Reviewer's report

Title: Polymorphisms in Cyclooxygenase-2 gene and breast cancer risk in Brazilians: a case-control study

Version: 1 Date: 23 February 2010

Reviewer: David Cox

Reviewer’s report:

1. Is the question posed by the authors well defined?
The question is indeed well defined. The hypothesis of PTGS2 polymorphisms and breast cancer risk is sound on the surface, however a large body of work (often marginalized by the authors, see the last paragraph of the discussion) has already been published with respect to variants in this gene and breast cancer risk.

Major Compulsory Revisions:
A more thorough review of the literature is warranted.

2. Are the methods appropriate and well described?
The methods are generally sound and fairly well described.

3. Are the data sound?
The data are more or less sound. The authors should be cautioned regarding over-interpreting their data. They see a borderline significant association between one polymorphism and breast cancer risk, however this effect is limited to heterozygotes. Would one expect to see a log-linear relationship between the polymorphism and breast cancer risk? If so, why is there an (albeit insignificant) inverse risk among homozygous carriers of the allele?

Major Compulsory Revisions:
Include discussion of the fact that the 'risk' is limited to heterozygotes. More caution should also be used in interpreting the association, as it is borderline (or non) significant, particularly in the post-genome era where p-values of 10-3 are still considered borderline.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
I would have to say that the discussion and conclusions can be a bit better balanced. There is little mention of the limitation of the study due to its relatively small size. The authors mention that 'haplotypic combinations should always be
considered in the future', however they have not used a haplotype tagging approach, and variants which are in the coding (or non-coding) regions of the gene may very well tag polymorphisms other than those tagged by the SNPs studied here. While I agree that the hypothesis that PTGS2 SNPs in regulatory regions would be of interest given the regulation of expression of PTGS2 (at the mRNA level, not protein as stated in first paragraph of the discussion), not screening the entire gene is a weakness of the study that should be discussed.

Major Compulsory Revisions:
Discuss limitations of the study, particularly with respect to power and not screening the entire gene.

6. Are limitations of the work clearly stated?
No, see comments above.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Yes.

8. Do the title and abstract accurately convey what has been found?
For the most part. I would suggest removing the results with respect to age from the abstract. Age is a recognized cancer risk factor, and the wording makes it unclear whether the authors are describing risk limited to a specific age range or in the overall population. The authors should also be more clear on what the p-value reported is (1df or 2df?)

Major Compulsory Revisions:
More clearly describe the statistical tests used, and what p-values are reported.

Minor Essential Revisions:
Remove or reduce the presentation and discussion of the age association.

9. Is the writing acceptable?
Yes, only minor grammatical and English errors.

**Level of interest:** An article whose findings are important to those with closely related research interests

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

**Statistical review:** Yes, and I have assessed the statistics in my report.

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