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## Early-onset colorectal cancer: A sporadic or inherited disease?

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### Abstract

Colorectal cancer is the third most common cancer diagnosed worldwide. Although epidemiology data show a marked variability around the world, its overall incidence rate shows a slow but steady decrease, mainly in developed countries. Conversely, early-onset colorectal cancer appears to display an opposite trend with an overall prevalence in United States and European Union ranging from 3.0% and 8.6%. Colorectal cancer has a substantial proportion of familial cases. In particular, early age at onset is especially suggestive of hereditary predisposition. The clinicopathological and molecular features of colorectal cancer cases show a marked heterogeneity not only between early- and late-onset cases but also within the early-onset group. Two distinct subtypes of early-onset colorectal cancers can be identified: a "sporadic" subtype, usually without family history, and an inherited subtype arising in the context of well defined hereditary syndromes. The pathogenesis of the early-onset disease is substantially well characterized in the inherited subtype, which is mainly associated to the Lynch syndrome and occa-

sionally to other rare mendelian diseases, whereas in the "sporadic" subtype the origin of the disease may be attributed to the presence of various common/rare genetic variants, so far largely unidentified, displaying variable penetrance. These variants are thought to act cumulatively to increase the risk of colorectal cancer, and presumably to also anticipate its onset. Efforts are ongoing in the attempt to unravel the intricate genetic basis of this "sporadic" early-onset disease. A better knowledge of molecular entities and pathways may impact on family-tailored prevention and clinical management strategies.

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**Key words:** Early-onset colorectal cancer; Epidemiology; Hereditary syndrome; Lynch syndrome; MUTYH-associated polyposis

**Core tip:** The phenotypic and genotypic heterogeneity of early-onset colorectal cancers (CRCs) clearly emerges from clinical studies. We can distinguish two distinct entities, an inherited subtype, usually with familial aggregation, accounting for a relatively low percentage of cases, with specific clinicopathologic features and a "sporadic" subtype, often without family history of CRC, with distinct location and histopathologic features. There is a significant variability in the mechanisms underlying the development of early-onset CRC and it is certainly a big concern for clinicians and oncologists for the implications on prevention, diagnosis and clinical management of the disease.

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## INTRODUCTION

Colorectal cancer (CRC) is the third most common diagnosed cancer (1.23 million cases, 9.7% of overall cancer, cumulative lifetime risk of 2%) representing an important health issue worldwide<sup>[1]</sup>. Almost 60% of cases occur in developed regions, particularly in the United States where colorectal is the third most common cancer site with approximately 142820 estimated cases<sup>[2]</sup>, whereas in the European Union (EU) it is the second diagnosed cancer with approximately 330000 estimated cases<sup>[3]</sup>. Furthermore, CRC is the fourth most common cause of death from cancer worldwide (608000 cases, 8% of overall cancer deaths, cumulative lifetime risk of 0.9%). There is less variability in mortality rates with the highest rates estimated in Central and Eastern Europe (20.3 per 100000 for male, 12.1 per 100000 for female), and the lowest in Middle Africa (3.5 and 2.7, respectively). Incidence and mortality rates are lower in women than in men<sup>[1]</sup>.

Over the past two decades, in these more developed countries (United States, EU), incidence and death rates have decreased about 2% per year<sup>[2,4,5]</sup>. This rapid decline has been largely attributed to the increase in screening programmes among individuals 50 years and older, allowing an early detection and treatment of CRC and precancerous lesions<sup>[1-7]</sup>.

For this reason, the evidence-based European Code Against Cancer and the American College of Gastroenterology in the United States, recommend that men and women from 50 years of age onwards should participate in colorectal screening<sup>[8-10]</sup>.

Conversely, in the less developed regions of the world, the annual incidence is expected to increase over the next two decades. This is likely due to the adoption of a more “westernised” lifestyle, population growth, a higher life expectancy and the lack of screening programs<sup>[1]</sup>.

## EARLY ONSET CRC

CRC incidence increases significantly beyond the fifth decade of life, therefore it is often thought of as a disease of the elderly and CRC screening is usually not recommended for individuals at average risk younger than 50 years<sup>[8-10]</sup>.

The major studies on CRC incidence among young adults have been performed by using the Surveillance, Epidemiology and End Result registries (SEER) database in the United States, and the World Health Organization database in the EU.

