 (6.14)	5 (6.49)	27 (6.08)		2.39 (0.61-9.31)	0.207
Descending Colon	27 (5.18)	5 (6.49)	22 (4.95)		2.83 (0.73-10.9)	0.13
Sigmoid	108 (20.73)	22 (28.57)	86 (19.37)		3.12 (0.98-9.92)	0.053
Rectum	166 (31.86)	24 (31.17)	142 (31.98)		2.21 (0.69-7.03)	0.177
Rectosigmoid Junction	39 (7.49)	4 (5.19)	35 (7.88)		1.57 (0.37-6.60)	0.536
Endoscopic Pattern of the Lesion						
Exophytic	362 (69.48)	54 (70.13)	308 (69.37)	0.505	Reference	
Annular Stenosing	159 (30.52)	23 (29.87)	136 (30.63)		0.96 (0.61-1.52)	0.894
Tumor Stage (according to the Eighth Edition of the American Joint Committee on Cancer's Staging Manual)						
0	5 (0.96)	-	5 (1.13)	0.209	-	-
I	48 (9.21)	3 (3.9)	45 (10.14)		0.39 (0.12-1.23)	0.111
II	128 (24.57)	16 (20.78)	112 (25.23)		0.78 (0.43-1.39)	0.409
III	177 (33.97)	32 (41.56)	145 (32.66)		1.13 (0.70-1.81)	0.603
IV	163 (31.29)	26 (33.77)	137 (30.86)		Reference	
Histological Subtype of Adenocarcinomas						
Conventional	417 (80.04)	40 (51.95)	377 (84.91)	**< 0.001**	0.36 (0.22-0.58)	**< 0.001**
Mucinous	80 (15.36)	21 (27.27)	59 (13.29)		Reference	
Signet Ring Cells	24 (4.61)	16 (20.78)	8 (1.80)		2.53 (1.59-4.03)	**< 0.001**
Histological Differentiation						
Well Differentiated	120 (23.08)	14 (18.18)	106 (23.93)	**0.004**	Reference	
Moderately Differentiated	360 (69.23)	50 (64.94)	310 (69.98)		1.19 (0.68-2.07)	0.538
Poorly Differentiated	40 (7.69)	13 (16.88)	27 (6.09)		2.78 (1.43-5.41)	**0.003**

Author's own research.

DISCUSSION

The issue of EOCRC is of increasing public health significance. Despite overall declines in both incidence and mortality of CRC due to enhanced screening efforts, there has been a marked rise in both metrics among individuals under 50 globally[13,14]. Specifically, EOCRC has seen an annual increase of 1%-2% since the 1990s, with an even sharper 3.8% annual rise among those aged 20 to 29 since 1987[15]. Our investigation found that 14.7% (n = 77) of the *de novo* CRC cases were patients under 50, with a higher incidence among females (n = 44, 57.14%). Previous estimates in Colombia place EOCRC between 17% and 26% of all CRC cases[16,17], while a Chilean study by Álvarez and colleagues[9] found that 17% (n = 72) of CRC patients were under 50, with females accounting for 54.2% (n = 39) of these cases. These figures suggest that EOCRC prevalence in South America exceeds that reported in developed countries. Projections for the United States indicate that by 2030, 10.9% of colon cancers and 22.9% of rectal cancers will be diagnosed in individuals under 50 — a significant increase from 4.8% and 9.5%, respectively, in 2010[18]. Notably, the prevalence of EOCRC differs between sexes, with a higher occurrence in females in South America, contrasting global trends where EOCRC is more commonly seen in males[15,19].

CRC diagnosed before the age of 50 is strongly linked to family history of the disease or related hereditary syndromes[20]. Our data showed that EOCRC patients had almost a fourfold increase in likelihood of having a familial CRC history compared to those with late-onset CRC. Gausman and colleagues[21] included 269 EOCRC patients, 2802 with late-onset CRC, and 1122 controls, highlighting that EOCRC patients were eight times more likely to report a family history of CRC than controls, and nearly triple that of patients over 50. Our findings also pointed to a statistically significant greater incidence of hereditary syndromes linked to CRC in younger patients. It is pertinent to note that while hereditary syndromes' prevalence is notably higher in EOCRC patients than in healthy controls, the link to family history of CRC in the absence of identified hereditary syndromes remains unclear[21,22].

