Colorectal Cancer: Comparative Analysis Between Two Series of Patients Separated by More Than Three Decades

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Abstract

Aim This study characterizes Colorectal Cancer (CRC) incidence in the University Hospital Ramon and Cajal, Madrid, and analyzes variations over time. It establishes risk groups, aiming to discover whether diagnosis can be determined in less advanced stages of disease.

Method Evolutionary epidemiological study of genetic and environmental factors contributing to the development of CRC in this district that enables the comparison of two cohorts of patients separated by 37 years: G1 (patients of current group) and G2 (patients of historical group). The main risk variables gleaned retrospectively were analyzed and the statistical association between cohorts was determined.

Results The mean age of patients increased significantly from 64 to 71 along with the incidence of ascending colon cancer. G1 scored higher than G2 for: the incidence of colon cancer in men, detection of adenomatous polyps (48.1%), percentage of resectability with curative intent (80.4%), and Dukes A stage (34.1%) ($p < 0.001$).

Conclusion Biological aspects of CRC have been compared against its profile three decades earlier. We can confirm the existence of concrete changes in the manifestation and staging at the time of diagnosis or following earlier treatment.

Keywords
- colorectal cancer
- risk factors
- tumor stage

What Does this Paper Add to The Literature?

This study explores aspects of the CRC profile over 37 years within a specified geographical population, ascertaining specific changes in its manifestation and at diagnosis.

Cover Letter

For the attention of the Drafting Committee of the journal Colorectal Disease, we—the authors—provide this manuscript "Colorectal cancer: comparative analysis between patient groups separated by three decades" wherein all content is entirely original and has not been previously posted or considered for any other publications.

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The authorship requirements have been fulfilled: All authors have read and approved the study, and they have all actively and relevantly participated in the article's design and development, assuming full responsibility for the contents and affirming their agreement with this final and definitive version of the article.

Likewise, we have received study approval, as evaluated by the Clinical Research Ethics Committee of the Ramón y Cajal University Hospital for Health Research, IRYCIS, Madrid, in Madrid, on July 3, 2015. We declare that we have followed the established protocols in accessing clinical records data in order to enable publication for the scientific community in compliance with the Organic Law of Protection of Personal Data (LO 15/1999).

Introduction

Colorectal cancer (CRC) is one of the most common neoplasms affecting Western populations. In Spain, 90,000 people suffer from CRC, two out of every thousand at all ages. Approximately 32,240 new patients are diagnosed each year, but more than 90% can be cured if the disease is detected early.[1,2] It is the second most common cancer in women, after the mammary tumor, and the third in men, after lung and prostate tumors.[1–3] In both genders, it has the highest incidence, at 15% of all diagnosed cancers.[4,5] The majority of cases appear between 65 and 75 years, though some are registered under 40, generally associated with genetic predisposition.[6]

The risk factors that predispose development of this neoplasm are age,[7] neoplastic polyps,[8] oncologic family history,[9] history of other tumors, especially gynecological, or several digestive pathologies such as inflammatory bowel diseases,[10] and biliary pathology.[11]

Symptoms usually prevail in advanced stages. Because of this, guidelines focus on preventive programs and identification of risk groups.[12] The main screening tests are fecal occult blood test (FOBT)[13] and colonoscopy,[14] which are the most effective methods for early detection and reduction of mortality and incidence.[15] There are several screening modalities, depending on the risk of developing sporadic or hereditary CRC due to familial adenomatous polyposis (FAP) and Lynch syndrome, and the control of preventable environmental factors.[16]

Surgical treatment is often curative for localized disease. However, once metastases have occurred, the prognosis is poor with palliation often being the sole option. Although recent therapeutic advances have changed the course of CRC,[17,18] the chances of improving survival lie mainly in early detection.

The aim of this study is to explore the biology and risk factors of this neoplasm, specifically through comparing the data longitudinally through three decades to determine and analyze any changes.

