

Dear Editors,

We are very pleased with the positive reviews to our work and we are delighted to provide you with the revised manuscript alongside annotated changes that were made in agreement to the reviewers. We would like to thank the reviewers for their precious help in addressing the most necessary changes to this review. We sincerely believe that this peer-review process has greatly improved the quality of the review. We hope that it will similarly meet the interest of readers of *World Journal of Gastroenterology* and we wish it will spark enthusiasm for further research and discussion on the topic.

Please find, on the next pages, our replies to the reviewers and to the Editor's changes.

Sincerely,

The Authors

REVIEWER 00036099

This is a well-written review concerning colorectal cancer screening from 45 years old. This review is interesting and informative, pro- and anti- arguments are rigorously developed. I have no major remarks. The different fields concerned by CCR screening in young people are discussed. Authors underline the need for scientific evidence from population studies especially in front of the heterogeneity of epidemiologic indicators across countries. May be this geographical heterogeneity is the major point that may question lowering the age for screening in all countries. The choice of the screening strategy (FIT then colonoscopy vs colonoscopy alone) is crucial too and may strongly depends from each public health officials. Authors argue that advanced-stage diagnosis from eoCRC is increasing over time. This has been observed in the US non-selected general population and started around 1998 (SEER program, Wang et al). If later stage at diagnosis could be related to lower screening and failure to recognize symptoms in young individuals, I wonder why this would have strongly changed over the past 20 years. Data on these trends are scarce.

Based on the SEER program data, trends over time in incidence were heterogeneous among race/ethnicity. The increase concerned young Non-Hispanic Whites. A European Irish recent population-based study (Ullah et al) exhibited a global increase in stage III and IV disease for patients <50 yrs, mostly influenced by stage of presentation in patients aged 20–29 years. Explanations for these trends are unclear and, as underlined by authors, more large epidemiological and medico-economic studies are urgently needed.

Minor remarks Paragraph 2.2.1, second paragraph: “This is proven by the increase in incidence among white adults”

- We sincerely thank the reviewer for the kind words of interest in our work, and we agree with the raised concern: the reason driving the increasing incidence of CRC at stage III and IV is largely unknown, and data are missing. Larger population-based studies will be necessary to develop a more comprehensive understanding of the epidemiology we are facing. An earlier start of screening colonoscopies might indeed be valid only in those geographical areas where this increasing rate of early onset colorectal cancer

has been noticed and reported.

The reference has been noted and added to bibliography, and highlighted, thank you (cfr. ref. 22. Ullah MF, Fleming CA, Mealy K. Changing trends in age and stage of colorectal cancer presentation in Ireland - From the nineties to noughties and beyond. *Surgeon*. 2018;**16**: 350-354 [PMID: 29680182 DOI: 10.1016/j.surge.2018.03.006]).

The word "mortality" has been removed from the noted sentence, thank you, and it now reads (highlighted) "This is proven by the increase in incidence among white adults", Section 2.2.1., second paragraph, second sentence.

REVIEWER 00503931:

The authors describe very clearly the epidemiology of colorectal cancer (CRC) and emphasize the increasing incidence of early onset CRC over recent decades, supported by recent epidemiological studies. I consider the article very beneficial, it will help to improve CRC screening and I think it will serve as a motivation for further population studies. The article is well-arranged and gives clear arguments and counter-arguments for early CRC screening.

- We sincerely thank the reviewer for the kind words and the interest in our work. We share similar hopes for future studies that might clarify the changing epidemiology of colorectal cancer.

I would have a few comments:

Measuring the benefit of screening is in the values of "Life years gained" and "Years of potential life lost". Authors should define these values so that readers will better understand what these values mean.

- Thank you for the valuable suggestion, it is indeed necessary to allow all audiences to familiarize with these terms.

We therefore added and highlighted the definition of YPLL to the beginning of section 2.2., which now reads: "Years of potential life lost (YPLL) is an estimate of the average years a person would have lived if he or she had not died prematurely. Measuring the impact of disease in terms of YPLL, (...)"

We added and highlighted the definition of LYG to the second paragraph of section 2.2., around line 10, which now reads: "Outcomes of these studies were expected benefits (life-years gained, LYG, an estimate of the number of years of life gained compared to no screening)"

Introduction, line 37: „Mortality from eoCRC has likewise increased by 11 % in 2005-2015 (SEER data).“ Can authors provide the reference of this argument?

- Thank you for noticing, the reference has been added and highlighted, "[26]"

Chapter 2.1. Burden of disease, line 18: „Incidence of CRC in the 40-49 age group is lower than in the 50-55 one...” It would be better to clarify the numbers of incidence.

- Thank you for noticing, the change has been done and highlighted, and it now reads: “Incidence of CRC in the 40-49 age group is lower than in the 50-55 one (31.4 versus 58.4:100,000)^[3,14]”

Chapter 2.1. Burden of disease, line 25: „...inflammatory bowel disease patients (relative risk 2.6-2.8)...” There is missing reference.

- Thank you for noticing, the reference has been added and highlighted, ^[49-51], (highlighted both in text and in references)

Chapter 2.2. Expected benefits, line 48: „In fact, CRC incidence in 40-44 is half of 45-49 age group. (17.6 versus 31.4 per 100000).” Please, provide reference.

