World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v22.i5.1736

World J Gastroenterol 2016 February 7; 22(5): 1736-1744
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

2016 Colorectal Cancer: Global view

Clinical and molecular features of young-onset colorectal cancer

Veroushka Ballester, Shahrooz Rashtak, Lisa Boardman

Veroushka Ballester, Shahrooz Rashtak, Lisa Boardman, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN 55905, United States

Author contributions: Ballester V and Rashtak S performed the analytic review of the literature; Ballester V, Rashtak S and Boardman L wrote the paper.

Conflict-of-interest statement: The authors have no conflicts of interest to report.

Correspondence to: Lisa Boardman, MD, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States. boardman.lisa@mayo.edu
Telephone: +1-507-2664338
Fax: +1-507-2660350

Received: July 9, 2015
Peer-review started: July 9, 2015
First decision: September 29, 2015
Revised: October 25, 2015
Accepted: December 14, 2015
Article in press: December 14, 2015
Published online: February 7, 2016

Abstract

Colorectal cancer (CRC) is one of the leading causes of cancer related mortality worldwide. Although young-onset CRC raises the possibility of a hereditary component, hereditary CRC syndromes only explain a minority of young-onset CRC cases. There is evidence to suggest that young-onset CRC have a different molecular profile than late-onset CRC. While the pathogenesis of young-onset CRC is well characterized in individuals with an inherited CRC syndrome, knowledge regarding the molecular features of sporadic young-onset CRC is limited. Understanding the molecular mechanisms of young-onset CRC can help us tailor specific screening and management strategies. While the incidence of late-onset CRC has been decreasing, mainly attributed to an increase in CRC screening, the incidence of young-onset CRC is increasing. Differences in the molecular biology of these tumors and low suspicion of CRC in young symptomatic individuals, may be possible explanations. Currently there is no evidence that supports that screening of average risk individuals less than 50 years of age will translate into early detection or increased survival. However, increasing understanding of the underlying molecular mechanisms of young-onset CRC could help us tailor specific screening and management strategies. The purpose of this review is to evaluate the current knowledge about young-onset CRC, its clinicopathologic features, and the newly recognized molecular alterations involved in tumor progression.

Key words: Young-onset colorectal cancer; Late-onset colorectal cancer; Microsatellite instability; CpG island methylator phenotype; Chromosomal instability; Microsatellite; Chromosome stable colorectal cancer

Core tip: Recent evidence supports that young-onset colorectal cancer (CRC) is a "heterogeneous disease". Newly recognized molecular alterations implicated in tumor progression, appear to contribute to its heterogeneity. Young-onset CRCs are remarkably different compared to late onset CRCs. These differences

are highlighted by distinctive histologic features, site of tumor location, stage at presentation, and molecular profile. These differences support the possibility that young-onset CRC may be a different entity than late-onset CRCs. Understanding the molecular mechanisms underlying the development of young-onset CRC, will ultimately help individualize screening strategies and management for this high risk group.

Ballester V, Rashtak S, Boardman L. Clinical and molecular features of young-onset colorectal cancer. *World J Gastroenterol* 2016; 22(5): 1736-1744 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i5/1736.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i5.1736

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in the United States and is the second leading cause of cancer related mortality after lung cancer[1]. Young-onset CRC is an "heterogenous disease", thought to have a strong hereditary component, although most cases are sporadic[2]. It accounts for 2% to 8% of all CRC. The incidence of CRC per 100000 young individuals, between the ages of 20-49 years, increased 1.5% per year in men and 1.6% per year in women from 1992 to 2005[3]. This contrasts with the incidence of late onset CRC, which has been decreasing, mainly attributed to an increase in CRC screening. A study by Chang *et al*[4] evaluated a cohort of 75 CRCs in patients younger than 40 years, and found that 22% of these tumors were due to hereditary cancer syndromes; 17% demonstrated abnormalities in the mismatch repair genes and 5% had germline genetic disorders predisposing to CRC. Different molecular alterations contribute to the "heterogeneity" of young-onset CRC and there is evidence to suggest that compared with late-onset CRC, young-onset CRC may have a different molecular profile[2] (Table 1). The increasing incidence of young onset CRC along with its aggressive nature, emphasize not only the importance of awareness of risk factors in this age group, but also the importance of early evaluation in young individuals with symptoms.

Young-onset CRC is one of the "hallmarks" for Hereditary CRC Syndromes. Although young-onset CRC raises the possibility of an hereditary component, hereditary CRC syndromes represent 15%-20% of cases in this group[2,3]. Hereditary CRC syndromes only explain a minority of young-onset CRC cases, consequently, the pathogenic mechanisms in the majority of young onset CRC cases remains to be elucidated.

The purpose of this review is to evaluate the current knowledge about young-onset CRC, its clinicopathologic features, and the newly recognized molecular alterations involved in tumor progression.

Table 1 Clinicopathologic and molecular differences between young-onset and late-onset colorectal cancer

Clinical and molecular characteristics	Young-onset CRC (≤ 50 yr)	Late-onset CRC (> 50 yr)
Proximal colon		X
Distal colon and rectum	X	
Synchronous and metachronous CRC	X	
Later stage at diagnosis (stage Ⅲ/Ⅳ)	X	
Mucinous/signet ring and poorly differentiated features	X	
Typically MSS	X	
MSI due to *MLH1* gene promoter methylation		X
CIN		X
CIMP-low	X	
CIMP-high		X
Microsatellite and chromosome stable CRC	X	
Hypomethylation of LINE 1	X	

CRC: Colorectal cancer; MSS: Microsatellite stable; MSI: Microsatellite instability; CIN: Chromosomal instability; CIMP: CpG island methylator phenotype; MACS: Microsatellite and chromosome stable CRC.

