Reviewer's report

Title: Numbers of Mutations To Different Types of Colorectal Cancer

Version: 1 Date: 23 March 2005

Reviewer: Suresh H Moolgavkar

Reviewer's report:

General

The manuscript lacks details on methods and modeling, which are presented in a previously published paper. However, in both the previous paper and this one the authors seem to be unaware of recent publications in the area, e.g., papers by Pinsky (JTB), Herrero-Jimenez et al. (Mut Res), and Luebeck (PNAS). The authors completely ignore the importance of clonal expansion of cells in adenomatous polyps. Consideration of clonal expansion would very likely change estimates of the number of required mutations. In fitting the data, the authors completely ignore temporal trends in colo-rectal cancer and adjust for competing causes of mortality only crudely using a life table for the US population, which may or may not be relevant to the population in which the cancers arose. The model itself makes approximations to the exact hazard function, which may be inadequate. Finally, the fitting is apparently based on equation 13 in a previous publication in AJP. Unfortunately, this formulation is in error: both numerator and denominator should be integrated with respect to the cause-specific hazard function and not the density. That is expression 13 should be replaced by \( \int(t_1,t_2)\{S(z)h(z)dz\}/\int(0,\inf)\{S(z)h(z)dz\} \), where \( S(z) \) is prob of survival from all causes and \( h(z) \) is the cause-specific hazard.

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

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

Discretionary Revisions (which the author can choose to ignore)

What next?: Reject because scientifically unsound

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal

Quality of written English: Acceptable

Statistical review: No

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