Regarding the revised version of manuscript 12251 "CRC Carcinogenesis – Update and Perspectives".

Dear Editor

We thank you for the opportunity to submit a revised version of the above-mentioned article.
We wish to thank the reviewers for their thorough revisions and comments. In the following sections, each comment made by the reviewer is followed by our response in red. In the submitted revised article, changes are highlighted with "track-changes".

1. Reviewer:
Classification: Very Good
This manuscript summarizes the topics of colorectal cancer. However, some more information needs to be added:

1. The authors cited recent comprehensive reports from the World Cancer Research Fund and the American Institute for Cancer Research, and the reports also mentioned the correlation between obesity and colorectal cancer. In this review, however, description of an important risk factor, obesity, is missing. Please add a section regarding obesity and colorectal cancer.

Authors: We appreciate the comment but the scope of the article is a review on the molecular biology and genetics related to colorectal cancer carcinogenesis and the clinical implications hereof. Lifestyle factors such as obesity and exercise was deliberately not included.

2. Some abbreviations are not used through the whole text, i.e. CRC for colorectal cancer, g for grams. Please modify this point.

Authors: We agree. The manuscript is revised accordingly.

2. Reviewer:
Classification: Excellent
The authors' have discussed the genetic and chromosomal basis of colorectal carcinogenesis in a lucid manner.

However, since the focus of this article is genetic implications in carcinogenesis, some sections are deviating from this theme and need to be edited. In the section on Lynch syndrome, it is suggested that the authors' simply describe the genetic mechanisms of the disease and omit evaluation and clinical parameters.

Authors: We agree, the clinical parameters and evaluation are deleted from the text.

Similarly, in the section titled 'Clinical Perspectives', the authors' have needlessly discussed surgical treatment including laparoscopic excision and local excision,as well as radiotherapy, which are not relevant to the topic under discussion.

Authors: We agree. The discussion has been changed accordingly

Instead, the authors' need to discuss the role of genetic testing of patients in order to tailor the treatment and individualise therapy.

Authors: We agree, discussion changed

3. reviewer:
Classification: Excellent
Congratulations for the excellence of your work.I commented only no reference to hypergastrinemia brougth about by longterm use of PPI.There are conflicting conclusions in medical litteratture,although most deny any influence,but the world experience is still short.My best regards.

Authors: We agree. Hypergastrinemia does not lead to significant clinical risk for most PPI users.

4. Reviewer:
Classification: Good
Dear Author Thank you for your interesting presentation

Authors: Thank you.

5. Reviewer:
Classification: Poor
I appreciate the scope of the review. However, and perhaps because of this scope, this review does not cover many aspects of colorectal carcinogenesis adequately. Parts of this review also appear somewhat disorganized and it is quite unfocused.

Authors: we respectfully disagree. The manuscript deliberately does not cover all risk factors and risk assessment but focuses on the molecular biology and genetics.

I would suggest starting the review with risk factors and protective factors divided by magnitude of risk - divide to strong, moderate and modest.

Authors: We deliberately did not include well-known lifestyle factors such as obesity and exercise although we did include relevant dietary factors, smoking and alcohol as they represent important chemical drivers for colorectal cancer carcinogenesis.
To include all known risk factors and discuss and asses their individual risk magnitude would require a vast amount of text space and make the manuscript more suitable for a text-book.

Then you could proceed with types of colorectal carcinogenesis pathways (CIN, MMR, CIMP).

Authors: We believe the CIN and MMR pathways are well described.
With regard to CIMP, it is correct that the CpG island methylator phenotype is a distinct phenotype in colorectal cancer. However, CIMP status as a prognostic factor and the interactions between CIMP status and response to chemotherapy have been contradictive. In all, we think that the role of CIMP in unclear and currently not clinically relevant.

If you decide to discuss polyposis syndromes then do it all or make a comprehensive table, don't be selective, for example HNPCC is broadly covered, yet the role of EPCAM gene is not covered.

Authors: The EPCAM gene encodes a carcinoma-associated antigen. The antigen is expressed on most normal epithelial cells and gastrointestinal carcinomas and functions as a calcium-independent cell adhesion molecule. EPCAM deletions cause MSH2 gene silencing by promoter hypermethylation.
The antigen has been used as a target for immunotherapy treatment of human carcinomas. So far, no additional benefit from EPCAM immunotherapy has been shown. At this point, we consider EPCAM of little interest for the clinician.

BRAF/V600E is briefly mentioned.

The role of MYH and other polyposis syndromes are simply missing.

Authors: We agree, MAP has been included in the text.

Large parts of text on dietary risk factors are simply speculative or inadequate.
For example the paragraph on fiber has 3 references, yet this is a topic with lots of evidence, including RCTs and metanalyses, most recent metanalysis on fiber and risk of adenomas was published this year in Gastro.

Authors: With all respect we have 6 references in the paragraph on fiber. As suggested, we have included the recent publication in Gastroenterology. The conclusion of this meta-analysis is in accordance with what is otherwise stated in our text.

Best regards, on behalf of the authors

Hans Raskov