LITERATURE RESEARCH

We extensively searched the literature for English articles and abstracts from 1946 through March 2015 on MEDLINE, EMBASE, Web of Science, Scopus, DDW.org and ClinicalTrials.gov. A combination of controlled vocabulary (MeSH, EMTREE) was used for MEDLINE and EMBASE. The terms "colorectal" or "colo rectal", "cancer", "adenocarcinoma", "carcinoma, "early onset" or "young onset" was applied in the searching process. Subject headings and publication types, including "clinical trials", "case reports", "case series", "controlled trials", "randomized controlled trials", "cohort studies", "retrospective/prospective studies", "major clinical studies", "meta-analysis", and "systematic review", were used to identify the relevant literature. Cited articles were selected based on the novelty and the relevancy to the purpose of this review.

CLINICOPATHOLOGIC CHARACTERISTICS OF SPORADIC YOUNG-ONSET CRC

Studies have shown that individuals with young-onset CRC have distinctive histologic features, site of tumor location, and stage at presentation. Compared with late-onset CRC, young-onset CRC occur most often in the distal colon and the rectum (69.0% *vs* 57.7%, $P < 0.001$)[5]. A study by Davis *et al*[6], which included data from the SEER Program of the National Cancer Institute, showed that in the 35 to 39 age group, 32% of tumors occurred in the rectum. This gradually decreased in subsequent age groups to a low of 15.1% in the 85 years and older age group[6]. The opposite trend was seen for cancers located in the cecum. In the 35 to 39 age group, 9.3% of the tumors occurred in the cecum. This increased in

Table 2 Clinical and molecular features associated with hereditary colorectal cancer syndromes

Hereditary CRC syndrome	Age of presentation	Gene(s)	Clinical features
Lynch syndrome	Average age of diagnosis of CRC is 42-45 yr	*MLH1, MSH2 MSH6,PMS2,EPCAM*	Lifetime risk of CRC 70% Risk of extracolonic cancers
Classic FAP	Average age of diagnosis of CRC is 39 yr	*APC MUTYH* (biallelic)	100-1000 adenomas CRC risk 90% without colectomy Risk of extracolonic cancers
Attenuated FAP	Average age of diagnosis of CRC is 51 yr	*APC, MUTYH* mutations detected in approximately 10%	10-99 adenomas
PJS	Polyps occur during childhood and early adulthood	*STK11*	Mucocutaneous pigmentation ⩾ 2 hamartomatous polyps in small bowel Lifetime cancer risks 80%-90%
JPS	Late childhood or early adolescence	*SMAD4, BMPR1A, ENG*	> 3-5 juvenile polyps in the gastrointestinal tract Congenital cardiac valvular disease and/or atrial and ventricular septal defects
PPAP	Second through fourth decades of life	*POLE POLD1*	Oligo adenomatous polyposis Young-onset CRC Endometrial cancer
Cowden disease	Second and third decades of life	*PTEN*	Variable CRC risk Macrocephaly Increased risk of thyroid, breast, and endometrial cancer

CRC: Colorectal cancer; FAP: Familial adenomatous polyposis; PJS: Peutz-Jeghers syndrome; JPS: Juvenile polyposis syndrome; PPAP: Polymerase Proofreading-Associated Polyposis.

subsequent age groups to a high of 23.2% in the 85 years and older age group[6]. Young-onset CRC is also associated with a higher percentage of synchronous and metachronous tumors. A study by Liang *et al*[7], which evaluated the clinicopathological and molecular characteristics of young-onset CRC, showed a higher incidence of synchronous (5.8% *vs* 1.2%, $P = 0.007$) and metachronous (4.0% *vs* 1.6%, $P = 0.023$) cancers in young individuals (younger than 40 years), when compared to older individuals.

Mucinous and signet ring features, as well as poorly differentiated histology, are typically associated with young-onset CRC. Data from the National Cancer Database showed that compared with later-onset CRC, young-onset CRC more frequently exhibited a mucinous and signet-ring histology (12.6% *vs* 10.8%, $P < 0.001$) and poor or no differentiation (20.4% *vs* 18%; $P < 0.001$)[8]. The reason for these histological differences is unknown, but differences in the molecular biology of these tumors may be a possible explanation[8]. Advanced-stage disease was more commonly diagnosed in young patients[5]. Later stage at diagnosis, could be related to lower screening rates and/or failure to recognize and evaluate symptoms in young individuals[8]. Data from the SEER from (1991-1999) showed that young individuals (20-40 years old) with CRC have a poorer overall 5 years survival compared with older individuals (60-80 year old) (61.5% *vs* 64.9%; $P = 0.02$)[8]. However, stage specific survival rates in patients with young-onset CRC equal or exceeded those with late-onset CRC[9]. In contrast to late-onset CRC, young-onset CRC has a higher incidence of recurrence and development of metastasis[10].

MOLECULAR FEATURES AND GENETICS OF SPORADIC YOUNG ONSET CRC

The pathogenesis of young-onset CRC is well characterized in individuals with an inherited CRC syndrome, in which a germline mutation in a cancer susceptibility gene is identified[11] (Table 2). Knowledge regarding the molecular features of sporadic young-onset CRC is limited[11]. Recent studies have reported that sporadic young-onset CRC may have a unique molecular profile. Sporadic young-onset CRC may be attributed to the cumulative effect of multiple genetic variants displaying variable penetrance[11]. A better understanding of these molecular mechanisms will help us tailor specific prevention and management strategies.