While this study did not perform molecular analyses on EOCRC patients, it is crucial to acknowledge the existence of various molecular classification methods. These are based on cellular events such as chromosomal instability (CIN), microsatellite instability (MSI) status, CpG island methylator phenotype (CIMP), and mutations in genes like *BRAF*, *TP53*, *CDKN1A*, *CDKN1B*, and *KRAS*[23].

Additionally, the prevalence of comorbid conditions was significantly higher in CRC patients over 50 compared to those with EOCRC, with notable differences in obesity (42.34% vs. 16.88%), smoking (26.80% vs. 14.29%), and diabetes *mellitus* (21.17% vs. 5.19%). Although a retrospective case-control study suggested certain dietary components are linked to EOCRC, obesity and diabetes were not identified as factors. However, Liu and colleagues[24] reported an association between obesity and increased EOCRC risk in women, underlining the necessity for prospective studies to delve deeper into this association.

The most commonly reported symptoms during colonoscopy for CRC patients included gastrointestinal bleeding, abdominal pain, weight loss, anemia, and constipation. Our research did not reveal statistical differences when comparing patients above 50 with younger patients. Nonetheless, certain symptoms and signs such as constipation (45.45% vs. 32.21%), abdominal pain (66.23% vs. 58.33%), rectal pain (28.57% vs. 19.57%), anemia (61.04% vs. 54.05%), stool narrowing (22.08% vs. 14.19%), and palpable abdominal mass (12.99% vs. 8.78%) were more frequently reported in EOCRC patients. There is a vital need to enhance awareness about EOCRC, as young CRC patients often lack knowledge about the disease, attributing their symptoms to benign conditions[25]. Health professionals are also more inclined to postpone diagnostic testing, such as fecal occult blood tests or colonoscopies, in younger individuals[26].

Evidence suggests distinct pathophysiology and tumor behavior in EOCRC compared with CRC in patients over 50[27]. EOCRC often shows a preference for the distal colon, especially the sigmoid colon and rectum[9,20]. In the study conducted by Holowatyj and colleagues[28], cases of EOCRC were stratified into distinct subgroups according to age ranges (15-19, 20-24, 25-29, 30-34, and 35-39 years). The findings elucidated a predominance of left-sided tumors within the 15-19 age cohort, accompanied by a gradual and consistent decline in the prevalence of right-sided tumors among patients aged 20-39 years. Our findings concur with the previous literature, indicating the rectum (31.17%) and sigmoid colon (28.57%) as prevalent sites in younger patients; however, there was no statistical difference when EOCRC cases were compared with patients older than 50. Additionally, no differences were seen in the prevalence ratio when comparing tumor staging by diagnosis age, although it has been suggested that malignancies in young adults may present different biology, are often diagnosed at more advanced stages, and have a poorer prognosis[29-31].

In individuals under 50 diagnosed with CRC, there was a notably higher incidence of mucinous adenocarcinoma (27.27%) and signet ring cell adenocarcinoma (20.78%) ($p < 0.001$), and these were more likely to be poorly differentiated (16%) compared to their older counterparts (6.09%) ($p < 0.01$). These histopathological patterns align with prior studies indicating that EOCRC tends to show more adverse

histological features, including perineural venous invasion, signet ring cell histology, and positive surgical margins[27,28,32].

The study faced limitations in its conduct and analysis. The array of variables, particularly comorbidities, was limited. Due to its cross-sectional design, the study cannot provide conclusions with substantial statistical weight regarding factor associations. Also, confirmatory diagnostic molecular analyses were not performed for genetic syndromes associated with CRC, suggesting the need for further longitudinal studies with larger sample sizes and stronger levels of evidence and degrees of recommendation.

CONCLUSIONS

This investigation offers an insight into the characteristics of EOCRC within a Latin American cohort, uncovering data on sociodemographic, clinical, endoscopic, and histological variables. Given the increasing prevalence of EOCRC, a shift in the management of this cancer type is imperative. Heightened awareness and the introduction of prevention, control, and early detection strategies are crucial areas to be addressed in the upcoming years worldwide.

Conflict of Interest

The authors have no conflicts of interest to declare in relation to the research, authorship, or publication of this article.

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