Reviewer's report

Title: Association between H-RAS T81C genetic polymorphism and gastrointestinal cancer risk: a population based case-control study in China

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Reviewer: Laura Ottini

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Title: Association between H-Ras T81C genetic polymorphism and gastrointestinal cancer risk: a population-based case control study in China

General

The paper by Zhang et al. investigated the possible effect of the H-Ras T81C polymorphism on the risk of gastrointestinal cancer in Chinese population. This topic deserves to be addressed since it has been investigated so far in different kinds of cancer, including bladder, oral and thyroid carcinomas, yielding conflicting results.

Overall, study design, laboratory methods and statistical analysis appear to be sound. Nevertheless there are some points that need to be elucidated.

-Major Compulsory Revisions

Methods

1. More details should be given about sampling procedure within the cohort. Why the Authors considered only cases alive at the end of follow up and not all incident cases? If the polymorphism examined is associated to survival the prevalence of H-RAS T81C polymorphism in cases could be underestimated (or overestimated). This could explain the negative result for colorectal cancer. Why the controls were selected at the end of follow up and not with a nested design? Again if the polymorphism examined is associated to other cancer(s), the prevalence of H-RAS T81C polymorphism in controls could be underestimated.

2. The Authors investigated the effect of H-RAS T81C polymorphism also by stratification of family history, cigarette smoking and alcohol drinking status and did not find any interactions. More details should be given about the questionnaire and the methods used to measure alcohol consumption and dietary history. Moreover, what do the Author mean by “family history of cancer”? (family history of gastric cancer, colon cancer or cancer in general?) This is an important issue since a subset of hereditary gastrointestinal cancers can be linked to specific molecular phenotype (e.g. microsatellite instability).

3. The genotyping results obtained by PCR-RFLP should be confirmed by sequencing analysis (e.g. a subset samples with each of the three possible genotypes for the H-RAS T81C polymorphism should be confirmed by sequencing and included on each genotyping assays as positive controls).
4. The description of the unconditional regression analysis should be better clarified indicating how the three genotypes were included in the model, what was the reference and that models with dominant inheritance were also tested. The confounders used should be indicated with more details (in continuous or as categorical variables?).

5. It’s not clear how interaction has been tested. I am convinced that interaction should be better tested using likelihood ratio test comparing models with and without interaction terms.

6. Meta-analysis methods should be described with more details, e.g. which specific test of heterogeneity was used?

Results

1. In the first paragraph: I suppose that “significantly” mean p<0.05, please specify.

2. I have some concern about the rationale to perform a meta-analysis in elation to different cancer sites. Although no heterogeneity was observed, this could be due to the low power of this kind of test. A descriptive table is enough.

-Minor Essential Revisions

1. Two-side is unnecessary in the first sentence of the statistical analysis paragraph.

2. Results section: page 10, line 10: p=0.000 became p<0.0001.

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

Quality of written English: Acceptable

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.