MICROSATELLITE INSTABILITY ANALYSIS

The majority of young-onset cancers does not show microsatellite instability (MSI), but rather are microsatellite stable (MSS) and lack DNA repair mechanism abnormalities (Figure 1A). MSI tumors in the younger population are mostly related to Lynch Syndrome (LS) and rarely to epigenetic inactivation of MLH1[12]. Recent studies have shown that the proportion of MSI found within young-onset CRC ranges from 19.7% to 41.0% depending on the age of onset[7,13]. This relatively high proportion of MSI tumors in young CRC patients has been attributed to the high number of patients with LS in that age group. Population-based studies have found MSI in only 7% to

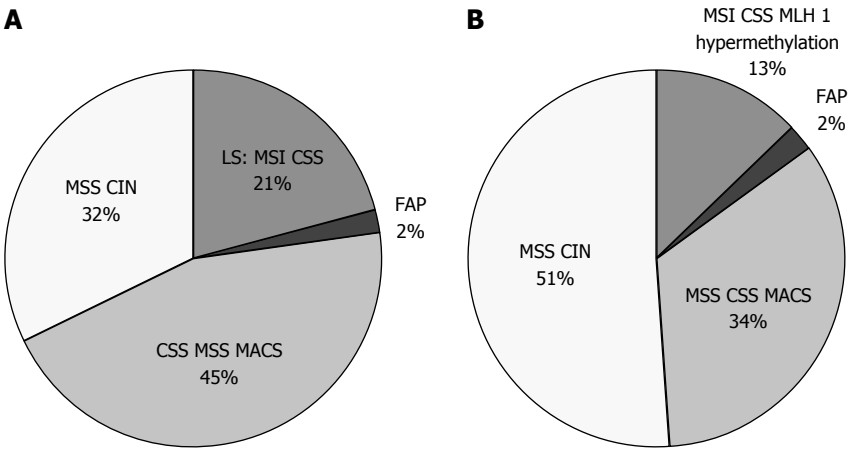

Figure 1 Molecular profile of young-onset (A) or late-onset (B) colorectal cancer.

17% of CRC patients under age 50[14]. A study by Yiu *et al*[15] showed that tumors with MSI in the older age groups (60-70 years and > 87 years) were associated with *MLH1* inactivation (83%) and *MLH1* promoter methylation (62%), while tumors in the young group (< 45 years) were associated with *MSH2* inactivation.

Typically, MSS tumors have a later stage of onset, are predominately found in the right colon, and are less likely to present with synchronous and metachronous tumors[4]. Several studies have evaluated the clinicopathologic features of this subset of CRC within the young-onset population[2]. Early-onset MSS tumors are remarkably different from those in late-onset MSS CRC (Figure 1B). Left colon location, low frequency of other primary neoplasms, and an important familial component are significant features of young-onset MSS CRC[16].

CPG ISLAND METHYLATOR PHENOTYPE

Methylation of CpG islands as a mechanism of silencing genes in colon tumors has been recognized as a third pathway involved in the development of CRC. CpG island methylator phenotype (CIMP) accounts for approximately 40% of all CRCs[16]. CIMP-high tumors are associated with proximal location in the colon, poor differentiation, MSI, and *BRAF* mutations[2]. Compared with late-onset CRC patients, those with young-onset disease have a higher rate of CIMP-low cases. But within LS patients who have young-onset CRC, a higher proportion will be CIMP-high compared to those LS patients who develop CRC at an older age. A study by Perea *et al*[16], which analyzed young-onset and late-onset CRC according to the three main carcinogenic pathways, showed that young-onset CIMP-high CRCs were associated with *MMR* gene germline mutations. In contrast, late-onset CIMP-high CRCs were more likely to be sporadic MSI tumors. This study showed marked differences between the young-onset and late-onset CRC. Young-onset CRCs were more commonly located in the left colon, had a higher rate of CIMP-low cases and had an important family component as a result of LS-related, but also LS-unrelated, cancer history[16].

MICROSATELLITE AND CHROMOSOME STABLE CRC

There is a subset of CRCs defined as microsatellite and chromosome stable CRC (MACS). This subset of CRCs are characterized by the absence of MSI-high and chromosomal instability (CIN). They may account for up to 30% of all sporadic CRCs[17]. They have been identified most frequently in younger cases. These tumors are most frequently located in the distal colon and rectum, have histologic features associated with poor prognosis, present with metastasis at diagnosis, and have early disease recurrence and lower survival than patients with MSI or CIN[17]. There is limited knowledge regarding the molecular profile of MACS. Recent studies have found out that MACS tumors are CIMP-low, are rarely associated with *BARF* mutations, have absent *MLH1* expression, and seem to have a different pattern of hypomethylation when compared to MSI and CIN CRC[2]. Some published studies suggest that MACS may be related to familial CRC syndromes, based on observed increased frequency in young patients[2].

LINE-1 HYPOMETHYLATION

LINE-1 hypomethylation is a unique feature of young-onset CRC[18]. LINE-1 hypomethylation is a "surrogate marker for genome-wide hypomethylation" and is associated with increased CIN[12]. The degree of LINE-1 hypomethylation has been recognized as an independent factor for increased cancer related mortality and overall mortality in CRC patients[18]. A study by Antelo *et al*[12] whose aim was to characterize the clinical, histological, and molecular features of a large cohort of young-onset CRCs in the context of the methylation status of LINE-1, showed that compared to older-onset colorectal tumors, young-onset CRCs

had significantly lower levels of LINE-1 methylation. This observation was validated in an independent set of young-onset CRC patients. These findings may help explain some of the biological mechanisms underlying young -onset CRC. Additional studies are needed to confirm this association and assess the prognostic value of LINE-1 in young-onset CRC.