Method

A retrospective analysis was performed on a database with a consecutive series of adult patients diagnosed with colorectal adenocarcinoma and admitted for surgery at the University Hospital Ramon and Cajal. The catchment area served by this hospital is densely urban, and hence the largest population assigned to a single health center in the greater Madrid area.

The sample was divided into two cohorts. The current group, comprised of 185 patients recruited between January 2014 and February 2015 (G1); and the historical group, comprised of 106 patients recruited between September 1977 and January 1979 (G2).

The following sociodemographic epidemiological variables were recorded: age and gender, habits involving toxicity, personal history, family history of cancer, tumor location, clinical, diagnosis time, anatomical pathology, and treatment.

This study's weaknesses lie in data differences between the two groups: currently, there are resources and therapeutic modalities that did not exist 37 years ago. Thus, the samples were not comparable across all items. This affected gauging the degree of tumor extension because, despite registering on the TNM staging system and using a modified Astler-Coller classification in G1, the Dukes stage was the common method used across both groups.

Nevertheless, this work's strength lies in the two series not having patient selection bridges, having been studied correlatively according to their entry into the Service, since its inception at the Ramon y Cajal University Hospital. This ensures an authentic depiction of how things were at that moment, before starting activities that could modify them.

Statistical and data analysis was performed using the Stata (StataCorp LLC., College Station, TX, US) 2013 software. Categorical variables were compared using the chi^2 test (Fisher exact test) and continuous tests with the Student t-test or analysis of variance (ANOVA). For cases in which we were unable to assume normality or homoscedasticity, the contrast between groups was performed with the Mann-Whitney U test or the Kruskal-Wallis H test. A p-value of $<$ 0.05 was considered to be statistically significant.

Results

In G1, 55.1% of the patients were men and 44.9% women, while in G2 the rates were 54.7% and 45.3%, respectively. The mean age of G1 patients was 71.4 years (95% confidence interval, CI: 69.8–73.1), with a median of 74 (range: 41–96). In G2, the mean age was 64.5 (95% CI: 63–66.7), with a median of 67 (range: 20–84) (p-value < 0.001) (►**Fig. 1**). In G1, 25.9% of the patients were smokers and 7% consume alcohol; in G2, the figures were 21.7% and 7.3%, respectively.

In terms of those with a personal history of adenomatous polyps, there was a 48.1% incidence in G1 patients, and 19.8% in G2, with significant differences. ►**Table 1** compares the number of patients with a personal history by category. There were significant differences in the histological type of polyps ($p = 0.001$), with a greater number of tubular adenomas registered in G1, 50.6 versus 12.5%, and a greater number of villous adenomas in G2, 37.5 versus 6.7% (►**Fig. 2**).

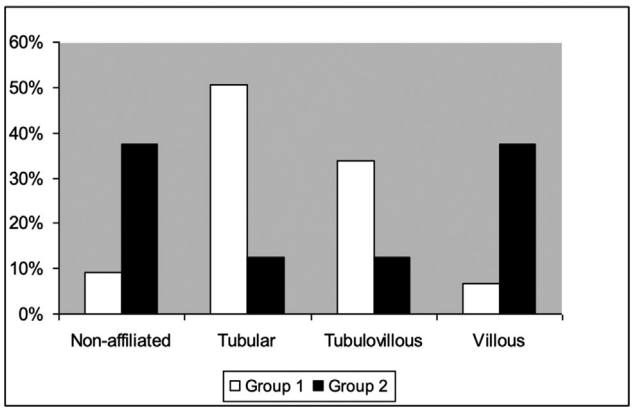

Fig. 1 Distribution of patients by age in both groups.

Table 1 Personal history

Personal history	Group 1	Group 2	*p*-value
Adenomatous polyps	89	21	0.001
Hepatobiliary disease	32	11	0.109
Previous colorectal cancer	13	2	0.448
Other previous cancers	11	3	0.214
Gynecological cancer	6	2	0.758
Non-affiliated gynecological cancer	5	3	0.949
HNPCC	3	1	0.964
Ulcerative colitis	N/R	1	0.78

Abbreviations: Hepato-biliary disease, hepatopathy and/or cholecystectomy and/or cholelithiasis; NPHCRC, hereditary non-polyposis colorectal cancer; N/R, not reported.

