Reply to Reviewers

Reviewer #1:

Scientific Quality: Grade C (Good)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: Thank you for this paper. This is a very important subject, as we gain more understanding of the interplay of the immune system and cancers, in particular MSI High tumors, this research will be increasingly relevant. This study is of course limited by the size of the cohort, so no definite conclusions can be made. I think the authors are cautious to avoid drawing any significant conclusions from the content. Although this is briefly mentioned, I think more focus needs to be given to the fact that disease severity is not known. in IBD patients, the risk of CRC is associated with duration of symptoms and likely severity of colitis. The use of immune modulating drugs can theoretically have a positive effect in that they can control the inflammation that is potentially acting as a stimulus for malignancy. Conversely, the drugs can decrease our immune surveillance in malignancy. There is too much confounding and missing information to understand the interplay between these. The number of patients exposed and unexposed will make it challenging to draw any definitive conclusions, but I think this needs to be emphasized as a limitation. While IBD increases the risk of LS associated cancers, rheumatologic conditions don't and so there is limitation in grouping these together. Although the author tries to address the diseases separately, when it comes to comparing exposed and unexposed, the autoimmune diseases are generally grouped together. These should be evaluated separately. Additionally, there is no cancer specific survival for these patients. In some series, patients with IBD and those taking immunosuppressive medications present with later stage disease or have worse survival when controlling for stage. The impact of medical immunosuppression on survival in patients with LS who develop malignancy.

Reply to Reviewer #1: Thank you for your excellent review and thoughtful comments. The authors appreciate your time and opinion and have addressed your queries in the manuscript and discuss them below.

We have now emphasized in the *Discussion* that the severity of IBD was not known for all patients. We have also pointed out in the *Discussion* with reference that the risk of CRC is associated with duration of symptoms and severity of colitis. The use of immune modulating drugs can theoretically have a positive effect in individuals with IBD alone by suppressing inflammation, but the effect is unknown in LS individuals when these drugs also suppress immune surveillance. The phenotypic characteristics of the patients

with IBD have already been described in Results. Per your suggestion, we also have separated results for the proportion of individuals who develop cancer based on disease type (IBD and rheumatic disease) . We agree that cancer specific survival rates are an outcome of interest, and this should be evaluated in future studies, which we have now recommended in the *Discussion*.

Reviewer #2:

Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: This study is the first to evaluate the relation between HNPCC and CID, as well as, the impact of biologics and immunomodulators on cancer risk in HNPCC. Due to the small sample, no statistical differences were identified. But this theme was novel and deserved valuable molecular researches to detect the interaction between these two diseases. A small detects was the meaning of the abbreviation of TAH-BSO in the results part was not clear. Good job!

Reply to Reviewer#2

Thank you for your excellent review and positive comments. The authors appreciate your valuable input. We have made the correction and added the full form of TAH-BSO per your suggestion.

Reviewer #3:

Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: Chronic inflammation is one of the causative factors of inflammatory bowel disease (IBD)-associated colorectal cancer, which induces cyclooxygenase (COX)-2, inflammatory cytokines, and chemokines. Immunomodulators have anti-inflammatory properties and are used as maintenance therapy in IBD patients. There is limited evidence for the chemopreventive role for immunomodulators in IBD in most studies. However, one meta-analysis by Lu et al. revealed an antineoplastic effect of thiopurines on colorectal neoplasia in patients with IBD, particularly amongst the patients with ulcerative colitis (published in Aliment Pharmacol Ther 2018 Feb;47(3):318-331), Please add this in issue in the DISCUSSION part.

Reply Reviewer #3

We thank you for your time in reviewing our study. We appreciate your valuable feedback and have added your recommendation to our manuscript along with the suggested reference. We look forward to your continued support for our paper.