HEREDITARY CRC SYNDROMES

Young age at onset is suggestive of a hereditary predisposition. The clinicopathological and the molecular features of young-onset CRC make it a "heterogenous disease". There is marked heterogeneity not only when comparing young and late onset CRC, but also within the young-onset group[11]. Young-onset CRC can be further characterized into two distinct subtypes: sporadic and inherited. Individuals with young-onset sporadic CRC usually have no family history, while inherited CRC, usually arise in the context of hereditary CRC syndromes[11]. The pathogenesis of young-onset inherited CRC is well characterized. Germline mutations in known cancer-susceptibility genes have been implicated in up to 5% of all CRC[19]. Most of these hereditary syndromes have typical phenotypes, and identification of germline mutations confirm the diagnosis.

LS

LS is the most common cause of inherited CRC and has been implicated in 2% to 4% of CRC cases[20]. It is an autosomal dominant condition defined by the presence of germline mutations in one of the mismatch repair genes *MLHI, MSH2, MSH6, PMS2* or loss of expression of the *MSH2* gene due to deletion in the *EPCAM* gene. MSI results from defective mismatch repair and is associated with loss of expression of *MLHI, MSH2, MSH6,* and *PMS2* proteins that can be detected by immunohistochemical analysis[21]. LS is characterized by a predisposition to develop colorectal and extracolonic malignancies such as endometrial, ovarian, urinary tract, gastric, small intestine, brain, hepatobiliary, and sebaceous neoplasms[1].

Lifetime risk for developing CRC is approximately 70%[22]. Progression through the adenoma-carcinoma sequence is thought to occur in less than 5 years, compared with sporadic carcinoma, which is thought to occur over a decade[23]. A more rapid progression to carcinoma may explain their increased lifetime risk for CRC. Patients with LS also have a high rate of metachronous CRC (16% at 10 years and 41% in 20 years)[24]. Therefore, recommendations for CRC surveillance include a colonoscopy every 1 to 2 years starting at the age of 20 to 25[21].

MOLECULAR FEATURES OF LS

LS is caused by a single dominant mutation in the germline. This increases the risk of cancer. LS-associated cancers develop only after a second hit occurs, which causes loss of function of the wild-type allele inherited from the unaffected parent[1]. Several genetic mechanisms are involved in the second hit including loss of heterozygosity and hypomethylation.

LS is characterized by an inactivation of one of the mismatch repair genes *MLHI, MSH2, MSH6*, and *PMS2.* Mutations in *MLH1* and *MSH2* account for up to 90% of cases, mutations in *MSH6* account for about 10% of cases, and mutations in *PMS2* account for 6% of all LS. Deletions in the 3' end codon of the *EPCAM* gene can result in LS through epigenetic silencing of the *MSH2* gene in tissues that express *EPCAM*[25]. A study by Kempers *et al*[26] showed that deletions in *EPCAM* carry a high risk of CRC.

MSI is characterized by expansion or contraction of microsatellite repeats and is found in more than 90% of CRC in patients with LS and in approximately 12% of patients with sporadic CRC[27]. MSI in CRC is due to a defect in one of the MMR genes caused by either a germline defect or a somatic change of the gene, as seen with hypermethylation of *MLH1*. MSI is characterized as MSI-high ($\geqslant$ 30% of markers are unstable), MSH-low (< 30% of markers are unstable), and MS-stable (no markers are unstable). Most of LS tumors are MSI-high[1]. The clinical significance of MSI-low has not been defined.

Immunohistochemistry evaluates for the loss of MMR protein expression and identifies patients with LS. Alterations in specific DNA MMR are indicated by loss or partial production of the MMR protein produced by that gene. Either somatic or germline alterations in specific *MMR* genes are indicated by loss or partial production of the protein produced by that *MMR* gene[1].

Somatic mutations in the *BRAF* gene at codon 600 are found in approximately 15% of sporadic CRC[1]. These CRC develop through the CpG island methylator pathway and are MSI-high through somatic promoter methylation of *MLH1*. Somatic mutation of *BRAF* V600 has been detected predominantly in sporadic CRC and is usually evidence against the presence of LS[28].

FAMILIAL ADENOMATOUS POLYPOSIS

Familial adenomatous polyposis (FAP) is the second most common inherited CRC syndrome and accounts for approximately 1% of the new CRC cases[19]. FAP is inherited in an autosomal dominant manner and is characterized by germline mutation in the adenomatous polyposis coli (*APC*) gene. Patients with classic FAP develop more than a 100 synchronous polyps beginning in the second or third decade of life. Their lifetime risk of developing CRC is estimated to exceed 99% in patients who do not undergo a colectomy[19]. Individuals with FAP are at increased risk for extracolonic cancers including: duodenal/ampullary tumors, which are the second leading cause of cancer

related mortality in individuals with FAP, papillary thyroid cancer, desmoid tumors, central nervous system tumors, and adrenal tumors.

The majority of the FAP cases are caused by a germline mutation in the *APC* tumor suppressor gene. Most mutations in *APC* are nonsense or frameshift mutations that cause premature truncation of the APC protein[29]. Studies have shown an association between the location of the A*PC* mutation and the phenotype in FAP patients[30]. The age of onset, amount of polyps, and the presence of extracolonic cancers appear to correlate with specific mutation sites[30].

Mutations located near the 5′ end of the *APC* gene or in the alternatively spliced region of exon 9 result in an attenuated phenotype of FAP[30]. Attenuated FAP is a milder variant of FAP, which presents with less number of colonic polyps, < 100, proximally located polyps, and an older age of presentation with CRC, compared to individuals with FAP.

