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 http://www.wjgnet.com

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology
ESPS manuscript NO: 24070
Title: Colorectal Cancer in the Young; many questions, few answers
Reviewer's code: 03002173
Reviewer's country: United Kingdom
Science editor: Yuan Qi
Date sent for review: 2016-01-05 10:27
Date reviewed: 2016-01-17 01:27

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This is an interesting and relevant topic. The section regarding genetics does not highlight the differences between colorectal cancer in the young patient compared to the older patient. Rather, it reads like a brief summary of the different genetic subtypes of colorectal cancer. The section regarding risk factors does not do so either. As such, I think the manuscript would benefit from revision of these two sections to highlight, compare and contrast the differences between young patients and older patients with colorectal cancer. In the section regarding pathology, the authors suggest that advanced disease stage at presentation in younger patients is suggestive of more aggressive tumour biology. Could this not be reflective of the fact that younger patients may either present late or be less likely to be referred by physicians for investigation of symptoms due to the perceived low risk in this group? Please could this be discussed.

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 http://www.wjgnet.com

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology
ESPS manuscript NO: 24070
Title: Colorectal Cancer in the Young; many questions, few answers
Reviewer's code: 03478899
Reviewer's country: United States
Science editor: Yuan Qi
Date sent for review: 2016-01-05 10:27
Date reviewed: 2016-01-19 08:09

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[Y] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

One of the principal structural defects of the review was a lack of clarity with regard to defining the "early onset" colorectal population. This is not an easy task because various groups and a variety of publications set different cut-off values, e.g. 40 y/o, 45 y/o, 50 y/o, 34 y/o; therefore, it is the review authors' obligation to make clear the age definition used in the study being cited. In a similar vein, the rapid-fire succession of statistics in the review only further clouds the issues because of the ambiguity regarding the study populations. Considering the numbers of reports in the last decade or so concerning the genetics of colorectal carcinoma, particularly its heritable syndromes, the section "Genetics" is both excessively brief and misleading. The authors do not clearly explain the difference between germline acquired mutations, which are hereditary, and spontaneous somatic mutations which may arise early in development. Both create a similar scenario for increased risk of early onset disease since fewer additional somatic driver mutations are needed to produce a tumor cell. I am also troubled by the lack of a clear explanation of the roles of CIN, MSI and CIMP. All three processes are mechanisms of genome instability that greatly increase overall mutagenesis in tissues; this acts in concert with a selective evolutionary process favoring cells harboring driver

mutations. The authors should also define Lynch Syndrome and HNPCC more clearly. Finally, I must take exception to the somewhat alarmist use of the statistics ascribed to Ref. 19. Yes, a 124 % increase in incidence of early onset rectal cancer over the next 15 years would be disturbing but even doubling the incidence of a rare entity – it's still a rare entity. Additionally, the cited projections were based upon historical trends over the last four decades. In a review, I would expect the authors to provide the necessary caveats which must accompany those projections, rather than "call(ing) for collective global thought and action."

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 http://www.wjgnet.com

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology
ESPS manuscript NO: 24070
Title: Colorectal Cancer in the Young; many questions, few answers
Reviewer's code: 03478694
Reviewer's country: United States
Science editor: Yuan Qi
Date sent for review: 2016-01-05 10:27
Date reviewed: 2016-01-21 12:27

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This review covers the recent increase in colorectal cancer among young patients and describes clinical features, potential etiologies, and screening considerations for early onset colorectal cancer. The manuscript is clear and well-organized. The family history section is a key section as many of these patients are presumed to have some inherited predisposition for early onset colorectal cancer. This section should be clarified and expanded. The first sentence in this section should be clarified that the hereditary component for CRC of 15-30% is based on aggregation of CRC among family members. The heritable syndromes in CRC listed in the next sentence, such as FAP and HNPCC, are only identified in 2-5% of CRC cases. Thus, no inherited cause is identified in most patients. Studies of patients with CRC diagnosed before the age of 50 years suggest that 5-10% of these cases have tumors that exhibit deficiency of a mismatch repair enzyme. The authors should consider describing other familial syndromes that may also contribute to early onset CRC. A recent study published by Mork et al in JCO evaluated for hereditary cancer syndromes in young patients (<35 years old) with colorectal cancer referred to the genetics service of an academic center. In this highly selected population of very young patients who met clinical criteria for genetics evaluation, the

authors describe that 35% of patients had an identifiable hereditary cancer syndrome with genetic testing (12% HNPCC, 9% FAP). The genetics section as written does not clearly outline the genetics of CRC as suggested in the core tip. This section should be developed further and comment on our understanding of common genetic alterations in CRC. The first sentence in this section is awkward and unclear – do the authors want to say "whether" CRC is sporadic or part of an inherited syndrome, it results from the cumulative effect of genetic alterations that activate growth and survival pathways? The authors note that the origins of colorectal cancer may be attributed to the presence of various common or rare genetic variants, so far largely unidentified. This statement refers to a study from 2010. Since that time, The Cancer Genome Atlas in Colorectal Cancer has been published and numerous series of CRC analyzed with NGS technology (e.g. a series of over 3000 CRC cases analyzed by Foundation Medicine reported at ASCO 2015) have characterized the most common genetic alterations in CRC, potentially actionable alterations, and differences between primary tumors and metastases. I don't believe any studies have clearly identified a genetic signature for early onset CRC, suggesting that somatic mutations alone may not distinguish early onset CRC from disease occurring in older patients. Do recurrent alterations in CRC, e.g. TP53, APC, KRAS, and BRAF mutations, vary between early onset CRC and cases occurring in older individuals? The point of the sentence "Even in the remainder, when CRC occurs in its 'sporadic' form, acquired somatic mutations are known to play a central role in its genesis" is unclear. The description of CIMP that notes that the CIMP pathway varies fundamentally from MSI makes it sound like these two pathways are mutually exclusive. In fact, many CIMP tumors are also microsatellite unstable through methylation of MLH-1. The authors should mention in the reference to the association of BRAF mutation to CIMP that this is usually due to promoter methylation and silencing of MLH-1. CIMP has often been associated with older age at presentation, female predominance, and right-sided tumors, in contrast to early onset CRC. The authors should comment on how common the CIMP pathway is involved in early onset CRC. The information about screening appears more nuanced in the conclusion than in the screening section. The authors provide data that screening younger patients may not lead to significant life-year gains, and then immediately discuss the ne