Table 2 Tumor location

Locations	Group 1, $n = 195$ (%)	Group 2, $n = 111$ (%)	*p*-value
Rectum	51 (26.2)	42 (37.8)	0.033
Sigmoid colon	43 (22.1)	23 (20.7)	0.786
Ascending colon	28 (14.4)	6 (5.4)	0.017
Cecal colon	23 (11.8)	7 (6.3)	0.121
Rectosigmoid junction	21 (10.8)	13 (11.7)	0.801
Transverse colon	10 (5.1)	8 (7.2)	0.457
Splenic flexure	7 (3.6)	5 (5)	0.801
Hepatic flexure	6 (3.1)	3 (2.7)	0.868
Descending colon	6 (3.1)	3 (2.7)	0.868
Appendix	N/R	1 (0.9)	0.775

Abbreviation: N/R, not reported.

In G1, 24.3% of the patients had one or more family history of cancer, in G2, the number is 35.8%, showing significant differences ($p = 0.036$).

The most frequent locations of tumors for both groups were in the rectum and rectosigmoid junction, with 36.9% in G1 and 49.5% in G2. Significant differences were found in relation to tumors in the rectum and ascending colon: the percentage of tumors in the rectum was higher in G2, 37.8 versus 26.2% ($p = 0.033$), and tumors in the ascending colon had higher rates in G1, 14.4 versus 5.4% ($p = 0.017$), as shown in ►**Table 2**.

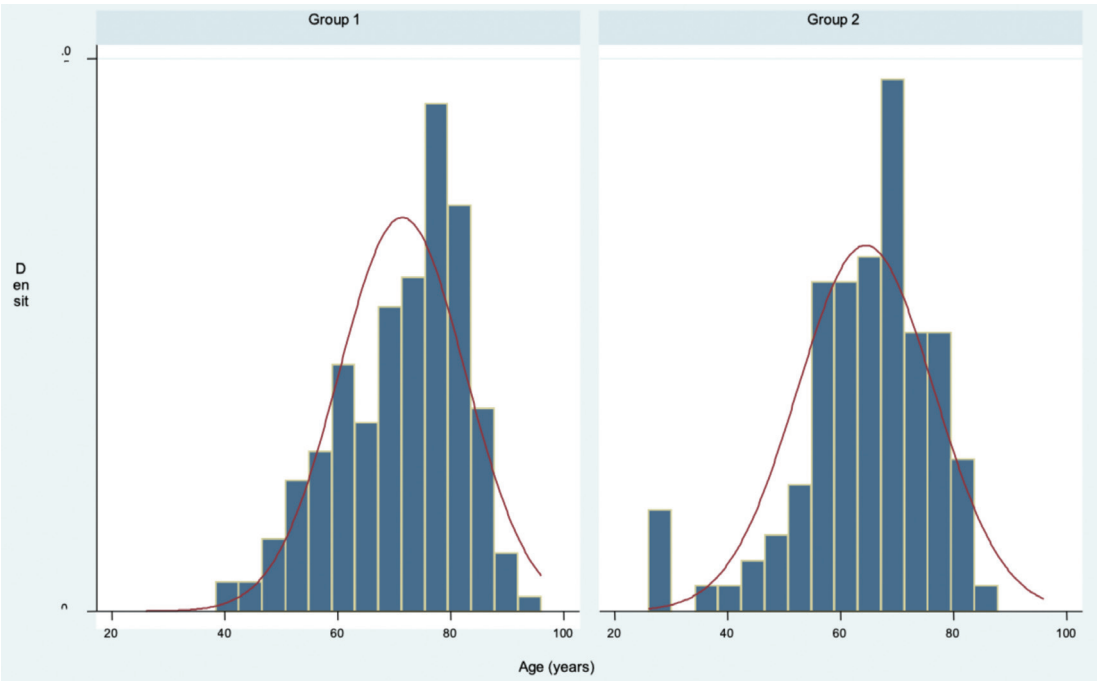

Fig. 2 Patients with a history of adenomatous polyps of both groups and their histological type.