MUTYH associated polyposis (MAP) is an autosomal recessive polyposis syndrome characterized by *MUTYH* gene mutation, most commonly Y179C and G396D. Biallelic *MUTYH* mutations account for 30% to 40% of cases with adenomatous polyposis in which an APC mutation cannot be detected[31]. Patients with biallelic MUTYH mutations can present with a variety of phenotypes. Some may present with colonic and extracolonic manifestations indistinguishable from FAP, but most cases present with oligopolyposis, with fewer than a 100 polyps[19]. Affected individuals have a later onset than FAP, approximately 10 years later. Biallelic carriers have an 80% cumulative lifetime risk of CRC by age 70. Some studies show that monoallelic carriers have a slightly increased risk of CRC. There appears to be a genotype-phenotype correlation with respect to cancer risk and age of onset. Individuals with homozygous Y179C mutation carriers have a more severe phenotype, with respect to age of onset and cancer risk, compared with individuals with the G396D allele[31]. A meta-analysis to assess the risk estimates associated with *MUTYH* variants, showed that individuals with biallelic gene mutation carriers have 28-fold increased risk, whereas those with monoallelic carries have less than 2-fold increased risk of developing CRC, when compared to the general population[32]. A study by Riegert-Johnson *et al*[33], which evaluated early onset CRC cases in which Lynch syndrome had been excluded by MSI testing, showed that *MUTYH* testing should be considered in patients with CRC diagnosed before the age of 50, found to have intact DNA MMR regardless of family history and the number of colon polyps.

PEUTZ-JEGHERS SYNDROME

Peutz-Jeghers syndrome (PJS) is an autosomal dominant hereditary CRC syndrome, which is characterized by hamartomatous polyps of the gastrointestinal tract and mucocutaneous hyperpigmented lesions. Germline mutation of the *STK11/LKB1* tumor suppressor gene is known to be the underlying defect. The multiple mutations identified in STK11/*LKB1* are responsible for the phenotypic variability[34]. Hamartomatous polyps are found throughout the gastrointestinal tract but most are found in the small bowel (60%-90%) and colon (50%-64%). The development of cancer in PJS polyps remains controversial. Malignant alterations have been described in hamartomas of individuals with PJS. A study by Giardiello *et al*[35] which evaluated 107 men and 106 women from 79 families, showed estimated cumulative cancer risks of 54% for breast, 39% for colorectal, 36% for pancreas, 29% for stomach and 21% for ovarian cancer by 64 years of age.

The only identifiable germline mutation in PJS is *STK11/LKB1*. It is located on chromosome 19p13.3 and acts as a tumor suppressor gene. Germline mutations of *STK11/LKB1* are found in up to 70%-80% of affected families[36]. Individuals with a truncation mutation in *STK11/LKB1*, have an earlier age of onset than those who have a missense mutation or when no mutation is detected in *STK11/LKB1*[36].

JUVENILE POLYPOSIS SYNDROME

Juvenile polyposis syndrome (JPS) is a hamartomatous polyposis syndrome, inherited in an autosomal dominant fashion. Unlike sporadic juvenile polyps, the polyps of individuals with JPS are more numerous and are located more proximal in the gastrointestinal tract. Individuals with JPS usually become symptomatic in childhood with symptoms of anemia, bleeding, or abdominal pain. The incidence of CRC is 17%-22% by the age of 35 and approaches 68% by the age of 60[37]. They are at increased risk for CRC and gastric cancer with a lifetime risk approaching 40%-50%[38]. This patients are also at increased risk of pancreatic and duodenal carcinomas.

Germline mutations in *SMAD4* and *BMPR1A* have been described in patients with JPS. BMPR1A mutations are found in 40%-100% of families without SMAD4 mutation[37]. These genes encode proteins involved in transforming growth factor-beta (TGF-beta) signaling pathway[36]. *SMAD4* mutations are more common and predispose to polyps in the upper digestive tract.

POLYMERASE PROOFREADING-ASSOCIATED POLYPOSIS

Germline mutations in the proofreading domains of 2 DNA polymerases, *POLE* and *POLD1*, are associated with an inherited colorectal adenoma and carcinoma syndrome, Polymerase Proofreading-Associated Polyposis (PPAP). This syndrome is inherited in an autosomal dominant manner, is highly penetrant, and is characterized by oligo adenomatous polyposis, young-onset CRC and endometrial cancer. The

loss of proofreading capability causes multiple mutations throughout the genome[38]. Compared to other dominantly inherited syndromes, tumors with exonuclease domain mutations in *POLE* and *POLD1* are MSS. Their primary mechanism or carcinogenesis is chromosomal instability, with "driver mutations" in *APC* and *KRAS* genes[39]. Germline variants in *POLE* and *POLD1* predispose individuals to either a multiple colorectal adenoma phenotype similar to that observed in MUTYH-associated polyposis or a Lynch phenotype, in which carriers develop young-onset CRC[40]. Germline mutations in the *POLE* and *POLD1* genes have been found to be responsible for a new form of CRC genetic predisposition[40].

PTEN HAMARTOMA

Cowden syndrome is caused by germline alterations in the phosphatase and tensin homolog (*PTEN*) tumor suppressor gene found in chromosome 10q23. It is an autosomal dominant syndrome that is characterized by mucocutaneous lesions, hamartomatous lesions, and increased risk of breast, thyroid, and endometrial cancer[41]. Bannayan Riley Ruvalcaba syndrome is an "allelic disorder" characterized by macrocephaly, pigmented penile macules, lipomas, and hamartomatous intestinal polyps[42]. Although published case reports have shown that 35%-85% of individuals with Cowden syndrome have gastrointestinal hamartomatous polyps, there is evidence that there is significant variability in the polyp phenotype[43]. A prospective series of *PTEN* carriers showed variability in the polyp histology and polyp number[43]. This study determined that hamartomatous, adenomas, serrated polyps, hyperplastic polyps, and ganglioneuromas constitute the Cowden syndrome polyp histology. It is important to note that in this study, 9 individuals (13%) were diagnosed with CRC at younger than age 50[43]. This finding suggests that individuals with *PTEN* mutation may benefit from early CRC screening.

