

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2017 July 28; 23(28): 5041-5256



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**NAME OF JOURNAL**  
*World Journal of Gastroenterology*

**ISSN**  
 ISSN 1007-9327 (print)  
 ISSN 2219-2840 (online)

**LAUNCH DATE**  
 October 1, 1995

**FREQUENCY**  
 Weekly

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**PUBLICATION DATE**  
 July 28, 2017

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## Colorectal cancer in young adults: A difficult challenge

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**Author contributions:** Campos FG contributed to the manuscript.

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

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**Manuscript source:** Invited manuscript

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Received: March 21, 2017

Peer-review started: March 22, 2017

First decision: April 20, 2017

Revised: June 7, 2017

Accepted: July 12, 2017

Article in press: July 12, 2017

Published online: July 28, 2017

### Abstract

Sporadic colorectal cancer (CRC) is traditionally diagnosed after the sixth decade of life, and current recommendations for surveillance include only patients older than 50 years of age. However, an increasing incidence of CRC in patients less than 40 years of age has been reported. This occurrence has been attributed

to different molecular features and low suspicion of CRC in young symptomatic individuals. When confronting young-onset CRC with older patients, issues such as biological aggressiveness, stage at diagnosis and clinical outcomes seem to differ in many aspects. In the future, the identification of the molecular profile underlying the early development of sporadic CRC will help to plan tailored screening recommendations and improve management. Besides that, differential diagnosis with CRC linked with hereditary syndromes is necessary to provide adequate patient treatment and family screening. Until we find the answers to some of these doubts, doctors should raise suspicion when evaluating a young adult and be aware of this risk and consequences of a late diagnosis.

**Key words:** Colorectal cancer; Young age; Hereditary; Prognosis

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**Core tip:** Colorectal cancer (CRC) is traditionally considered a disease affecting people with more than 50 years of age. However, numerous researches have detected a rising incidence of CRC in young people, mainly rectal cancer. This finding raises the need for increasing clinical suspicion when evaluating symptoms of a young patient. Furthermore, these groups of patients must be aware of this possibility.

Campos FG. Colorectal cancer in young adults: A difficult challenge. *World J Gastroenterol* 2017; 23(28): 5041-5044 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i28/5041.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i28.5041>

### INTRODUCTION

Colorectal cancer (CRC) is the most common gastrointestinal neoplasia. As it is widely considered a

disease that affects people after the 5<sup>th</sup> decade of life, screening is not indicated before 50 years of age, when the risk is lower<sup>[1]</sup>. Over the past years, the increasing use of screening colonoscopy in adults aged 50-75 years has declined CRC incidence by at least 4% per year due to resection of adenomas, also improving the detection of more early lesions<sup>[2]</sup>.

The finding of CRC in adolescents or young adults has always raised attention due to issues such as the emotional impact at diagnosis, the disease behavior and the possibility to be associated with genetic diseases<sup>[3]</sup>.

However, the definition of age to be considered young is controversial. In an analysis of 6425 patients from 55 publications, O'Connell *et al*<sup>[4]</sup> found that 37 manuscripts considered young those below 40 years of age, while 14 (25%) and 4 (7%) defined as young those below 30 and 35 years of age, respectively. In the literature, most publications refer the CRC incidence in patients with less than 40 years of age<sup>[4-6]</sup>.

The incidence of CRC diagnosed before 40 years of age varies from 0.8% to 15%<sup>[5]</sup>. Series published during the last decade reveal great variation due to biases associated with experiences from one institution or reference centers. Recently, a greater incidence of young age CRC has been documented<sup>[7]</sup>. Within this group, a proper investigation to discharge hereditary forms of CRC is fundamental.

So far, age is not universally accepted as an independent prognostic factor. Otherwise, CRC diagnosis in young people is always difficult, as both patients and physicians underestimate symptoms and postpone diagnosis and management<sup>[6]</sup>.

## EPIDEMIOLOGY

CRC lifetime risk is around 5%<sup>[8]</sup>. Since 1998, the CRC overall incidence has decreased in the United States, as a probable effect of CRC screening<sup>[9]</sup>. However, in a contrast to these overall trends, this pattern is different among young adults.

Studies from *Surveillance Epidemiology and End Result* have presented important findings regarding the epidemiologic trends of CRC in different age groups. Bailey *et al*<sup>[10]</sup> reported a growing incidence rate (10%) among patients from 20 to 50 years and a 20% reduction after 50 years. Using resource data from 1987 to 2006, Davis *et al*<sup>[11]</sup> found raising incidences within patients aged 20-49 years, especially among those between 40-44 years (from 10.7 in 1988 to 17.9 per 100 thousand in 2006). From 1973 to 2005, Meyer *et al*<sup>[12]</sup> identified 7661 CRC patients with less than 40 years in a retrospective study. Age variation throughout time revealed stable rates for colon and increased rates for rectal cancer. Consequently, the authors emphasize that symptomatic young adults should be endoscopically investigated to avoid a late diagnosis, as malignant tumors in young predominates in segments distal to the splenic flexure.