Siegel *et al*<sup>[11]</sup> published data from the SEER database. CRC was considered occurring in young adults (ages 20 to 49 years) between 1992 and 2005. They reported an increased incidence overall rate of 1.5% per year in men and 1.6% in women. Specifically, the incidence rate increased among non-Hispanic whites by 2% in men and 2.2% in women, and it was slightly higher in Hispanic men (by 2.7%). Moreover, they showed that the largest annual percent increase in CRC incidence was in

the youngest age group (20-29 years): 5.2% per year in men and 5.6% per year in women. The analysis by anatomic sites revealed a predilection for distal colon and rectum in both sexes. Their findings were consistent with previous epidemiological studies of Cress *et al*<sup>[12]</sup> and O’Connell *et al*<sup>[13]</sup> that used the SEER databases as well. O’Connell *et al*<sup>[13]</sup> focused their study on patients under 40 years of age and reported trend for increased incidence, but they did not examine trends by race and ethnicity. Cress *et al*<sup>[12]</sup> focused their analysis on rectal cancer. Likewise, Meyer *et al*<sup>[14]</sup> conducted an analysis on SEER databases between 1973 and 2005, and compared patients aged under 40 years with cancer of the rectum to patients with cancer localized in the colon. They observed that over the examined period the incidence of rectal cancer increased significantly whereas that of colon cancer remained unchanged (annual percent change, 2.6%,  $P < 0.0001$  and 0.2%,  $P = 0.50$ , respectively). Unlike the results of Siegel *et al*<sup>[11]</sup>, the rise in prevalence was independent of sex or race.

Bosetti *et al*<sup>[4]</sup> published data on CRC mortality in Europe. They reported “CRC rates at age 30-49 years were between 3 and 5/100000 in most large European countries in both genders (though higher in men) and tended to decline between 1997 and 2007. As for all ages, rates were higher and trends were less favourable in Eastern Europe, including Hungary (over 9/100000 men, and over 6/100000 women), Bulgaria, the Czech Republic (with, however, a decline in men to 4.4/100000 in 2007) and Slovakia. In the EU as a whole, CRC mortality at age 30 to 49 declined from 4.8 in 1997 to 3.9/100000 in 2007 for men, and from 4.1 to 3.3/100000 in women, *i.e.*, about 10% per quinquennium<sup>[4]</sup>. The European and United States trends of CRC incidence appear to be opposite. However Bosetti *et al*<sup>[4]</sup> did not include patients under 30, whereas Siegel *et al*<sup>[11]</sup> showed that the highest increase was among this age group.

Further, several reports regarding CRC in young adults under 40 or 50 years of age have been published over the last few decades, describing data from the United States or EU on single-institution series<sup>[15-32]</sup>. The prevalence ranged between 3.0% and 8.6% with a peak of 17.1%, in the study of Safford *et al*<sup>[15]</sup>, performed on the Army Tumour registry. Soliman *et al*<sup>[16]</sup> carried out a study on an Egyptian series of 1608 patients. A clearly higher prevalence (35.6%) was found in Egypt than in the EU or the United States. Similar conclusions were drawn by Yilmazlar *et al*<sup>[17]</sup> on a smaller Turkish series of 237 patients (19.4%).

CRC comprises a large proportion of familial cases (approximately 15%-30%)<sup>[33]</sup>, in which young affected individuals are expected to have a significant familial history and/or genetic predisposition. The cited studies<sup>[15-32]</sup> aimed at identifying prevalence and clinico-pathological features of early-onset CRC. It was noted that the presence of family history is not always reported, resulting in a considerable spread in the estimated frequency of familial cases (from 3% to 20%). Moreover, only a few studies specified data on genetic predisposition, *i.e.*, famil-

