Reviewer’s report

Title: Evaluating Risk Factor Assumptions: A Simulation-Based Approach

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Reviewer: Cesrae Hassan

Reviewer’s report:

> 1. Is the question posed by the authors well defined? Yes
> 2. Are the methods appropriate and well described? Yes
> 3. Are the data sound? Yes
> 4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes
> 5. Are the discussion and conclusions well balanced and adequately supported by the data? Yes
> 6. Are limitations of the work clearly stated? Yes
> 7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes
> 8. Do the title and abstract accurately convey what has been found? Yes
> 9. Is the writing acceptable? Yes

The manuscript aimed to compare the different mechanisms that would allow a change in the incidence and mortality of colorectal cancer within an unselected population simulated within a microsimulation model. In particular, the Author compared the different impact of changing parameters related with the initial prevalence of adenomas vs. those parameters associated with an accelerated carcinogenesis from two different perspectives: 1) the relative change in CRC mortality 2) the efficacy of a programmatic screening with colonoscopy.

From a clinical perspective, the article is highly informative, since it clearly explains how different assumptions of the input parameters may change the simulation of the natural history of CRC. However, it could be helpful whether the Authors could add the simple life-time estimate of CRC incidence/mortality alongside the RR for the same measurements. This would allow the clinicians to better translate to their clinical practice the different model assumptions.

Similarly, it would be helpful if the Authors could add an estimate of the cost-effectiveness ratio of colonoscopy screening alongside the estimate of LYG. Indeed, clinicians are much more friendly with cost-effectiveness ratios rather than with an absolute estimate of LYG. This should be pretty easy for the Authors since they already provided CEA measurements.

I would also be curious to better understand how the different mechanisms to change the risk are synergistic among themselves. Although the Authors reported some two-way sensitivity analysis, they could further explore the
synergistic effect of simultaneous variations of two or more of them.

The only limitation I can recognize in this model is the fact that no possibility to simulate de novo cancers (i.e. not from adenomatous polyps) has been included. The Authors should report it in the discussion.

The last point is to translate these assumptions on the validation phase. Although I understand that this is out from the purposes of this paper, it would be useful to know how the Authors feel that they may validate their different assumptions. For instance, microsimulation could ‘ask’ clinicians to provide better data on the age-specific prevalence rate of adenomas or on the rate of advanced neoplasia within small polyps, etc.

Overall, the Authors did a very brilliant work in clarifying the different approaches for including a risk factor in a microsimulation model. Because of the potential high clinical implications of this manuscript, I would advise a further effort in translating the model results into the clinical field, in order to allow the comprehension of the implications not only to experts in statistics, but also to clinicians.