Reviewer's report

Title: Association between the Cytotoxic T-Lymphocyte Antigen 4 +49G>A polymorphism and cancer risk: a meta-analysis

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Reviewer: Ranjeny Thomas

Reviewer's report:

In this manuscript, Zheng et al carry out a meta-analysis of available studies which examine the association of the CTLA4 +49G>A gene variant with cancers of all types. The polymorphism is functionally relevant because it can reduce CTLA4-mediated downregulation of T cell responses. This is an important question from an immunological and cancer pathogenesis perspective, and a meta-analysis is needed to get a better understanding of the overall effect of this variant because its effect size is relatively small. Thus the number of cases in individual studies may be too small to see an effect. With the combined data in the analysis they are also able to determine potential major influences on the effect, such as ethnicity and tumor type. They find that the variant is associated with cancer overall, that there are effects of ethnicity and tumor type.

Specific points to address:

1. There are no page numbers, making it difficult to identify sections. I am not familiar with the term yellow race to identify ethnicity. Asian might be a better category?

2. Page 2 of results, top. These studies could be identified by reference rather than by first author’s name.

3. Quantitative data synthesis section. The text needs to be reworded into complete sentences as it is often difficult to follow.

4. Comparing major influences: ethnicity. I was unclear which groups were included in the Caucasians and the yellow races and which groups were remaining. This needs to be clarified in the methods. This also pertains to discussion last page where it is stated that Caucasians, yellow race and Chinese might have a much higher association with the polymorphism. It was not clear which ethnic group was remaining, which might not show an association. Tumor type: it is difficult to get a feel from the way the results are presented which tumor types are associated with the variant. The figures present some data on certain tumors e.g. breast cancer, but it would help to have a figure showing all studies, as identified by cancer type rather than by first author. It may be helpful to compare epithelial vs non-epithelial tumors, given the associations with breast and skin and not with non-solid tumors.

5. Figures 2-5 should be reformatted to be more user-friendly for the reader. The intent of the figure should be clear and the information should be conveyed so the reader can grasp the message. At the moment these figures look like
print-outs from a statistical program.

**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, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare I have no competing interests