**Table 1** Early onset colorectal cancer: Comparison of published studies

Author	Year	Patient age	Young onset CRC/overall CRC n (%)	5-yr survival	Tumour site	Advanced stage	Adverse histological features (mucinous and poorly differentiated)
Lee <i>et al</i> <sup>[24]</sup>	1994	< 40	62/2000 -3.1	Dukes C 40% Dukes D 7%	Not specified	71% <sup>1</sup>	Not specified
Fante <i>et al</i> <sup>[25]</sup>	1997	< 40	14/1298 -1.1	70%	Left sided 63%	57% <sup>1</sup>	21.4% mucinous
Pitluk <i>et al</i> <sup>[26]</sup>	1983	< 40	31/861 -3.6	22%	Left	Not specified	Not specified
Minardi <i>et al</i> <sup>[27]</sup>	1998	< 40	37	26%	Left 51.3%	59% <sup>1</sup>	58% mucinous
Domergue <i>et al</i> <sup>[28]</sup>	1988	< 40	93/2600 -3.6	30%	Left 74% (rectal 55)	80% <sup>1</sup>	40% poorly differentiated
Palmer <i>et al</i> <sup>[29]</sup>	1991	< 40	105		Left sided	63% <sup>1</sup>	Not specified
Behbehani <i>et al</i> <sup>[30]</sup>	1985	< 40	47 vs 525	23%	Left sided 58%	Not specified	26% mucinous
Parramore <i>et al</i> <sup>[20]</sup>	1998	< 40	36/418 (8.6)	Not specified	Not specified	78% <sup>1</sup>	21% poorly differentiated 28% poorly differentiated 26% mucinous
Soliman <i>et al</i> <sup>[16]</sup>	1997	< 40	572/1608 (35.6)	Not specified	Rectal > 50%	Not specified	30.6% mucinous
Yilmazlar <i>et al</i> <sup>[17]</sup>	1995	< 40	46/237 (19.4)	Not specified	Left sided 80%	76% <sup>1</sup>	48%
Isbister <i>et al</i> <sup>[21]</sup>	1990	< 40	131/2420 (5.4)	Not specified	Not specified	Not specified	Not specified
Adloff <i>et al</i> <sup>[22]</sup>	1986	< 40	32/1037 (3)	Not specified	Not specified	Not specified	Not specified
Safford <i>et al</i> <sup>[15]</sup>	1981	< 40	140/819 (17.1)	Not specified	Not specified	Not specified	Not specified
Moore <i>et al</i> <sup>[23]</sup>	1984	< 40	62/1909 -3.2	Not specified	Left sided 58%	Not specified	32.3% mucinous 98% poorly differentiated
Mäkelä <i>et al</i> <sup>[18]</sup>	2010	< 40	59/1272 -4.6	58%	Left sided 42%	Not specified	Not specified
Torsello <i>et al</i> <sup>[19]</sup>	2008	< 40	58/1340 -4.2	48.9%	Left sided 82.7%	46.5% <sup>2</sup>	14% poorly differentiated 26% mucinous
Chang <i>et al</i> <sup>[53]</sup>	2012	< 40	55/1160 -4.7	53%	Left sided 80%	63%	24% mucinous
Myers <i>et al</i> <sup>[31]</sup>	2013	< 50	49/437 -11.2	Not specified	Left sided 62.1%	53% <sup>2</sup>	12% poorly differentiated 19% mucinous

<sup>1</sup>Dukes classification, stages C and D; <sup>2</sup>Tumor node metastasis staging, stages III and IV. CRC: Colorectal cancer.

ial aggregation. In particular, Fante *et al*<sup>[25]</sup> observed the presence of Hereditary Non polyposis Colorectal Cancer Syndrome (HNPCC) or Familial Polyposis in 15.5% of their series. Meyer *et al*<sup>[4]</sup> reported just one out of 180 early-onset CRC patients to have a family history of cancer, in accordance with the Amsterdam Criteria.

As to the clinico-pathological features of CRC in young onset patients, the prevalent anatomic site was the distal colon (50%-80% of the cases), the histopathological characteristics identified were mucinous (9%-49% *vs* 17% of the general population), poorly differentiated (12%-98%, *vs* 15% of the general population) and advanced tumour stage (Dukes C or D in 71%-80% of the cases)<sup>[15-32]</sup>. Data on prognosis in early-onset patients are, at present, still controversial. Several single-institution studies reported a poor prognosis with a 5-year survival rate of 10% to 29%<sup>[26,27,30-32]</sup>, whereas other authors found equivalent or higher survival rates than in older patients (33%-60%)<sup>[20-25]</sup>. However, some authors hypothesized that early-onset CRCs are more aggressive due to their typical histopathological features (mucinous and poorly differentiated)<sup>[20,27,32]</sup> (Table 1).

