

Author's response to reviews

Title: Cancer risk in MLH1, MSH2 and MSH6 mutation carriers; different risk profiles may influence clinical management

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Dear Sir,

Thank you for reviewing our paper. Taking the constructive criticism of the editor and the reviewers in account, we have revised the manuscript 'The risk of Lynch syndrome related malignancies in *MLH1*, *MSH2* and *MSH6* mutation carriers.'

Included you will find the revised version of the manuscript. We hope that our revised article will be suitable for publication in Hereditary Cancer in Clinical Practice and we are looking forward to your reaction.

Yours sincerely,

D. Ramsoekh, MD

Concerning the comments of reviewer #1

1. It would be good if more detail was provided as the method of ascertainment of the cancers reported. For example, were cancer only documented if the patient volunteered the information, was there a proforma that elicited the same information from each patient, were reports themselves actually checked or verification obtained by some other means eg a state cancer registry? How limited was the recording of cancers as I not that breast and brain cancers were not found, in contrast to references.

The remark of the reviewer was welcome and gives us the opportunity to clarify this issue. At our department of Clinical genetics we have a routine mode of operation. During the first visit subjects are asked to fill in family forms. These forms include data concerning the persons in the family and the type and data of cancers that occurred in the family. The forms are used to create a family pedigree.

All subjects affected with cancer or their close relatives (in case they are deceased) are requested to give informed consent for retrieving clinical data, since this is necessary for the counseling process. With the informed consent we obtain the data from the different hospitals and these include pathology reports or medical records. All these records were sent to our department and were checked and verified in our department. We could not double check these data in a state cancer registry because these data are recorded anonymously in the registry and therefore cannot be linked to the person affected. However, because we have the pathology and medical reports on file we have verified that the cancer has occurred and all these reports were checked by the first author. In some cases, there were no pathology or medical reports and these cases have not been included in our study.

With respect to breast cancer, this type of cancer is not associated with Lynch syndrome and therefore we have not included this in our analysis. Brain tumors, on the other hand, are associated with Lynch syndrome, and they were reported by the counseled subjects. However, the brain tumors could not be verified by medical or pathology reports and therefore we excluded these cases from our analysis.

We have changed the methods section on page 5, emphasizing that all included cancers were confirmed by pathology and/or medical reports.

Concerning the comments of reviewer #2

1. Are the discussion and conclusions well balanced and adequately supported by the data? Yes, very much so. It would however be helpful if a table was included with the ages of diagnosis for each associated cancer (discretionary)

As suggested by the reviewer we have added a table with the median ages and range of the age at diagnosis for each associated cancer.

2. The last sentence of the first paragraph of background doesn't seem to make sense, please consider revising.

We have revised the last sentence of the first paragraph. It now states that subjects carrying a mutation in one of the MMR genes have a higher risk for developing colorectal cancer, but also for endometrial carcinoma and malignancies of the stomach, small bowel, ovaries, upper uroepithelial tract, biliary tract, skin and brain.[6-9]

3. Second paragraph of the same section, 5th sentence, should read CRC and EC, not CRC an EC.

We have changed the 5th sentence of the second paragraph.

4. In the results section under study population, 3rd paragraph, the second sentence is difficult to follow, please consider revising .

As suggested by the reviewer we have revised the sentence. It now states that one of the 69 mutation carriers had previously been diagnosed with endometrial cancer and developed colorectal cancer while being under colonoscopic surveillance.

5. Under life time risks, it would be helpful if you could define all LS-associated tumors, ie does this statement included CRC and EC

We considered colorectal, endometrial, stomach, ovaries, upper uroepithelial tract, biliary tract, skin and brain cancer as LS associated tumors. This is stated in the Methods section on page 5. To make this more clear we added the tumors included in the legend of figure 1.