Table 3 Most common first, main, and associated symptoms: First symptom

First symptom	Group 1, $n = 153$ (%)	Group 2, $n = 83$ (%)	*p*-value
Lower gastrointestinal bleeding	43 (28.1)	28 (33.7)	0.379
Change in bowel habits	32 (20.9)	32 (38.6)	0.014
Abdominal pain	23 (15.0)	20 (24.1)	0.085
Incomplete intestinal obstruction	3 (2.0)	3 (3.6)	0.735
Asthenia and other symptoms	52 (34.0)	N/R	0.001

Abbreviation: N/R, not reported.

Table 4 Most common first, main, and associated symptoms: Main symptom

Main symptom	Group 1, $n = 115$ (%)	Group 2, $n = 83$ (%)	*p*-value
Lower gastrointestinal bleeding	60 (52.2)	36 (43.4)	0.221
Abdominal pain	30 (26.1)	18 (21.7)	0.476
Incomplete intestinal obstruction	16 (13.9)	5 (6.0)	0.075
Change in bowel habits	9 (7.8)	24 (28.9)	0.001

Table 5 Most common first, main, and associated symptoms: Other associated symptoms

Other associated symptoms	Group 1	Group 2	*p*-value
Weight-loss	29 (15.7)	41 (38.7)	0.001
Asthenia	27 (14.6)	25 (23.6)	0.054
Perforation	16 (8.6)	N/R	0.002
Anorexia	15 (8.1)	17 (16)	0.037
Lower gastrointestinal bleeding	10 (5.4)	6 (5.7)	0.927
Change in bowel habits	2 (1.1)	22 (20.8)	0.001
Abdominal pain	1 (0.5)	12 (11.3)	0.001

Abbreviation: N/R, not reported.

Establishing the classic locations of the digestive tract and using the Bonferroni correction to obtain the *p*-values, right colon cancers were significantly higher in G1, 26.1 versus 12.6% ($p = 0.02$).

In men, there were more colon tumors in G1, 75.7 versus 57.4% ($p = 0.013$). Comparing gender and tumor location, excluding synchronous cancers, colon cancer was more frequent in G1 males, at 78.4%, and rectal cancer in G2, 44.8% ($p = 0.002$).

Clinically, 82.7% of G1 patients, and 78.3% of G2 had symptoms. As shown in ►**Tables 3–5**, the first and most frequent symptom was lower gastrointestinal bleeding (LGIB) in G1 and change in bowel habits (CBH) in G2. There is a significant difference in CBH as the first symptom, which is higher in G2 at 38.6 versus 20.9%; $p = 0.003$. The most frequent main symptom was LGIB in both groups, higher in G2 at 43.4 versus 39.2%, although the only significant difference was CBH, which was higher in G2 at 28.9 versus 7.8%; $p < 0.001$. Significant differences were found in the associated symptoms such as constitutional syndrome, CBH and abdominal pain, more frequent in G2, whereas perforation was only recorded in G1.

Table 6 The Dukes staging system

Tumor staging	Group 1, $n = 185$ (%)	Group 2, $n = 106$ (%)	*p*-value
Dukes stage A	63 (34.1)	7 (6.6)	< 0.001
Dukes stage B	57 (30.8)	30 (28.3)	< 0.001
Dukes stage C	53 (28.6)	25 (23.6)	< 0.001
Dukes stage D	11 (5.9)	32 (30.2)	< 0.001
Non-affiliated	1 (0.5)	12 (11.3)	< 0.001

The time elapsed from the first symptom to the diagnosis was 2 months of average in G1, with a standard deviation (SD) = 82.4, and 6.5 months in G2, SD = 208.1. Although the study showed significant differences, it was not suitable due to the variation of sample sizes.