## HEREDITARY CRC SYNDROMES

Young age at onset is usually included among the indica-

tors of an inherited CRC syndrome. Therefore, when dealing with an early onset CRC patient, one should take into account the possibility of an hereditary CRC syndrome (HCCS).

CRC has a large proportion of familial cases (approximately 30%) and mutations in important cancer susceptibility genes are detectable in about 5%-10% of CRC<sup>[53]</sup>.

The most prevalent HCCS are characterized by adenomatous polyps and/or cancer. Namely, the Lynch syndrome has a 80% lifetime risk for CRC, familial adenomatous polyposis (FAP) has a 100% lifetime risk of CRC. In contrast, MUTYH associated polyposis (MAP) does not have a defined lifetime risk for CRC. Other less common HCCS are characterized by hamartomatous polyps, as in the Peutz Jeghers syndrome (PJS) and the juvenile polyposis syndrome (JPS) which are associated with about 39% lifetime risk of CRC. The very rare Cowden syndrome involves little, if any, CRC risk. The Serrated Polyposis syndrome (SPS) is characterized by hyperplastic polyps and serrated adenomas and is associated with more than 50% of CRC lifetime risk. All these syndromes have an autosomal dominant inheritance with the exception of MAP, which is caused by a bi-allelic recessive gene mutation, and SPS which is rarely inherited.

Classical FAP, PJS and JPS have typical phenotypes, often evident at endoscopic examination. As to classical FAP, CRC develops between 30-40 years of age and is associated with over than 100 polyps, the typical “carpet” of colonic polyps. In PJS the typical diagnostic feature is the muco-cutaneous melanosis which appears during childhood. In this syndrome, the most frequent site of polyp occurrence is the small bowel, with obstruction and/or bleeding signs, rather than cancer development, usually appearing at a young age. In JPS, polyps typically develop in the stomach and in the colon and rectal bleeding is a frequent symptom. The syndromes are usually suspected at endoscopic examination and the identification of the causative germline mutation confirms the diagnosis<sup>[33]</sup>.

## FROM EARLY-ONSET CRC TO THE DIAGNOSIS OF AN HEREDITARY CONDITION

### **MUTYH-associated polyposis**

MAP is an autosomal recessive syndrome caused by mutations in *MUTYH* gene. This gene is a component of the base excision repair system that protects genomic information from oxidative damage and it was first described in 2002. Bi-allelic germline mutations in the *MUTYH* gene predispose to multiple colorectal adenomas and somatic G:C→T:A mutations<sup>[34,35]</sup>. MAP can mimic both FAP and LS phenotypes. Affected individuals most often display an attenuated phenotype, developing less than 100 colorectal adenomas, often with a predominance in the right side of the colon and with a later onset than FAP (about 10 years later)<sup>[36,37]</sup>.

A few studies in a large series of CRC patients<sup>[38,39]</sup> suggest that in a small percentage of CRC cases, bi-allelic *MUTYH* gene mutations can be found in the absence of the polyposis phenotype. Knopperts *et al.*<sup>[38]</sup> screened for *MUTYH* gene mutations a series of 89 MSI-L or MSS early-onset (under 40) CRC without a polyposis phenotype, and compared them with 693 non-CRC patients with 1-13 adenomatous polyps for the *MUTYH* hotspots. They did not observe *MUTYH* bi-allelic mutations in any of the examined cases.

Giráldez *et al.*<sup>[39]</sup> screened 140 CRC under 50 years for LS (MSI analysis and immunohistochemistry for the four MMR genes). In MMR-deficient patients they performed an MMR germline mutation analysis and also evaluated bi-allelic *MUTYH* mutations in all cases. They found 4 mutated cases (2.8%) and suggested to carry out *MUTYH* screening in this subset of CRC patients. Also Lubbe *et al.*<sup>[40]</sup> in their study on CRC risk associated with *MUTYH* mutations suggested screening of early-onset CRC MSS cases.

