Author's response to reviews

Title: Numbers of Mutations To Different Types of Colorectal Cancer

Authors:

Peter Calabrese (petercal@usc.edu)
Jukka-Pekka Mecklin (jukka-pekka.mecklin@ksvax9.kshp.fi)
Heikki J Jarvinen (heikki.jarvinen@hus.fi)
Lauri A Aaltonen (lauri.aaltonen@helsinki.fi)
Simon Tavare (stavare@usc.edu)
Darryl Shibata (dshibata@usc.edu)

Version: 3 Date: 26 August 2005

Author's response to reviews:

Response to Reviewer (Dr. Suresh H. Moolgavkar)

Major Compulsory Revisions:

1) There are a number of approaches to model cancer that differ in assumptions and details. The reviewer correctly notes that our model ignores clonal expansion in polyps. There clearly is growth in cancers, but in our model this growth occurs quickly and at a very late stage, after all required mutations have been acquired. Our model (previously published in Reference 11) is consistent with a number of observations. It is different from the well-known adenoma-cancer tumor progression model because it postulates that most "cancer" mutations first accumulate in normal appearing colon and are effectively neutral.

We provide a "biological" basis for our model by noting (on page 9 of the Discussion) that adenomas do not generally appear until after the age of 50 years, and that "Genetically engineered mice and familial cancer syndromes reveal that many oncogenic mutations are compatible with normal phenotypes......". In other words, somatic mutations are detectable in tumors such as adenomas, but cells engineered to specifically contain some but not all of the oncogenic mutations needed for transformation maintain normal phenotypes. Although we do not know exact how many "cancer" mutations are compatible with normal phenotypes, potentially many mutations are needed to acquire a polyp phenotype. We discuss the differences between our model and the adenoma-cancer sequences in the last three paragraphs of the Discussion, and illustrate the differences in Figure 3.

2) At the reviewer's request, for the SEER data we have also fitted our model by the "exact hazard function method" (Luebeck, E.G. and S.H. Moolgavkar. Multistage carcinogenesis and the incidence of colorectal cancer. PNAS 99: 15095-15100 (2002)). The number of mutations inferred by this method is the same as for our method (Table 2). We could not fit the Finnish data by the "exact hazard function method" because we analyzed only cancers with molecular data (ie it was measured whether they were HNPCC or MSI) and not all of the cancers that arose in the Finnish population. This difference from the SEER data (ie incomplete ascertainment from the population at risk) was one of the reasons for developing our method. The two methods are different, but since they infer the same number of mutations for the SEER data, we believe they are capturing much of the same information. We have reported this (page 5) at the end of the Methods.

3) The reviewer is certainly correct that our assumption of independence is incorrect. However, as we have stated in a previous paper (Calabrese, P., S. Tavare, and D. Shibata. Pretumor progression: clonal evolution of human stem cell populations. American Journal of Pathology 164: 1337-1346 (2004)), since "colon cancer is a relatively minor cause of death, the assumption of independence is appropriate."

Minor Essential Revisions

1) We have included a new sentence in the Methods (page 5), which states that we ignore temporal trends. ("The analysis ignores temporal trends, which may influence our mutation estimates.")