Reviewer's report

Title: Infrequent cyclooxygenase-2 overexpression in serrated colorectal polyps

Version: 1 Date: 22 September 2007

Reviewer: Tina Edmonston

Reviewer's report:

General

In their manuscript “Infrequent cyclooxygenase-2 overexpression in serrated colorectal polyps” Kawasaki et al. investigate the level and frequency of COX-2 protein expression by immunohistochemistry in hyperplastic polyps, sessile serrated adenomas (SSA), mixed polyps with SSA and adenoma, traditional serrated adenomas, non-serrated adenomas, adenomas with intra-mucosal carcinoma and adenocarcinoma with and without serration.

Knowing the COX-2 expression level of various colorectal precancerous lesions might have significant clinical implications, as COX-2 serves as a chemopreventive target now that Aspirin and COX-2 inhibitors are being investigated and increasingly being used to prevent colorectal cancer. Therefore, the finding that COX-2 overexpression is uncommon in hyperplastic polyps, SSA, and mixed polyps (SSA and adenoma) may be clinically important.

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

1. The scoring criteria for the immunohistochemical stain should be described more specifically. How were the thresholds set for weak vs. strong overexpression? The controls should be described in more detail. Does a "negative" score (i.e. "no overexpression") imply that there is no staining at all, or could there be weak staining (a baseline level of "expression" as opposed to "overexpression")? If yes, how is it distinguished from “weak overexpression”. Was there a minimal percentage of cells that had to be positive? If the distinction between COX-2 negative and weak overexpression is not explained more clearly, one could ask whether the weak overexpression of COX-2 in traditional serrated adenomas could also be interpreted as negative in the sense of low baseline expression, which would change the overall findings of the study.

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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)

1. In this manuscript the term “serrated colorectal polyp” is restricted to SSA and mixed polyps but does not include traditional serrated adenomas. This might be
confusing to the reader, as traditional serrated adenomas have elsewhere also been called “serrated polyps”. Therefore, the term “serrated colorectal polyp” should be avoided in order to prevent misunderstandings. The distinction is essential, because according to this manuscript and other publications, traditional serrated adenomas behave differently when COX-2 expression is compared to SSA and mixed polyps.

2. The fact that traditional serrated adenomas as well as non-serrated adenomas show COX-2 overexpression with about the same frequency is not sufficiently emphasized in the manuscript, where the low levels of COX-2 expression in HP, SSA and mixed polyps are repeatedly compared to non-serrated adenomas only even though COX-2 expression in serrated adenomas is very much like the one in non-serrated adenomas.

3. It is not quite clear whether the mixed polyps are mixed SSA and tubular/tubulo-villous adenoma or mixed SSA and traditional serrated adenoma or possibly either.

Discretionary Revisions (which the author can choose to ignore)

1. In this study as in other publications, COX-2 overexpression seems to be as common in adenocarcinoma with serration as in adenocarcinoma without serration. Also, COX-2 expression in traditional serrated adenomas seems to be similar to non-serrated adenomas. As the authors point out, these findings suggest that COX-2 becomes more frequent in higher-grade neoplasias. Looking at COX-2 expression in adenomatous polyps depending on the degree of dysplasia could help support these conclusions. The low frequency of COX-2 expression seem to be restricted to the more uncommon SSA and mixed polyps as well as hyperplastic polyps (in this study only lesions with a size of >1cm are included).

In this context it would be of interest to also specifically discuss COX-2 expression in the serrated vs. the adenomatous component of the mixed polyps. The overall question is, whether the low frequency of COX-2 expression in hyperplastic polyps, SSAs and mixed polyps is a function of the serrated pathway or due to COX-2 overexpression being a "later" event in carcinogenesis.

2. It is suggested that a second pathologist review the slides to determine the histologic type of the serrated lesions to minimize subjectivity in the classification of these lesions.

3. Figure 2 might benefit from higher resolution

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: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests