Reviewer's report

Title: Numbers of Mutations To Different Types of Colorectal Cancer

Version: 2 Date: 2 July 2005

Reviewer: Suresh H Moolgavkar

Reviewer's report:

General

First, I would like to apologize to the authors for taking so long to review this revision, but travel and grant applications came in the way of a speedy review.

I agree with the authors that there are many ways to formulate models. But basic assumptions should be justified, particularly if they appear not to square with the biology. I think that revision to incorporate the suggestions given below will strengthen the manuscript.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. How can ignoring clonal expansion in polyps be biologically justified? This assumption clearly needs to be discussed and defended, particularly in light of the goal of this ms. to estimate the number of mutations in the two types of colon cancer. As I pointed out earlier the estimates could be profoundly affected by consideration of clonal expansion in polyps.
2. Why use an approximate hazard function when an exact one is easily available? The approximation could be poor at later ages. Just because this has been done in the past is no reason to continue to do so. Use of the exact hazard function could affect the estimate as well.
3. I continue to disagree with the authors regarding their mathematical analyses. In the formulation they describe in their letter, they use two random variables X and Y, which they assume are independent. The problem is that they are not because the life-table contains colon cancer deaths, which are clearly correlated with colon cancer incidence. To get around this they have to either use the hazard function, as I suggested, or eliminate colon cancer deaths from the life table. In addition to assuming that colon cancer deaths are independent of other deaths, both these procedures make the assumption that the probability of not developing colon cancer by a certain age is a good approximation to the probability of not dying from it. That is a reasonable approximation, in my view. However, analyzing the separate sub-types remains a problem with the second approach (dropping colon cancer deaths in the life-table).

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. The authors ignore temporal trends, which can also influence the results of analyses, but in my view it would be sufficient to simply point this out as a limitation of the work.

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Discretionary Revisions (which the author can choose to ignore)
What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:
I declare I have no competing interests below.