Author’s response to reviews

Title: Lack of association between screening interval and cancer stage in Lynch syndrome may be accounted for by over-diagnosis; a Prospective Lynch Syndrome Database report

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Author’s response to reviews:

Reviewer #1: This is a very interesting epidemiological paper suggesting that MSI-H cancer may spontaneously regress due to high immunogenicity and actually putting into question the guidelines for surveillance of Lynch syndrome mutation carriers. There is an apparent controversy between the presented data and a relatively well-established clinical benefit from a regular colonoscopy in Lynch syndrome mutation carriers. This controversy needs to be discussed in an explicit way.

Answer: We acknowledge that this is a controversial finding since it has been well recognized that colonoscopy surveillance is beneficial compared to no surveillance. There are, however, accumulating data that follow-up with colonoscopy may not have the degree of preventive effect to CRC as hoped for. Data from PLSD and other consortiums show no benefit from short colonoscopy intervals in terms of CRC cumulative incidence or survival compared to three-yearly intervals between colonoscopies.
The comparison of different surveillance strategies has been done and discussed in our previous report (Seppälä et al 2017, Hered Cancer in Clin Pract), which is why it was not within the scope of the current analysis. We have added a paragraph to discuss why other benefits of shorter intervals than reduced CRC incidence need to be studied if short intervals are to be recommended. The current paper is the last one in a series of PLSD reports describing the effects of clinical guidelines by age, gene and gender. Based on these, additional studies will be designed to try to clarify why the PLSD prospective observations reported are as they are, and which may include additional study parameters.

The Summary is missing an important data. It is stated that the numbers of cancers detected within <1.5, 1.5-2.5, 2.5-3.5 and at >3.5 years since last colonoscopy were 36, 93, 56 and 33, respectively. To my understanding, the absolute number do not matter much. The proportion between the number of detected cancers and the number of analyzed patients is essential.

Answer: The absolute number of cancers in each group depends on the observed last colonoscopy interval since the previous examination. This may be accounted for by several factors, such as recommended interval, patient compliance, the performance of the health care provider etc. This was not an analysis of the ability of different intervals to detect CRCs but an attempt to study if short intervals were associated with lower stage in patients that did get CRC. Therefore, we did not compare the number of detected cancers to the number of patients undergoing colonoscopies but not getting a CRC.

The number of detected cancers in each group is informative to the reader. Apparently, there were more patients with short interval since previous colonoscopy than longer interval. Because there are enough patients in each group for a reliable analysis, there is no reason to assume that it would change the stage distribution within the interval groups.

One would expect that longer interval since the last examination will result in higher proportion of subjects detected to have a cancer.

Answer: Yes indeed, and which was examined in our previous paper (Seppälä et al 2017, Hered Cancer in Clin Pract) and found not to be true. With that added to our previous PLSD reports that CRC was not prevented as much as expected by follow-up with adenomectomy, we can justify our suggested hypothesis. In the current paper, we validate the parallel expected consequence
that, on average, cancers detected at longer time since last colonoscopy should have had more advanced stage, but found that to not be true, either.

There is a number of inaccuracies. For example, see the phrasing in the lines 14/15 of the Conclusions of the Summary; the line 7 of the Background section; references in the line 53/54 of the 2nd page of the Discussion.

Answer: We apologize for the typos that have been corrected in the revised manuscript.

Reviewer #2: Herein authors present results suggesting that there is no association between CRC staging and the frequency of colonoscopy surveillance. Due to small numbers of advanced cancers this finding can be regarded as preliminary but is interesting since it supports the thesis of possibility of potential spontaneous regression of CRC in Lynch syndrome. Authors do not evaluate the question of the effectiveness of colonoscopy screening in detection of precancerous and cancerous lesions - they provide no data such as numbers of detected polyps / CRCs and numbers (frequency) of colonoscopy screening.

Answer: We agree with the referee that this manuscript did not analyze the diagnostic effectiveness of colonoscopy surveillance. We have compared the cumulative incidence of CRC according to different recommendation for colonoscopy surveillance and found lower incidence of CRC by longer recommended intervals (Seppälä et al 2017 Hered Cancer in Clin Pract) that together with the present finding support our hypothesis that some CRCs during colonoscopy can be found because of overdiagnosis.

The diagnostic yield by different strategy was outside the scope of this manuscript. Instead, we performed this analysis to study if there were some other benefits (lower stage) from short colonoscopy intervals – compared to longer intervals – than incidence or mortality. Studies on detected/removed polyps that could be related to incidence of CRC and frequency of colonoscopic screening by age, gene and gender, are obviously indicated, already initiated, and will be reported when results are available and quality controlled.

In summary the paper fulfills criteria needed for publication in HCCP Journal.