Also, data from the American Cancer Society also noticed an increase in the global incidence from 1992 to 2005 among adults between 20 and 49 years, demonstrating a 3.5% increase per years among men and 2.9% per year in women<sup>[13]</sup>. More recently, a report from the National Cancer Database identified a consistent incidence increase from 1998 to 2007 by analyzing a group of young-onset (64068, 11%) and later-onset (52480, 89%) CRC<sup>[14]</sup>.

## CLINICO-PATHOLOGICAL AND GENETIC ASPECTS

There exists lots of discussion regarding the disparities related to age at CRC diagnosis and tumor biology, recurrence rates, treatment and outcomes. Most publications emphasize that the incidence of young-onset CRC has increased mainly between 40-49 years, when they are more likely to be found in the distal colon and rectum and also advanced stages at presentation.

Although controversial, young patients have been considered to have a more aggressive biological behavior and worst prognosis<sup>[15-17]</sup>. Furthermore, It has been also described a greater prevalence of mucinous and less differentiated tumors<sup>[18]</sup> within this group, characteristics also associated with bad prognosis. For these reasons, the question of considering 40 years as the basis for colonoscopic surveillance has been a constant matter of debate, mainly for men<sup>[19]</sup>.

This behavior is generally attributed to the discovery of a more advanced disease, as stages III and IV predominate among the young<sup>[14,18,20]</sup>. Our group evaluated the question if a late diagnosis could result from less diagnostic efforts in an apparent health group, and we found that symptoms duration was equal (13.8 mo vs 14.5 mo,  $P = 0.5$ ) among the young and control group<sup>[5]</sup>. Others<sup>[21]</sup> have similarly emphasized that the greater proportion of patients with advanced-stage could not be simply explained by delay in diagnosis.

These results suggest that identification of high-risk young people for screening and recognition of alert symptoms is now a real medical problem. For this, complaints such as persistent rectal bleeding, abdominal pain or anemia should require endoscopic work-ups even in average-risk young people.

One of the main challenges in a young population is to distinguish sporadic from the hereditary forms of CRC. Overall, only 2%-5% of CRC are caused by highly penetrant genes<sup>[22]</sup>, and 15%-20% of CRC in young age population are hereditary<sup>[23,24]</sup>. An additional problem is that a familiar history of CRC in almost one fifth of hereditary syndromes patients is not recognized<sup>[14,25]</sup>. Besides this, when diagnosed with a CRC, a young patient should undergo genetic tests, even in the absence of clinical phenotype or normal MSI-IHC studies<sup>[26]</sup>.

So far, knowledge regarding the molecular features of sporadic young-onset CRC is limited. It is generally thought that they derive from a cumulative effect of multiple genetic variants displaying variable penetrance. Probably, the molecular profile in young is heterogeneous and different from late-onset CRC patients<sup>[27]</sup>.

## FINAL COMMENTS AND PERSPECTIVES

Important information may be extracted from the present data. Within a young group, CRC is usually diagnosed later and potentially associated with worst prognosis. Thus, a greater suspicion rate is necessary when evaluating young patients with common symptoms. Moreover, educational and preventive programs should provide adequate information regarding alert symptoms and risk populations.

The recognition that CRC incidence at an early age may be correlated with modern dietary factors and epidemic obesity requires improvement in medical awareness and population information about these risk factors<sup>[28]</sup>. Moreover, young people may develop sporadic cancers that are not usually detected through current screening programs, suggesting a possible drawback in the CRC screening recommendations adopted so far. This fact raised the idea to lower the screening age of those not associated with a high risk (although there is no consensus about it so far), even though the impact of such attitude on early detection, costs and survival has not been fully appreciated yet<sup>[29]</sup>. In addition, there are lots of barriers to overcome in terms of adherence to preventive colonoscopy at a young age.

In terms of colonoscopic surveillance for risk groups, both patients and physicians should be aware about the importance of establishing a family pedigree. This is based on previous knowledge and investigations demonstrating that the existence of a young family member or a first-degree relative with CRC is risk factors for advanced lesions (including cancer)<sup>[30]</sup>.

Eventually, young age may affect therapeutic decisions, as patients with sporadic cancers before 50 years have been considered for a subtotal colectomy, although this decision not always translates into a greater survival<sup>[31]</sup>. Otherwise, the recognition of a hereditary syndrome would certainly support the indication of a total colectomy and suggest familial surveillance, besides the absence of prospective randomized trials comparing extended and segmental resections<sup>[32]</sup>. This tendency correlates with the fact that the presence of mismatch repair deficiency raises the risk of subsequent metachronous neoplasia<sup>[33]</sup>.

Aside from those involved in Lynch Syndrome, many other genes (APC, KRAS, P53, BRAF) may influence tumor genesis and biology. In this context, mutations in FBXW7 and POLE genes were found to prevail in younger patients with CRC<sup>[34]</sup>. Thus, the most crucial challenge for the future is the understanding of how

genetic profile may affect CRC incidence and outcomes of treatment interventions in different age cohorts.

In the absence of genetic information, however, individual decisions should be taken on the basis of health status, family history, opportunity to undergo postoperative follow-up, quality of anal sphincters and patient consent information.

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**P- Reviewer:** Milone M, Lakatos PL, Sag AA **S- Editor:** Qi Y  
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ISSN 1007-9327

