Reviewer's report

Title: Quantile-based Fecal Hemoglobin Concentration for Assessing Colorectal Neoplasms with 1,263,717 Taiwanese Screenees

Version: 1 Date: 03 Jan 2019

Reviewer: Iris Lansdorp-Vogelaar

Reviewer's report:

I would like to thank the authors for their careful response to the concerns of the reviewer. I feel the manuscript has clearly gained in clarity and the importance of their analysis can now be better appreciated. However, I still have some remaining concerns:

1. Add the importance of using quantile-based fHb to the abstract. Currently the reader cannot appreciate why it would be important to study the statistical properties of this method. Suggest to add that current studies on fHb association with risk of colorectal neoplasm are hampered by skewedness of the data.

2. The results of the abstract do not align well with the methods: the Results start with the term "adjusted", however nowhere do the methods mention anything about adjusting. The results of the abstract mention fHb for the normal group, however no value is provided for this group. Suggest to add value of 0 there.

3. I find the sentence with colorectal neoplasia risk hard to follow: do these numbers reflect the risks at their respective median values. i.e. risk of 4.0% of non-advanced adenoma at 57; risk of 4.8% of AA at 82.4 and risk of 29.5% for CRC at 163.1? I suggest to present risks at one fixed value for all three types and then may be present different types. Would be easier to follow for the reader. For example, similar to how you have presented the results in appendix table 5.

4. Conclusion of the abstract is not really a conclusion, but rather a method description.

5. The introduction is very long and some methods are intertwined.

6. I find the inclusion and exclusion of cases at baseline extremely confusing. Do I understand it correctly that for the fHb AFT model you include cases at baseline, but for predicting future risk with the Bayesian inversion method you exclude them?

7. Methods, page 10, final two paragraphs contain results.
8. I continue to have difficulty with imputing fHb values of screendetected cancers for interval cancers. Biologically interval cancers could be non-bleeding cancers that are therefore missed at screening. It is agreed that there are some cancers that never bleed. If you would do a FIT on these cancers just before clinical diagnosis you would still get a zero FIT result. Imputing values of screendetected cancers in that case, in my eyes would bias the analysis.

9. Suggest to omit the univariable analysis. The manuscript is already quite long, and the univariable analysis does not add much.

10. I don't agree with the result that median fHb is so much higher for non-advanced adenomas than for normals (Table 1). Previous studies have shown that sensitivity of FIT for non-advanced adenomas is very low and that most of them will be found by chance rather than by the test. The fact that the median f-Hb concentration for non-advanced adenomas is so much higher than for normals is in my opinion due to detection bias. Non-advanced adenomas with f-Hb concentrations below 20, would be misclassified as normals. I understand the reply of the authors that they also included interval cancers and findings at later exams, but we all now that many people with adenomas (40% of the population!) would never develop symptoms or have their adenomas found. So all these people would be classified in your analysis as normal, while in fact they actually have non-advanced adenomas. This limitation of the study should be addressed in the discussion.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review
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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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