Reviewer's report

Title: Association between cigarette smoking, APC mutations and the risk of developing sporadic colorectal adenomas and carcinomas

Version: 1 Date: 9 January 2006

Reviewer: Kirsti Husgafvel-Pursiainen

Reviewer's report:

General

This is a carefully conducted study with the ambitious aim to investigate the role of cigarette smoking in development of colorectal adenomas and carcinomas. The study subjects, all ethnic Norwegians, presenting with adenomas (n = 48) and the screening-negative controls (n = 334) were drawn from an extensive well-characterised study base recruited for a colorectal cancer prevention study (NORCCAP), whereas the colorectal carcinoma (CRC) patients (n = 94) were patients admitted to Telemark hospital. The study design involves to approaches: It includes a molecular epidemiology part with a full spectrum (base substitutions as well as deletions) of APC gene mutations investigated; in addition, the study comprises a part utilizing a case-control design.

The main question addressed, ie. cigarette smoking in colorectal cancer, is a highly important issue, with multiple studies showing positive association with both adenomas and carcinomas, but without full understanding of the relationship as yet. In this context, the molecular epidemiological approach, such as the present one, has great potential to contribute to our understanding of the involvement of various etiological factors.

The present study shows interesting findings. Although the mutational spectra did not differ between ever- vs never-smokers, the case-control setting found an increased but non-significant risk (OR 1.73, 95% CI 0.83-3.58) for ever smoking among the adenoma cases, and, among the CRC cases, it indicated a statistically significant OR of 2.86 (1.06-7.7) for duration of smoking for >30 years. In the setup where the authors separately compared APC+ or APC- cases with control population, the risk elevations were mostly found among truncation mutation negative cases. APC- adenoma cases exhibited statistically significant association to ever smoking (OR 3.97, CI 1.26-12.51), and the CRC cases without mutation showed an increased risk for duration of smoking >30 years (4.06, 1.20-13.7). In the case-case comparisons (APC+ vs APC- cases), where both adenomas and CRCs were pooled together, the risk ratios were all non-significant but there too was a tendency for elevated risks associated with smoking parameters (average daily smoking, mean yrs and duration of smoking) to occur among mutation negatives, except for the parameter 'starting smoking =40 yrs ago' that was associated with increased risk (2.24, 0.73-6.86) among the truncation mutation positive CRCs. In all, the various analyses appeared to indicate that smoking may rather contribute to the development of APC truncation mutation negative colorectal tumours, both adenomas and CRCs, than mutation carrying ones.

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

- The CRC cases were recruited into the study using a different study design as compared to adenoma patients and the controls. The authors should appropriately discuss justification of this,
and estimate whether the inclusion of these different populations may somehow affect the analysis and results.

- The study is focused on sporadic cases, but the paper does not indicate which were the criteria used for exclusion of possible hereditary ones. Were there any data on eg. microsatellite instability positivity?

- The authors should discuss more thoroughly which might be the explanations for their main findings indicating that the various smoking parameters were mostly associated with APC truncation mutation negative cases. Is it likely that there are other factors (eg. dietary, hereditary, tumour subsite, other genes), that may play a major role in development of these tumours? This would be important, in particular as there are literature data suggesting that MSI positive cases were more likely to smoke =20 cigarettes (Slattery et al., JNCI, 2000), or that smoking may play a role in p53 negative tumours and be associated with tranversion mutations (Diergaarde et al. Carcinogenesis, 2003).

- I would also like to suggest that the authors wrote a bit more about what might be the mechanisms through which 'starting smoking =40 yrs ago' (associated to increased truncation mutations in CRC) may function in colorectal tumorigenesis. Would it rather be just 'early initiation' (and thus long constant exposure to the variety of tobacco carcinogens and a long time span for accumulation of alterations), as mentioned now, or is it likely that there might be some other (perhaps site specific) biological mechanisms involved?

- In my opinion, the results presented in Table 5 do not fully justify the conclusions as presented in the abstract and on page 13 (last few sentences), but the role for this one smoking parameter (starting smoking =40 yrs ago) indicating an association to truncation mutation positive CRCs is too strongly underlined.

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

- There are a few unclear sentences (e.g. Abstract: 3rd sentence of the 'results' section; page 5: 1st sentence; page 9: the two last sentences appear repetitive; page 11: 2nd para, 6th sentence, starting with 'For adenomatous polyps...'); these should be clarified. In general, language revision would be beneficial for the paper.

- The recent IARC monograph on tobacco smoking (vol. 83, 2004) should be cited for current data on smoking and colorectal cancer.

- In Tables 4 and 5, it should be indicated in the title that the mutation status refers to truncation mutations. Also, in all of the tables, I sometimes found that the superscripts for the footnotes could be replaced closer to the figure/item they refer to, for easier reading.

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Discretionary Revisions (which the author can choose to ignore)
What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes

Declaration of competing interests:

I declare that I have no competing interests.