- Thank you for noticing, the reference has been added and highlighted, ^[3,14]”

Chapter 2.2.1. Additional expected benefits to the 50-55 age group, line 15: „In fact, trials indicate that a negative sigmoidoscopy or colonoscopy provides long term protection from CRC for 17 and 20 years, respectively (the longest duration of completed follow-up).” Reference is missing.

- Thank you for noticing, the reference has been added and highlighted, ^[60,62]”

Chapter 2.3. Sustainability, line 4: „ Moreover, younger adults have a lower rate of complications, so morbidity should be a smaller issue than expected in older populations.”

Are there data about compliance of younger individuals to screening CRC compared to the compliance of older individuals? Is it assumed that younger individuals will have higher compliance?

- Thank you for the question, it is an interesting topic of discussion. To date, screening for individuals younger than 50 is only offered to a selected population at higher risk for colorectal cancer (i.e., individuals with a first degree relative whose colorectal cancer was diagnosed before the age of 50, or individuals at high risk for IBD or hereditary cancer syndromes). However, there are no data concerning compliance of young individuals whose risk is

not increased compared to the general population. Indeed, some studies investigated the compliance in young, at risk, individuals, but such results cannot be generalized: knowing to have a higher than average risk for cancer probably motivates individuals more strongly.

We added a short sentence with respect to this interesting topic, and it is highlighted in text: "However, compliance with screening colonoscopy in younger individuals needs to be further evaluated, and at present, it is unpredictable how compliant younger individuals will be."

Chapter 2.4. Society guidelines, line 19: "With some variation across European countries, most screenings begin between 50 and 60 years of age."

There are also European guidelines in which CRC screening from 50 years of age is recommended. Regarding the list of US guidelines, I recommend adding European guidelines:

1. European Colorectal Cancer Screening Guidelines Working Group, von Karsa L, Patnick J, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication. *Endoscopy*. 2013;45(1):51-9. doi: 10.1055/s-0032-1325997.

- We thank you for the valuable suggestion. The reference has been inserted in text and in the references section. The main text now reads: "European guidelines similarly recommend screening from the age of 50^[73]"

Table 2: in paragraph Society guidelines should be next to the USPSTF and USMSTF also listed European guidelines, which recommend CRC screening from 50 years of age.

- Thank you, again, for noticing. We added and highlighted the European guidelines in the table too, which now reads: "USPSTF⁵, USMSTF⁶ and ECCSGWG⁷ support screening from 50 years of age"

Dear Editor,

We sincerely thank you for the help in drafting the manuscript in agreement with your quality standards. We would apologize for any inconsistency that you might have previously found with respect to your instructions.

We have modified the manuscript thanks to your suggestions, specifically:

- **Non-Native Professional English Language Editing**

This has been provided by the AJE (American Journal Experts). On April 15, 2019, they issued their editorial certificate that “certifies that the manuscript listed below was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at American Journal Experts”. The certificate verification key is the following: 1602-1F97-4E31-3AC6-C69F

- **Audio Core Tip**

After following your instructions on the website, we have uploaded a .mp3 audio file. In this file, the first author described the final core tip, and the file size is 1.3 MB/10 MB.

- **Video**

We have uploaded a .mp4 video file where the viewer can be guided through the main topics of the review.

- **Photo**

After following your instructions on the website, we have uploaded a .jpeg image file, which describes the core findings of the review.

- **Spacing and Font:**

All text is 12 point Book antiqua, 1.5 spacing, with ample margins

- **Manuscript NO**

This was added in the first page, as requested (47208), and highlighted

- **Corresponding author**

we provided the corresponding authors' name, title and detailed address with phone number and email address. changes have been highlighted

- **Copyright**

The copyright agreement form was uploaded previously, and it has been re-uploaded. Moreover, the following statement has been added to the main text, after the abstract, as highlighted: "**©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.**"

- **Open access**

As requested, the following sentence has been added to the main body after the conflict-of-interest statement: "**Open Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial.**

See: [//creativecommons.org/licenses/by-nc/4.0/](https://creativecommons.org/licenses/by-nc/4.0/)".

- **Paragraph titles**

As suggested, we changed the format so that main titles are bold and capitalized, subtitles bold and italicized, and sub-subtitles bold. The paragraph titles that were changed have been highlighted.

- **References**

Each reference item now lists all authors (first author in bold), with PMID and DOI for all available items. The volume number has been written in bold according to instructions. Moreover, all references are now written with 1.5 spacing. Finally, all references are now in superscript, as requested, in square brackets, with sequential numbering, without separating spaces. There are no

repeated references.

However, the following references cite websites, presentations or registries, and as such they do not have a DOI/PMID: 25, 27, 28, 47, 62, 66, 87, 89, 117.

As it is described in the "instructions to authors, these have been highlighted in the reference section.

- **Table:**

All tables are black and white for high contrast. Titles do not contain acronyms. All acronyms used in the tables are explained in the corresponding table legends. We have replaced superscript letters with superscript numbers, as requested. All changes have been highlighted accordingly. Italics have been avoided.

Concerning table 1, the information in the legend is specific to the table. If we inserted this information in the main text, it would interrupt and perturb the reader's experience, in the opinion of the authors. Authors would most respectfully ask the editors to let them place such notions in the table's legend, if agreeable.