CONCLUSION

CRC incidence and mortality are significantly increasing in individuals younger than 50 years of age. There is significant heterogeneity in the underlying mechanisms of young-onset CRC, which have implications in the prevention, diagnosis and management of these individuals. Currently there is no evidence that supports that screening of average risk individuals less than 50 years of age, will translate into increased early detection or increased survival. However, there should be a raise in awareness of the increasing incidence of young-onset CRC. Physicians could potentially play a central role, by evaluating the risk of CRC in each patient and recommending earlier screening to those with high risk personal and family history. Further studies are warranted to increase our knowledge of the molecular mechanisms underlying young-onset CRC, and to evaluate the benefit of screening high risk individuals younger than 50 years of age. These findings will help us tailor specific prevention and management strategies.

REFERENCES

1 **Giardiello FM**, Allen JI, Axilbund JE, Boland CR, Burke CA, Burt RW, Church JM, Dominitz JA, Johnson DA, Kaltenbach T, Levin TR, Lieberman DA, Robertson DJ, Syngal S, Rex DK. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. *Am J Gastroenterol* 2014; **109**: 1159-1179 [PMID: 25070057 DOI: 10.1038/ajg.2014.186]

2 **Silla IO**, Rueda D, Rodríguez Y, García JL, de la Cruz Vigo F, Perea J. Early-onset colorectal cancer: a separate subset of colorectal cancer. *World J Gastroenterol* 2014; **20**: 17288-17296 [PMID: 25516639 DOI: 10.3748/wjg.v20.i46.17288]

3 **Siegel RL**, Jemal A, Ward EM. Increase in incidence of colorectal cancer among young men and women in the United States. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 1695-1698 [PMID: 19505901 DOI: 10.1158/1055-9965.EPI-09-0186]

4 **Chang DT**, Pai RK, Rybicki LA, Dimaio MA, Limaye M, Jayachandran P, Koong AC, Kunz PA, Fisher GA, Ford JM, Welton M, Shelton A, Ma L, Arber DA, Pai RK. Clinicopathologic and molecular features of sporadic early-onset colorectal adenocarcinoma: an adenocarcinoma with frequent signet ring cell differentiation, rectal and sigmoid involvement, and adverse morphologic features. *Mod Pathol* 2012; **25**: 1128-1139 [PMID: 22481281 DOI: 10.1038/modpathol.2012.61]

5 **You YN**, Xing Y, Feig BW, Chang GJ, Cormier JN. Young-onset colorectal cancer: is it time to pay attention? *Arch Intern Med* 2012; **172**: 287-289 [PMID: 22157065 DOI: 10.1001/archinternmed.2011.602]

6 **Davis DM**, Marcet JE, Frattini JC, Prather AD, Mateka JJ, Nfonsam VN. Is it time to lower the recommended screening age for colorectal cancer? *J Am Coll Surg* 2011; **213**: 352-361 [PMID: 21737316 DOI: 10.1016/j.jamcollsurg.2011.04.033]

7 **Liang JT**, Huang KC, Cheng AL, Jeng YM, Wu MS, Wang SM. Clinicopathological and molecular biological features of colorectal cancer in patients less than 40 years of age. *Br J Surg* 2003; **90**: 205-214 [PMID: 12555297 DOI: 10.1002/bjs.4015]

8 **Ahnen DJ**, Wade SW, Jones WF, Sifri R, Mendoza Silveiras J, Greenamyer J, Guiffre S, Axilbund J, Spiegel A, You YN. The increasing incidence of young-onset colorectal cancer: a call to action. *Mayo Clin Proc* 2014; **89**: 216-224 [PMID: 24393412 DOI: 10.1016/j.mayocp.2013.09.006]

9 **O'Connell JB**, Maggard MA, Liu JH, Etzioni DA, Livingston EH, Ko CY. Do young colon cancer patients have worse outcomes? *World J Surg* 2004; **28**: 558-562 [PMID: 15366745]

10 **Yeo SA**, Chew MH, Koh PK, Tang CL. Young colorectal carcinoma patients do not have a poorer prognosis: a comparative review of 2,426 cases. *Tech Coloproctol* 2013; **17**: 653-661 [PMID: 23460362 DOI: 10.1007/s10151-013-0977-z]

11 **Stigliano V**, Sanchez-Mete L, Martayan A, Anti M. Early-onset colorectal cancer: a sporadic or inherited disease? *World J Gastroenterol* 2014; **20**: 12420-12430 [PMID: 25253942 DOI: 10.3748/wjg.v20.i35.12420]

12 **Antelo M**, Balaguer F, Shia J, Shen Y, Hur K, Moreira L, Cuatrecasas M, Bujanda L, Giraldez MD, Takahashi M, Cabanne A, Barugel ME, Arnold M, Roca EL, Andreu M, Castellvi-Bel S, Llor X, Jover R, Castells A, Boland CR, Goel A. A high degree of LINE-1 hypomethylation is a unique feature of early-onset colorectal cancer. *PLoS One* 2012; **7**: e45357 [PMID: 23049789 DOI: 10.1371/journal.pone.0045357]

13 **Losi L**, Di Gregorio C, Pedroni M, Ponti G, Roncucci L, Scarselli A, Genuardi M, Baglioni S, Marino M, Rossi G, Benatti P, Maffei S, Menigatti M, Roncari B, Ponz de Leon M. Molecular genetic alterations and clinical features in early-onset colorectal carcinomas

and their role for the recognition of hereditary cancer syndromes. *Am J Gastroenterol* 2005; **100**: 2280-2287 [PMID: 16181381]