Riegert-Johnson *et al.*<sup>[41]</sup> tested a consecutive series of 229 samples referred for LS testing for the two *MUTYH* mutations most common in the Caucasian population. They only included cases with early-onset CRC (under

50 years of age), either MSS stable or MSI-L and found 4 (2%) bi-allelic and 6 mono-allelic mutation carriers. They concluded that *MUTYH* mutation testing is a “reasonable cascade test in early-onset CRC found to have proficient DNA MMR system, regardless of pattern of family history or number of polyps”.

### **Lynch syndrome**

The LS is an autosomal dominant condition with incomplete penetrance, predisposing to CRC and other malignancies at a young age due to a germline mutation in one of the mismatch repair (*MMR*) genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*)<sup>[42-44]</sup>.

In rare cases, LS can be caused by germ-line hypermethylation of *MLH1* promoter<sup>[45,46]</sup>, constitutional 3' end deletions of the *EPCAM* gene (formerly known as *TACSTD1*), and subsequent epigenetic silencing of *MSH2*<sup>[47]</sup>. CRC of patients with LS shows MMR deficiency, defined by the presence of microsatellite instability (MSI) and loss of the MMR protein expression, which is the hallmark of this disorder<sup>[44]</sup>. The syndrome accounts for 2%-4% of all CRCs, and the lifetime risk of developing CRC in the MMR mutation carriers is estimated to be 50%-80%<sup>[33,48]</sup>. Therefore, patients with LS and their relatives must undergo intensive surveillance and appropriate management in order to improve survival<sup>[49-51]</sup>.

The most widely used diagnostic strategy for LS is based on selecting patients who fulfil the Amsterdam Criteria<sup>[43]</sup> or any of the Revised Bethesda Guidelines<sup>[52]</sup>. Tumour tissues of these patients are then tested for MSI and/or immunostained by IHC to detect MMR proteins, if any. MMR-deficient cases are finally tested for germline mutations. In this respect it may be of interest to note that the stringency differs in the Amsterdam and Bethesda Criteria. The Amsterdam Criteria select probands on the basis of familial segregation and early age at onset of either CRC or any other cancer in LS spectrum. The Revised Bethesda Guidelines are less stringent and separately consider age at onset, presence of synchronous/metachronous cancer (multiple primary cancers), MSI-H phenotype at age < 60 years, and family history of cancer in the LS spectrum. Possibly due to differences in the inclusion criteria, the prevalence of LS in early onset-CRC cohorts resulted extremely variable in different studies accounting for about 4% to 20%<sup>[39,53-67]</sup>.

Among these studies, the family history of CRC was an important associated factor, likely to influence the different prevalence of LS. Indeed, if we only consider the cases without family history<sup>[55,61,65]</sup>, the prevalence rate decreases to 3.5%-6.4% and becomes more homogeneous. Furthermore, the feature typical of LS, *i.e.*, occurrence in the right colon is not frequent in the early-onset group, either in the above mentioned studies or in the studies that specifically analyze LS prevalence. In these studies, a predilection for the distal colon was reported in 55%-80% of the cases.

Therefore, we might consider the existence of two different clinico-pathological entities in early onset CRC:

the “sporadic” and the inherited forms. The former, more frequent, usually presents with left-sided CRC without relevant family history. The latter, less frequent, arises in the context of a well defined hereditary syndrome.

## PATHOGENESIS OF CRC

CRCs are highly heterogeneous both histopathologically and at the molecular and genetic levels. Furthermore, the genetic alterations and molecular mechanism of early-onset CRCs have not yet been fully clarified.

The pathogenesis of CRC varies according to genetic or epigenetic changes, which are related to each other to a variable extent. They follow the multiple-stage patterns theorized by Fearon and Vogelstein<sup>[68]</sup>. Such genetic and epigenetic alterations are directly responsible for a specific event within the sequence that leads to CRC, by contributing to the initiation of neoplastic transformation in the healthy epithelium, and/or determining the progression towards more malignant stages of the disease.

The different carcinogenesis pathways are characterized by several distinctive models of genetic instability, subsequent clinical manifestations, and pathological features.

Most of the CRCs follow the chromosomal instability (CIN) pathway, which is characterized by widespread imbalances in chromosome number (aneuploidy) and loss of heterozygosity<sup>[68,69]</sup>. The second, less frequently involved pathway is MSI, which is due to derangement of the DNA MMR system and, ultimately, microsatellite instability<sup>[70-72]</sup>. More recently, other systems and pathways of CRC pathogenesis have been uncovered which include: (1) DNA methylation [CpG island methylator phenotype (CIMP) pathway]<sup>[73,74]</sup>; (2) inflammation (inflammatory pathway)<sup>[75-78]</sup>; and (3) microRNA (miRNA) involvement<sup>[79-82]</sup>.

