Reviewer's report

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

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Reviewer: Kathy A Cronin

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This paper investigates an important question on how to incorporate the effect of risk factors when modeling the natural history of disease and the affect of interventions such as screening. The paper considers a number of possible scenarios on how the presence of risk factors could influence disease, increased initiation, promotion of disease through faster growth or earlier transition from adenoma to cancer or affect on other cause mortality. It is very well written and clear.

My main comment is that it considers several possibilities for how risk factors can change the natural history of disease and gives a sensitivity analysis for each, but the paper never gives the context of what is known about CRC risk factors. It is hard to understand how the ranges included reflect known risk factors and without that context difficult to interpret.

The paper does not address how one might take epidemiological information that is typically available for a risk factor and incorporate it in one or more of the ways this could effect disease progression.

It would help the paper to take at least one risk factor and give some insight into how you might model it based on available information in risk. This would ground the work and make it seem less hypothetical.

On the bottom of page 4 the paper says that once a tumor becomes clinically detectable, the size, stage and survival are based on SEER. Does this mean that the risk factor under study has no influence on the cancer after detection? If so then the model assumes that change in incidence will be similar to change in mortality. Therefore relative measures for screening and other outcomes would not be appropriate and the paper should focus on absolute measures.

This seems a strong assumption and given the hypothetical nature of the paper not necessary. Why would faster growth and earlier transition not be associated with worse survival or later stages?

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.