14 **Salovaara R**, Loukola A, Kristo P, Kääriäinen H, Ahtola H, Eskelinen M, Härkönen N, Julkunen R, Kangas E, Ojala S, Tulikoura J, Valkamo E, Järvinen H, Mecklin JP, Aaltonen LA, de la Chapelle A. Population-based molecular detection of hereditary nonpolyposis colorectal cancer. *J Clin Oncol* 2000; **18**: 2193-2200 [PMID: 10829038]

15 **Yiu R**, Qiu H, Lee SH, García-Aguilar J. Mechanisms of microsatellite instability in colorectal cancer patients in different age groups. *Dis Colon Rectum* 2005; **48**: 2061-2069 [PMID: 16374936]

16 **Perea J**, Rueda D, Canal A, Rodríguez Y, Álvaro E, Osorio I, Alegre C, Rivera B, Martínez J, Benítez J, Urioste M. Age at onset should be a major criterion for subclassification of colorectal cancer. *J Mol Diagn* 2014; **16**: 116-126 [PMID: 24184227 DOI: 10.1016/j.jmoldx.2013.07.010]

17 **Banerjea A**, Hands RE, Powar MP, Bustin SA, Dorudi S. Microsatellite and chromosomal stable colorectal cancers demonstrate poor immunogenicity and early disease recurrence. *Colorectal Dis* 2009; **11**: 601-608 [PMID: 18637931 DOI: 10.1111/j.1463-1318.2008.01639.x]

18 **Ogino S**, Nosho K, Kirkner GJ, Kawasaki T, Chan AT, Schernhammer ES, Giovannucci EL, Fuchs CS. A cohort study of tumoral LINE-1 hypomethylation and prognosis in colon cancer. *J Natl Cancer Inst* 2008; **100**: 1734-1738 [PMID: 19033568 DOI: 10.1093/jnci/djn359]

19 **Stoffel EM**, Kastrinos F. Familial colorectal cancer, beyond Lynch syndrome. *Clin Gastroenterol Hepatol* 2014; **12**: 1059-1068 [PMID: 23962553 DOI: 10.1016/j.cgh.2013.08.015]

20 **Hampel H**, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, Clendenning M, Sotamaa K, Prior T, Westman JA, Panescu J, Fix D, Lockman J, LaJeunesse J, Comeras I, de la Chapelle A. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. *J Clin Oncol* 2008; **26**: 5783-5788 [PMID: 18809606 DOI: 10.1200/JCO.2008.17.5950]

21 **Syngal S**, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol* 2015; **110**: 223-62; quiz 263 [PMID: 25645574 DOI: 10.1038/ajg.2014.435]

22 **Aarnio M**, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, de la Chapelle A, Peltomäki P, Mecklin JP, Järvinen HJ. Cancer risk in mutation carriers of DNA-mismatch-repair genes. *Int J Cancer* 1999; **81**: 214-218 [PMID: 10188721]

23 **Edelstein DL**, Axilbund J, Baxter M, Hylind LM, Romans K, Griffin CA, Cruz-Correa M, Giardiello FM. Rapid development of colorectal neoplasia in patients with Lynch syndrome. *Clin Gastroenterol Hepatol* 2011; **9**: 340-343 [PMID: 21070872 DOI: 10.1016/j.cgh.2010.10.033]

24 **Win AK**, Parry S, Parry B, Kalady MF, Macrae FA, Ahnen DJ, Young GP, Lipton L, Winship I, Boussioutas A, Young JP, Buchanan DD, Arnold J, Le Marchand L, Newcomb PA, Haile RW, Lindor NM, Gallinger S, Hopper JL, Jenkins MA. Risk of metachronous colon cancer following surgery for rectal cancer in mismatch repair gene mutation carriers. *Ann Surg Oncol* 2013; **20**: 1829-1836 [PMID: 23358792 DOI: 10.1245/s10434-012-2858-5]

25 **Kovacs ME**, Papp J, Szentirmay Z, Otto S, Olah E. Deletions removing the last exon of TACSTD1 constitute a distinct class of mutations predisposing to Lynch syndrome. *Hum Mutat* 2009; **30**: 197-203 [PMID: 19177550 DOI: 10.1002/humu.20942]

26 **Kempers MJ**, Kuiper RP, Ockeloen CW, Chappuis PO, Hutter P, Rahner N, Schackert HK, Steinke V, Holinski-Feder E, Morak M, Kloor M, Büttner R, Verwiel ET, van Krieken JH, Nagtegaal ID, Goossens M, van der Post RS, Niessen RC, Sijmons RH, Kluijt I, Hogervorst FB, Leter EM, Gille JJ, Aalfs CM, Redeker EJ, Hes FJ, Tops CM, van Nesselrooij BP, van Gijn ME, Gómez García EB, Eccles DM, Bunyan DJ, Syngal S, Stoffel EM, Culver JO, Palomares MR, Graham T, Velsher L, Papp J, Oláh E, Chan TL, Leung SY, van Kessel AG, Kiemeney LA, Hoogerbrugge N, Ligtenberg MJ. Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch syndrome: a cohort study. *Lancet Oncol* 2011; **12**: 49-55 [PMID: 21145788 DOI: 10.1016/S1470-2045(10)70265-5]

27 **Aaltonen LA**, Peltomäki P, Leach FS, Sistonen P, Pylkkänen L, Mecklin JP, Järvinen H, Powell SM, Jen J, Hamilton SR. Clues to the pathogenesis of familial colorectal cancer. *Science* 1993; **260**: 812-816 [PMID: 8484121]

28 **Nakagawa H**, Nagasaka T, Cullings HM, Notohara K, Hoshijima N, Young J, Lynch HT, Tanaka N, Matsubara N. Efficient molecular screening of Lynch syndrome by specific 3' promoter methylation of the MLH1 or BRAF mutation in colorectal cancer with high-frequency microsatellite instability. *Oncol Rep* 2009; **21**: 1577-1583 [PMID: 19424639]