## PATHOGENESIS OF EARLY-ONSET CRC

Literature on pathogenesis, molecular features, clinical outcome and recurrence of the early-onset CRC is still scanty and controversial. One of the main reasons for such discrepancies is the heterogeneous genetic background underlying the onset of CRC at a young age.

### **Genetic background: Susceptibility genes and genetic/epigenetic variants**

With regards to the hereditary subtype, a considerable and variable proportion of heritability still remains unidentified<sup>[39]</sup>. Indeed, about 30% of the overall CRC burden seems to involve inherited genetic differences<sup>[83,84]</sup>. In fact, there are several possibilities why the genetic component(s) involved in the increased susceptibility of CRC might be missed: (1) the relatively large number of missense, silent, intronic and deep intronic variants of unknown clinical significance in the main CRC susceptibility genes<sup>[85]</sup>; and (2) the presence of other yet unidentified moderately/highly penetrant CRC susceptibility genes.

Concerning the “sporadic” subtype, where mendelian

inheritance has been excluded, the origin of the disease may be attributed to the presence of a large number of common, low-penetrance genetic variants each exerting a small influence on risk. They may act according to a polygenic inheritance model<sup>[86]</sup>. Indeed, according to the common disease-common variant (CDCV) hypothesis<sup>[87,88]</sup>, if a disease that is heritable is common in the population (a prevalence greater than 1%-5%, as in CRC), then the genetic contributors, *e.g.*, specific variations in the genetic code - will also be common in the population<sup>[89]</sup>. This CDCV hypothesis has been recently supported by a remarkable number of recently published genome wide association studies<sup>[90-93]</sup>. A few loci that confer an increased risk of CRC particularly early-onset CRC have been identified (rs10795668, rs3802842, rs4779584)<sup>[94]</sup> (Table 2).

Alternatively, “sporadic” early-onset CRC may arise as a consequence of a cumulative effect of multiple rare variants (population frequency < 1%). These variants might act as independent dominant susceptibility factors, each conveying a moderate but significant increase in cancer risk as suggested by Bodmer *et al*<sup>[95]</sup> in the common disease-rare variant (CDRV) hypothesis. Based on this hypothesis, Bonilla *et al*<sup>[96]</sup> examined the influence of rare variants of the cancer candidate cyclin D1 (*CCND1*) gene on the development of multiple intestinal adenomas and on the early onset of CRC. The authors identified a subset of rare variants that, in combination, contribute to a significant increase in colorectal tumour risk (OR = 2). This increase was also observed for the early-onset group, although statistical significance was not reached probably due to the small sample size (OR = 1.4, *P*-value = 0.50) (Table 2).

A certain number of other gene variants and/or epigenetics alterations have been investigated in recent years in the attempt to identify early-onset CRC-specific genomic signatures. As to the epigenetic status of early-onset CRCs, a study from Antelo *et al*<sup>[97]</sup> analysed the methylation status of LINE-1 elements in early-onset CRC samples compared to elderly cases and observed a statistically significant LINE-1 hypomethylation status in the former set of samples. At variance, in July 2013 Walters *et al*<sup>[98]</sup> reported the association of an overall hypermethylation of DNA repetitive elements, including LINE-1, in white blood cells from early-onset CRC patients compared to controls (Table 2). To our knowledge, no other studies on a possible epigenetic signature of early-onset CRC have been published so far.

