Rosalind and Morris Goodman Cancer Centre

Cancer Pavilion
McGill University
1160 Pine Avenue W.
Montreal, Quebec, Canada, H3A 1A3

Centre de recherche sur le cancer Rosalind et Morris Goodman

Pavillon cancer
Université McGill
1160, rue des pins ouest
Montréal (Québec) Canada, H3A 1A3

Tel. : (514) 398-3535
Fax : (514) 398-6769

Dr. Nicole Beauchemin
514-398-3541
Nicole.Beauchemin@mcgill.ca

Monday, June 15th 2015

Dr. Lian-Sheng Ma,
President and Company Editor-in-Chief
World Journal of Gastroenterology

RE: Review ID (01685437) "Colitis-Associated Colon Cancer: Is it in Your Genes?"
ESPS Manuscript NO: 18830

Dear Dr. Ma,
Please find uploaded on your site the revised review entitled "Colitis-Associated Colon Cancer: Is it in Your Genes?" that we had accepted to provide for World Journal of Gastroenterology. We were only provided with one review at this point but since it has been close to two months since we submitted our review and 6 weeks since we have received the requested revisions, we have now proceeded with the revisions that were requested by this unique reviewer. The Response to Reviewer is appended to this letter.

We have formatted this review according to the instructions available on your Website and according to a recent review published in your journal. We have also prepared two new color figures for this review that are uploaded as pdf documents (Fig. 1 as a reduced pdf owing to the size of the photos). When the original Figures are needed for publication, we will organize to transfer them to you taking into consideration to the size of these photos (Fig. 1 = 20.9 mB, Fig. 2 = 355 k).

We appreciate your feedback on this paper. Please note that we cannot download the document "Copyright Transfer Document" as the Web link provided is non-functional. We request that you send us this document as a pdf attachment please.

Nicole Beauchemin, Ph.D.
McIntyre Building, Room 702A
McGill University
3655 Promenade Sir-William-Osler
Montreal, QC, Canada
H3G 1Y6
Tel : 514-398-3541 Fax : 514-398-6769
e-mail: nicole.beauchemin@mcgill.ca

June 15, 2015

Response to Reviewer 1:

We thank Reviewer 1 for insightful comments and revisions on our review entitled: "**Colitis-Associated Colon Cancer: Is it in Your Genes?"** Please find below a detailed response to the questions raised by Reviewer 1:

1. "I find it surprising that I could not find any mention of PSC, as a strong risk factor for CRC in IBD, anywhere in the paper. Why is there such a huge risk associated with PSC from the basic science perspective and is there a genetic component there as well? can modelling and extrapolation be done from this subset of patients to try and understand the molecular basis behind CRC development in IBD? -"
We have now included a new section on p. 6 of the present manuscript on Primary Sclerosing Cholangitis and how it relates to IBD development. Unfortunately, the genetics risks associated with this condition have not been studied in great detail in the literature and whatever is found is contradictory. We have therefore added the necessary references in this section but not commented further on genetic assessment of Primary Sclerosing Cholangitis-mediated IBD development.

2. "I also find it surprising that the most controversial point of this clinical situation is only lightly discussed (page 5): do 5ASA agents actually reduce the risk of CRC in UC? there has been a lot of controversy around this issue and I think for the average reader of such an article this needs to be tackled with more vigour, do other agents reduce this risk as well e.g. UDCA? -"
To answer this request, we have now also added a paragraph on ASA therapy on p. 5 of the present manuscript. Several references have been included in the list to point out the controversy in the literature. We have also mentioned UDCA treatments in the section on Primary Sclerosing Cholangitis on p. 6: " there is some evidence to suggest that treatment with ursodeoxycholic acid (UDCA) may reduce risk of CA-CRC, although additional testing is still necessary [36]."

3. "There is mention of increased numbers of prophylactic colectomy on page 8, please clarify if this is for patients with familial predisposition to CRC or IBD patients?, if its the latter where is the data to support this claim? -"
We have indicated in this section (p. 10) that prophylactic colectomy is for IBD patients with appropriate references: " In part, this maybe due to high numbers of **IBD** patients undergoing colectomy, making identification of IBD patients with and without CA-CRC difficult [53, 54].

4. "On page 4 there is a statement that suggests that the incidence of CRC is almost equal between UC and colonic CD, the reference for this statement is very old, is there a more updated reference that can be used?"
We have now included more up-to-date references for this statement on p. 4: "Both UC- and CD-CRC are early-onset conditions presenting with an average age of onset between 40 - 55 years of age [6, 8-10]."

5. "also, please indicate that only a small proportion of CD patients have isolated colonic disease as this is clinically relevant. -"
We have included this statement on p. 4, as requested: "whereas CD-CRC is more evenly distributed between the right-colon (ascending), sigmoid colon and rectum [6, 11], although only a small proportion of CD patients have colonic disease."

6. "In the summary of risk factors of CRC in IBD, some other risk factors should be added to the list such as shortened colon, pseudo-polyps, histologic inflammation, PSC, family history,....etc -
Should a brief mention of surveillance be included? I will leave this part to the editors to decide?"

To answer this request, we have now included on p. 4, one significant paragraph and associated references including other risk factors and possible surveillance of the disease.

"According to the American Cancer Society, individuals at increased risk for CA-CRC should undergo routine colonoscopy at 1-2 year intervals starting 8-12 years post-disease diagnosis (www.ccfa.com). It is also recommended that at least four random colonic biopsies be taken for every 10 cm of colon examined during these routine colonoscopies, as approximately 20-50% of colon dysplasia cannot be detected by visual inspection alone [12, 13]. Intraepithelial neoplasms are highly variable with respect to appearance and may present as raised (pendunculated or sessile) or flat (plaque or bump) lesions [14]. Flat lesions are a unique feature to CA-CRC, rarely being detected in familial or sporadic CRC, and are generally associated with high risk of transformation into CA-CRC [15]. The identification of CA-CRC can also be further complicated by large benign inflammatory pseudopolyps, which form during mucosal regeneration and ulcer healing."