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# Quantification of Crypt and Stem Cell Evolution in the Normal and Neoplastic Human Colon

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In the originally published version of this article, we discovered several errors relating to the analysis of the crypt fission rate.

(1) In fresh-frozen (FF) tissue samples, enzymatic deficiency of CCO can be measured using a cytochrome C oxidation assay (two-color enzyme histochemistry). In formalin-fixed paraffin-embedded (FFPE) samples, since the CCO enzyme is no longer active, immunohistochemistry (IHC) for CCO protein is required. Deficiency of enzymatic activity, as measured in FF samples, can be caused by mutations that alter either enzyme function or cause loss of expression, whereas only loss-of-expression mutations are detectable in FFPE samples. Consequently, the rate of detection of CCO- patches is expected to differ between the two methods. Although we intended to analyze exclusively enzyme histochemistry of fresh-frozen samples, it has come to our attention that IHC data from 6 FFPE samples was mistakenly included in the analysis of crypt fission rate. To examine the consequence of this, we removed the FFPE samples from our original dataset and re-fitted the mathematical model to the remaining FF data. The mean fission rate was not altered significantly ($\kappa_{\text{original}} = 0.028$ divisions/crypt/year versus $\kappa_{\text{FF-only}} = 0.027$ divisions/crypt/year).

(2) An error was found in the line of code that was used to perform a correction to account for the probability of two independent CCO- events occurring by chance in adjacent crypts. This mistake means that the number of doublets was underestimated by 6.7%. This had a minimal effect on our estimate of the crypt fission rates ($\kappa_{\text{original}} = 0.028$ divisions/crypt/year versus $\kappa_{\text{correction}} = 0.027$ divisions/crypt/year).

(3) Finally, in our original study, single isolated CCO- crypts (patches of size 1) were omitted in the mathematical fitting procedure of the crypt fission model. When single CCO- crypts are included, we found that the mean fission rate of the disease-free cohort is lower than our previous estimate ($\kappa_{\text{original}} = 0.028$ divisions/crypt/year versus $\kappa_{\text{CCO}\geq 1} = 0.009$ divisions/crypt/year). We note that this revised estimate is similar to the crypt fission rate (0.0068 divisions/crypt/year) recently reported by Nicholson et al. (2018) using an alternative marker of clonal lineages.

All raw patch size data and the original and a Jupyter notebook detailing the revised calculations of crypt fission rates are available via GitHub: https://github.com/CalumGabbutt/PatchSizeRevisions. We are particularly grateful to Calum Gabbutt for uncovering these errors and preparing the revised estimates and code.

The authors regret these errors.

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