Regarding to Dukes staging system, we found significant differences in all stages. In G1 the most frequent was the stage A with 34.1% and the less frequent was the stage D with 5.9%. In G2 the most frequent was the stage D with 30.2% and the less frequent was stage A with 6.6% (►**Table 6**). On average, 18.7 lymph nodes (95% CI: 17.3 - 20.2) were examined in G1 and 12.6 in G2 ($p = 0.008$).

In G1, 99.4% of the patients were operated on and in G2 the 94.8%. The percentage of operability did not show significant differences but there was the percentage of resectability: in G1, 80.4% of the surgery was performed with resection R0 with only 58.2% in G2 (►**Table 7**).

Discussion

This comparative study did not reveal significant differences in the diagnosis of CRC and gender, predominating in both groups in men, but the mean age did increase significantly to 71.4 years in G1, when compared with 64.5 in G2, as published by Devesa et al.[9] This change could be related to a greater longevity and delay in the appearance of this disease, although it is logical to consider the involvement of

Table 7 The residual tumor (R) classification in 1987 by the Union for International Cancer Control (UICC)

Resectability	Group 1 $n = 184$ (%)	Group 2 $n = 98$ (%)	*p*-value
R0	148 (80.4)	57 (58.2)	< 0.001
R1/R2	17 (9.2)	29 (29.6)	< 0.001
Non-affiliated	19 (10.3)	12 (12.2)	< 0.001

Abbreviations: R0, resection, tumor negative, "clean", "negative margin", resection for cure or complete remission; R1, tumor positive, microscopic residual tumor; R2, tumor positive macroscopic residual tumor.

other factors. We also found that in G1 the mean age was higher in men ($p < 0.001$), and in G2 it was higher in women ($p = 0.02$). Both series remained in the established age line of development of this neoplasia in developed countries, such as across Europe.[1–3] As reported by the literature, CRC is more frequent in men and in patients over 70 years old.[7,19]

In relation to smoking[20] and alcohol consumption,[21] there were no significant differences between groups, and although health campaigns probably translate their impact on smokers, the reduction of a toxic habit as casual in disease incidence takes years occur.[22]

Regarding medical history, there were differences in the numbers affected by adenomatous polyps,[8] G1 being higher. Although welcome, we have no conclusive data to link it to the increase in colonoscopies.[6] This early screening test for precancerous lesions continues to be the most appropriate for a significant reduction in CRC incidence and mortality.[23,24] In turn, tubular adenomas evolve towards villous adenomas over time, in the adenoma-cancer sequence[8], which would also explain the percentage of tubular adenomas being significantly higher in G1 and villous adenomas in G2, since they are currently diagnosed more efficiently than before.

There were more patients with a history of CRC in G1. This is attributable to a greater survival to the first tumor,[25] better diagnosis of the second cancer thanks to the follow-up programs,[26,27] and to a more advanced age, associated with increased life expectancy. These same considerations can be applied for the history of other cancers, especially gynecological,[28] because their prevention and early diagnosis are subject to campaigns in health catchment areas such as the University Hospital Ramon and Cajal.

Regarding the detection of patients with relatives who had cancer, which established them as an intermediate high-risk population, the rates were superior in G2. We could attribute this to the greater implication in the anamnesis thirty years ago, before the technological improvements. It may be paradoxical, since there is a constant oncological significance in that subjects with relatives with a history of cancer are more likely to develop CRC than the average population.[29]

Recently, the advance of science has uncovered certain hereditary factors, the so-called population groups with high incidence of CRC, from 10% to 15% and a spectrum that can reach 100% in individuals with genetic mutations, such as familial adenomatous polyposis (FAP).[30] However, if the early screening tests were only limited to these subjects, most CRC would be over-looked.[31]