As to other potential early-onset CRC-related highly penetrant genes, Fernandez-Rozadilla *et al*<sup>[99]</sup> found an early-onset CRC patient (MMR proficient and no family history) with a 7.326-Mb heterozygous deletion in the 10q22-q23 region involving the bone morphogenetic protein receptor type-1A (*BMPR1A*) gene (Table 2). Alterations in this gene have been recently related to CRC development in patients with familial colorectal cancer type X<sup>[100]</sup>. Moreover, they account for 20% and 50% of the JPS and Hereditary Mixed Polyposis syndrome (HMPS) cases, respectively. No other cases of *BMPR1A*

**Table 2 Genetic background of early-onset colorectal cancer: Susceptibility genes and genetic/epigenetic variants**

High risk susceptibility genes	Related hereditary syndrome
<i>MLH1</i>	Lynch
<i>MSH2</i>	Lynch
<i>MSH6</i>	Lynch
<i>PMS2</i>	Lynch
<i>EpCAM</i>	Lynch
<i>MUTYH</i>	MAP
<i>BMPR1A</i>	Juvenile polyposis
<i>SMAD4</i>	Juvenile polyposis
<i>PTEN</i>	Cowden
Genetic/Epigenetic variants	Related colorectal tumour
rs10795668 <sup>1</sup>	CRC < 50 yr
rs3802842 <sup>1</sup>	CRC < 50 yr
rs4779584 <sup>1</sup>	CRC < 50 yr
≥ 1 <i>CCND1</i> rare variants <sup>2</sup>	multiple adenomas or CRC < 50 yr
LINE-1 hypomethylation <sup>3</sup>	CRC < 50 yr
DNA repetitive elements hypermethylation <sup>4</sup>	CRC < 60 yr
10q22-q23del <sup>5</sup>	Two synchronous CRC at 49 yr of age

<sup>1</sup>Colorectal cancer (CRC) genetic susceptibility single nucleotide polymorphisms with a *P*-value < 0.05<sup>[92]</sup>; <sup>2</sup>*P*-value = 0.04 and OR = 2.0<sup>[94]</sup>; <sup>3</sup>Comparison of long interspersed nuclear element 1 (LINE-1) hypomethylation status between early-onset CRC and other groups of CRC: *P*-value < 0.0001<sup>[95]</sup>; <sup>4</sup>DNA repetitive elements hypermethylation in a cohort of early-onset CRC patients compared to healthy controls: LINE-1 (OR = 2.34, *P*-value < 0.001), Sat2 (OR = 1.72, *P*-value < 0.001) and Alu repeats (OR = 1.83, *P*-value = 0.02)<sup>[96]</sup>; <sup>5</sup>The 10q22-q23 deletion in the patient involves the *BMPR1A* gene<sup>[97]</sup>. MAP: *MUTYH* associated polyposis.

mutations in sporadic early-onset CRC patients have been reported so far. In addition, a recent study on gene expression profiles of early-onset CRC was published by Luo *et al.*<sup>[101]</sup>. The aim of the study was to uncover protein-protein interaction network-based biomarkers of early-onset CRC to be used as potential targets for therapeutic intervention. Indeed, the authors identified five proteins (CDC42, TEX11, QKI, CAV1 and FN1), as representative elements of early-onset CRC-specific networks. However, further investigation is obviously needed to confirm these findings.

### Pathological and molecular features

Many studies have focused in recent years on the characterization of the clinical, pathological and molecular features of this peculiar early-onset disease.

In 2009, Yantiss *et al.*<sup>[102]</sup> compared clinical risk factors of malignancy, and pathological features predictive of outcome in early-onset (< 40 years) versus late-onset (≥ 40 years) CRC patients. Ninety-two percent of tumours from young patients occurred in the distal colon (*P* = 0.006), and 75% were stage III or IV. Tumours from young patients showed more frequent lymphovascular (81%, *P* = 0.03 and/or venous (48%, *P* = 0.003) invasion, an infiltrative growth pattern (81%, *P* = 0.03) and  $\alpha$ -methylacyl-CoA racemase expression (83%, *P* = 0.02) compared with controls. Cancer samples in this early-onset group showed significantly increased expression of miR-21, miR-20a, miR-145, miR181b, and miR-203 (*P* ≤ 0.005 for all comparisons with controls). The results

of this study indicated that early-onset CRC commonly showed pathological features associated with an aggressive behaviour, and that posttranslational regulation of mRNA may be a crucial step for the development of CRC in young patients.