29 **Nagase H**, Nakamura Y. Mutations of the APC (adenomatous polyposis coli) gene. *Hum Mutat* 1993; **2**: 425-434 [PMID: 8111410 DOI: 10.1002/humu.1380020602]

30 **Nieuwenhuis MH**, Vasen HF. Correlations between mutation site in APC and phenotype of familial adenomatous polyposis (FAP): a review of the literature. *Crit Rev Oncol Hematol* 2007; **61**: 153-161 [PMID: 17064931]

31 **Terdiman JP**. MYH-associated disease: attenuated adenomatous polyposis of the colon is only part of the story. *Gastroenterology* 2009; **137**: 1883-1886 [PMID: 19879216 DOI: 10.1053/j.gastro.2009.10.017]

32 **Theodoratou E**, Campbell H, Tenesa A, Houlston R, Webb E, Lubbe S, Broderick P, Gallinger S, Croitoru EM, Jenkins MA, Win AK, Cleary SP, Koessler T, Pharoah PD, Küry S, Bézieau S, Buecher B, Ellis NA, Peterlongo P, Offit K, Aaltonen LA, Enholm S, Lindblom A, Zhou XL, Tomlinson IP, Moreno V, Blanco I, Capellà G, Barnetson R, Porteous ME, Dunlop MG, Farrington SM. A large-scale meta-analysis to refine colorectal cancer risk estimates associated with MUTYH variants. *Br J Cancer* 2010; **103**: 1875-1884 [PMID: 21063410 DOI: 10.1038/sj.bjc.6605966]

33 **Riegert-Johnson DL**, Johnson RA, Rabe KG, Wang L, Thomas B, Baudhuin LM, Thibodeau SN, Boardman LA. The value of MUTYH testing in patients with early onset microsatellite stable colorectal cancer referred for hereditary nonpolyposis colon cancer syndrome testing. *Genet Test* 2007; **11**: 361-365 [PMID: 18294051 DOI: 10.1089/gte.2007.0014]

34 **Campos FG**, Figueiredo MN, Martinez CA. Colorectal cancer risk in hamartomatous polyposis syndromes. *World J Gastrointest Surg* 2015; **7**: 25-32 [PMID: 25848489 DOI: 10.4240/wjgs.v7.i3.25]

35 **Giardiello FM**, Welsh SB, Hamilton SR, Offerhaus GJ, Gittelsohn AM, Booker SV, Krush AJ, Yardley JH, Luk GD. Increased risk of cancer in the Peutz-Jeghers syndrome. *N Engl J Med* 1987; **316**: 1511-1514 [PMID: 3587280 DOI: 10.1056/NEJM198706113162404]

36 **Chen HM**, Fang JY. Genetics of the hamartomatous polyposis syndromes: a molecular review. *Int J Colorectal Dis* 2009; **24**: 865-874 [PMID: 19381654 DOI: 10.1007/s00384-009-0714-2]

37 **Schreibman IR**, Baker M, Amos C, McGarrity TJ. The hamartomatous polyposis syndromes: a clinical and molecular review. *Am J Gastroenterol* 2005; **100**: 476-490 [PMID: 15667510]

38 **Church JM**. Polymerase proofreading-associated polyposis: a new, dominantly inherited syndrome of hereditary colorectal cancer predisposition. *Dis Colon Rectum* 2014; **57**: 396-397 [PMID: 24509466 DOI: 10.1097/DCR.0000000000000084]

39 **Palles C**, Cazier JB, Howarth KM, Domingo E, Jones AM, Broderick P, Kemp Z, Spain SL, Guarino E, Salguero I, Sherborne A, Chubb D, Carvajal-Carmona LG, Ma Y, Kaur K, Dobbins S, Barclay E, Gorman M, Martin L, Kovac MB, Humphray S, Lucassen A, Holmes CC, Bentley D, Donnelly P, Taylor J, Petridis C, Roylance R, Sawyer EJ, Kerr DJ, Clark S, Grimes J, Kearsey SE, Thomas HJ, McVean G, Houlston RS, Tomlinson I. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. *Nat Genet* 2013; **45**: 136-144 [PMID: 23263490 DOI: 10.1038/ng.2503]

40 **Esteban-Jurado C**, Garre P, Vila M, Lozano JJ, Pristoupilova A, Beltrán S, Abulí A, Muñoz J, Balaguer F, Ocaña T, Castells A, Piqué JM, Carracedo A, Ruiz-Ponte C, Bessa X, Andreu M, Bujanda L,

Caldés T, Castellví-Bel S. New genes emerging for colorectal cancer predisposition. *World J Gastroenterol* 2014; **20**: 1961-1971 [PMID: 24587672 DOI: 10.3748/wjg.v20.i8.1961]

41 **Zbuk KM**, Eng C. Cancer phenomics: RET and PTEN as illustrative models. *Nat Rev Cancer* 2007; **7**: 35-45 [PMID: 17167516]

42 **Pilarski R**, Stephens JA, Noss R, Fisher JL, Prior TW. Predicting PTEN mutations: an evaluation of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome clinical features. *J Med Genet* 2011; **48**: 505-512 [PMID: 21659347 DOI: 10.1136/jmg.2011.088807]

43 **Heald B**, Mester J, Rybicki L, Orloff MS, Burke CA, Eng C. Frequent gastrointestinal polyps and colorectal adenocarcinomas in a prospective series of PTEN mutation carriers. *Gastroenterology* 2010; **139**: 1927-1933 [PMID: 20600018 DOI: 10.1053/j.gastro.2010.06.061]

P- Reviewer: Linnebacher M **S- Editor**: Ma YJ **L- Editor**: A
E- Editor: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327