The localization of cancer in the ascending colon was higher in G1, and in the rectum in G2, which is in accord with the tendency towards an increase in neoplasms in the right colon,[19] to the detriment of the rectum, a fact that can be linked not only with a possible change in the tumor biology per se, but with the fact that rectal tumors prevention is simpler and more effective. Also, when performing an endoscopy, the rectal examination is guaranteed while examinations of the right colon may be unsuccessful, being incomplete in approximately 10% of cases. In Spain, there are 1.56 times more cancers of the colon than the rectum.[6]

Colon cancer was more common in men in G1 than in G2. We do not have an explanation for this. It might be linked with the broader epidemiology of colon and rectal cancer.[9]

Clinically, a change in bowel habits (CBH) was significantly more frequent in G2, both as the first and main symptom, and also as the paraneoplastic syndrome. We do not believe that this has a special exegesis, except for the result of more advanced tumor stages in G2. Perhaps the frequency of these symptoms as the first and principal also supports the claim that, in the historical series, the most commonly used initial diagnostic test was fecal occult blood test (FOBT)[9,13] because it was more comfortable and faster back then.

What is noteworthy is the difference in the reduction of the mean time to CRC diagnosis in G1, when compared with G2, since the appearance of the first symptoms, 2 versus 6.5 months, respectively. Although, due to the sample size, no statical significance can be established. Regarding the tumor location, in G1 this interval was greater for tumors in the transverse and right colon, at 3.1 and 2.2, respectively, which may justify patient non-compliance with the CBH, whose diagnostic time interval was also greater, such as the first symptoms in G1 at 2.3 and G2 at 8.6 months. In this regard, it is important that awareness programs not only talk about lower gastrointestinal bleeding (LGIB), but also about CBH without apparent cause, and asthenia with anemia, which are symptoms of a neoplastic pathology of the colon requiring medical consultation.

In G2, the diagnostic time was longer for rectal tumors and transverse colon tumors, at 8.3 and 6 months, respectively. This delay, especially when the first and main symptom was rectal bleeding, could explain doctors' common misinterpretation of the diagnosis as hemorrhoids, with a rectal examination being discounted without further study. Therefore, bleeding or other symptoms were added.[9] Likewise, the age in both groups was higher as the decades advanced.

In the extension of the disease, according to the Dukes classification,[32,33] in G1 the most frequent stage was Dukes A and in G2 it was D. That is to say, in more than three decades, the figures for local disease and metastasized disease have been inverted. Although part of this result can be ascribed to the use of neoadjuvant therapy[17,18] in rectal cancers of G1,

and the frequencies according to location, as rectum cancer was more frequent in G2, it does not sufficiently clarify this difference, and it remains a fact that the percentage of local disease is associated with an earlier diagnosis,[15] and to the advances in medical practice itself. This fact corroborates the Dukes stage D percentages in each group, as they are not adulterated by any previous procedure.

Regarding the anatomical-pathological quality, the number of nodes examined was significantly higher in G1, although in G2 it was above 12, which is the minimum number for optimal staging.[19,34]

Finally, the surgical treatment revealed that, although the percentage of operability showed no differences, the percentage of resectability with negative margin (R0) was significantly higher in G1.

In conclusion, this is a study of CRC, a malignant disease with high prevalence and mortality in Spain, comparing two series of patients from the same catchment area and separated by more than three decades, revealing interesting differences that favor the current period. Regarding the identification of risk groups for this neoplasm, in order to establish prevention programs, this study reveals that it is necessary to implant prevention programs because of diagnosis in earlier stages of disease, to increase the percentage of surgical treatment with a curative intent and subsequent improvement in prognosis.

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Conflict of Interests
The authors have no conflict of interests to declare.

Authors Contribution
J.M. Devesa contributed to the study conception and design, the acquisition, analysis and interpretation of the presented data; the article drafting and critical revision and final approval for publication. All authors have read, revised and approved the final manuscript.

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