Perea *et al.*<sup>[103]</sup> classified early-onset CRCs into four molecular subtypes: early-onset MSS, early-onset MSI/CIMP-high, early-onset MSS/CIMP-high and early-onset MSS/CIMP-low. Each of these subtypes differs in tumour location, BRAF mutation status (V600E), and presence or absence of family history. The first subtype is characterized by CRCs more commonly located in the left colon and proven family history as compared with cancer of the elderly. In the second subtype, MSI/CIMP-high early-onset CRC cases are prevalently associated with LS, whereas the elderly cases displayed BRAF V600E mutations. In the third subtype, early-onset MSS/CIMP high CRCs were more frequently of the mucinous subtype and right-sided compared to elderly cases (most of them related to LS). Finally, the early-onset MSS/CIMP-low differed from the elderly cases in location, stages, incidence of primary neoplasms and presence/absence of family history. The authors conclude that the age at onset should be the major criterion to consider when classifying CRC.

Chang *et al.*<sup>[53]</sup> compared histologic, molecular and immunophenotypic features of tumours from sporadic early-onset CRC (≤ 40 years of age) to a cohort of consecutively resected CRCs from patients > 40 years of age. The conclusions drawn by the authors is that early-onset CRCs are not frequently the result of underlying cancer-predisposing genetic conditions. As to tumour location and characteristics, they observed a striking predilection for distal colon (80%), particularly the sigmoid colon and the rectum, and a higher prevalence of adverse histologic factors such as signet ring cell differentiation, venous invasion, and perineural invasion. Furthermore, early-onset CRCs in their series are not frequently associated with precursor adenomatous or serrated lesions and do not appear to harbour frequent activating *BRAF* or *KRAS* mutations, suggesting that the molecular events in tumour development differ in this patient population.

### CONCLUSION

The phenotypic and genotypic heterogeneity of early-onset CRCs clearly emerges from clinical studies. Moreover, the cut-off age for early-onset CRC is not well defined and ranges between < 40 and < 50. For individuals ≥ 50 years there is a clear recommendation for CRC screening. Therefore, we suggest to use < 50 years of age as a cut-off to identify early-onset CRC patients. As to the phenotype, we can distinguish two distinct entities, an inherited subtype, usually with familial aggregation, accounting for a relatively low percentage of cases, with specific clinico-pathologic features such as a prevalent proximal location, a poor differentiation status, a higher mucin production, and a “sporadic” subtype, often without family history of CRC. This subtype has

distinct location and histopathologic features, such as a prevalence at distal sites, (mostly recto-sigmoid), and less favourable histological characteristics.

As to genotypic heterogeneity, despite the variable expressivity of the well defined CRC-prone syndromes, the overall heterogeneity belongs mainly to the “sporadic” subtype of the disease, suggesting a prominent role of the genetic background, *i.e.*, many genetic alterations equally or differentially contributing to the disease. As to this latter scenario, the following possible processes may occur: (1) a combination of genetic variants in multiple common low penetrance genes leading to an increase in the overall CRC risk; and (2) genetic variants of rare, moderate to high penetrance gene/s, so far mostly unidentified; and (3) a combination of both common low penetrance variants with rare or single family-specific high penetrance gene variants, conferring an overall increased risk of CRC and determining onset anticipation. This latter cancer predisposition pathway is certainly the most intriguing and debated one.

The significant variability in the mechanisms underlying the development of early-onset CRC is certainly a major concern for clinicians and oncologists, and bears implications on prevention, diagnosis and clinical management of the disease. Current National Comprehensive Cancer Network guidelines<sup>[104]</sup> suggest CRC screening in individuals at average risk (age > 50, no history of adenoma or CRC, inflammatory bowel disease and negative family history) and individuals at increased risk (personal history of adenoma/CRC, inflammatory bowel disease and positive family history). Whereas the efficacy of screening is clearly evident in the above-mentioned individuals, there is no evidence that specific screening programs on adolescent and young adults at average-risk would increase early detection and impact on survival<sup>[104]</sup>. With regard to the clinical management of the early-onset disease all affected individuals should be referred to a clinical geneticist. Following genetic risk assessment and molecular testing, patients with hereditary syndromes are included in surveillance programs according to specific international guidelines<sup>[104]</sup>. Conversely, patients with a “sporadic” CRC presently undergo established disease surveillance and management programs similar to late-onset CRC patients.

Further studies are warranted in order to gain a better insight in the pathogenesis and molecular features of this latter CRC subtype. These data may then be used to tailor cancer screening protocols to subjects under 50 years of age and to establish specific treatment and follow-up care for affected individuals.

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