19-Nov-2020,

Dear Dr. Song

# BMJ-2020-061335 entitled "Risk of colorectal cancer in first-degree relatives of patients with colorectal polyps: a nationwide case-control study in Sweden"

Thank you for sending us this paper, which we sent for peer review and discussed at our manuscript meeting. Unfortunately we do not consider it suitable for publication in its present form. However if you are able to amend it in the light of our comments and our external reviewers' comments below, we would be happy to consider it again.

Our reasons are explained below in the report from the manuscript meeting. As you will appreciate we receive a large number of articles and often have to reject valuable and worthwhile work. When making an editorial decision we take the comments of the reviewers into account and also consider whether a piece will interest and inform our readers and whether it adds sufficiently to previous work.

The reviewers' reports are available at the end of this letter.

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**Report from The BMJ’s manuscript meeting**

At the manuscript meeting the Editor makes the final decisions on accepting original papers submitted to the journal. At the manuscript meeting each article is discussed by The BMJ’s international team of research editors and one statistician. When making decisions we take into account each paper’s originality, scientific merits, and interest to a general readership in comparison with other submitted papers. We take reviewers’ reports fully into account too, but the final decision on acceptance or rejection of a paper rests with the editors.
These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Wim Weber (chair), Jon Deeks (statistician), Elizabeth Loder, Nazrul Islam, John Fletcher, Tiago Villanueva, David Ludwig

Paper: BMJ-2020-061335

Decision: rejection

Detailed comments from the meeting:

- Statistician comments:
  This seems to be looking at whether family history of colonic polyps should be added to the screening criteria for CRC.
  Unclear how and why people get diagnosed with polyps in Sweden. The usefulness of this as a marker for screening will depend on how polyps get picked up. Are these from routine screening colonoscopy or from symptomatic investigations?
  Given that screening is considered on the basis of family history, having polyps will only make a difference in those without family history. Thus I am really interested in the group who have no family history, but have polyps compared to not. Little data are presented on this group – the value of this finding depends on the size of this group, and the OR in this group.
  There are no data on the absolute increase in CRC from detecting polyps. Very hard to see that it is going to make a substantial difference in absolute numbers based on the points above.

Editor's comments:
- We liked the research question. But since we know that CRC is a byproduct of poly growth, it does not seem surprising that family history of colorectal polyps (which are now removed long before CRC develops) is associated with CRC risk. We’re not convinced this will change screening recommendations.
- Isn’t the design wide open to ascertainment bias? Colon cancer may be asymptomatic for years. If first degree relatives of people with a polyp are more likely to worry about their own risk or more likely to consult a doctor earlier than people without family awareness then any observed association will be overstated.
  It may possible to at least explore this if they have access to the number of diagnostic investigations performed in people with and without a family history of polyps. Without this information you could just discuss this as another limitation.

Reviewer: 1

Recommendation:

Comments:
The new information this manuscript brought to light is intuitive, logical and novel the connection between first degree relatives with polyps and individual cancer risk has not been exhaustively studied. The connection between a family history of colorectal cancer and increased incidence is well established. Finding a similar connection between a first degree relative having polyps and increased risk in family members particularly in younger people may lead to this being a new recognized additional risk factor to be considered this may have a positive impact on encouraging a population with an increased risk to get screened.
These new risk criteria could help young people determined to be at elevated risk obtain screening at an earlier age and therefore avoiding and/or down staging cancer as an outcome. The challenge of reducing the incidence and severity of colorectal and who will most benefit from screening is always difficult. This new factor might just be the extra motivation needed for the test to be done. The paper is well organized and provides a good foundation building on established research evidence. In this time when due to the pandemic many are avoiding medical treatment this new evidence may help the most at risk be identified and scheduled for screening. As a consumer-patient reviewer the impact of this being published would be a significant help to patients.

Additional Questions:

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This study addresses an important topic—what is the risk of CRC among relatives of those with colorectal polyps. Comments and suggestions to enhance the manuscript:

At first look, the study design is addressing risk of polyps among the relatives of those with CRC. And it seems the starting point should have been those with colonic polyps and then assess risk of CRC among the relatives. Please comment in the manuscript why the current design is appropriate.

Does ESPRESSO capture all CRC in Sweden? What about site unspecified CRCs?

Colectomy is used for management of CRC and therefore the exclusion must have been colectomy some time before CRC diagnosis. Suggest clarifying that.

I am assuming the databases identify some/most individuals with hereditary syndromes and they were excluded. This has implications on the younger group results in particular and other results and so should be mentioned. If not available, this should be discussed.

Some readers would be interested in looking at more of the validity data—NPV as well as PPV, sensitivity, specificity for the specific kinds of polyps in ESPRESSO. Please consider adding to appendix.

Could controls develop CRC after the index date and then be included as cases?

CRC codes 153 and 154—do they capture the same CRCs as the codes used in ESPRESSO? Why not use ESPRESSO to identify CRC in FDRs, similar to that used for identifying cases? How do ESPRESSO and ICD-9 compare with each other?

“Second, the nationwide polyp data in ESPRESSO are confined to 1965 and onwards, with limited coverage prior to 1990.” It would be helpful to have a discussion of the effect of this issue on the results of the study.
The following does not follow from the results presented and suggest moderating. Effectiveness of screening in the young, for example, would be an additional factor, which would need to be determined. “Our findings suggest that early screening may be considered for better prevention of early-onset CRC in FDRs of individuals with polyps, particularly those with multiple FDRs having a history of polyps and whose FDRs’ polyps are diagnosed at a younger age”

The prevalence of polyps seems lower than that reported in other studies. Is it similar to that reported elsewhere in Sweden? In any case, please discuss why lower.

Hyperplastic polyps in FDR are reported in this study to be associated with increased risk of CRC in index cases. This is difficult to understand, when HP in index cases are known not to increase the risk in the index cases. Suggest to mention caution on use of this finding, as it has the potential of markedly increasing colonoscopy screening.

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Reviewer: 3

Recommendation:

Comments:
Thank you for this comprehensive analysis of family history of polyps and CRC using the excellent nationwide Swedish databases. This study includes novel findings and was well performed, and would also be suited for a gastroenterology journal.

The manuscript and the analyses were thoughtfully prepared. These are comments:
1) The mean age at diagnosis of CRC among the index patients was 63.5 years. Please discuss why this average age is lower than in other population-based or registry-based studies.
2) The authors observed higher odds ratios in younger birth cohorts, which might be due to more frequent diagnostic testing / endoscopy in more recent years, which may have reduced the amount of potential misclassification of FDRs with 0/1+ polyps. Please discuss or analyze whether adjusting for birth cohort / year of diagnosis in the index patients /controls would changes the estimates, or why this should not be done.
3) An analysis by year of CRC diagnosis among the index patients/controls should be added in order to assess such potential dynamics.
4) In Table 2, a line for the reference group of people with 'no polyp FDRs' should be added.

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