Reviewer's report

Title: Association between an 8q24 locus and the risk of colorectal cancer in Japanese.

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Reviewer: Sonja Berndt

Reviewer's report:

This study examines the association between two polymorphisms in the 8q24 region and the risk of colorectal cancer in a Japanese population. This study confirms the previously observed association between rs6983267 and colorectal cancer, but does not replicate the association for rs10090154. This study makes a contribution to the literature on 8q24, as most of the studies published to date have focused on populations of European descent and very few have examined the association in other ethnic populations.

Major Compulsory Revisions

1. The authors mention in the introduction that GWAS have revealed an “association between variants within a 600-KB region of a longer 1.18-B (Mb?) sequence”. Some clarification of this is sentence is needed as it is not clear which regions are included in this statement.

2. In the statistical methods, the authors state that they assumed scores for categories of alcohol, folate, etc... Although it is unlikely that these variables will be significant confounders for this study, I question whether assuming a linear score for these variables is the best statistical model. I would if including these factors as indicator variables or just as continuous measures would be more appropriate.

3. As this is one of the few studies to examine rs10090154 in Japanese, some mention of how this study compares to the previously reported study would be nice. Are the odds ratios in the same direction as the previous study?

4. In the discussion, the authors state that “the internal validity of this hospital-based study is a potential threat to causal inference”. Although true, I’m not sure that causality can be inferred from any one study. Perhaps this can be reworded to clarify the potential selection bias from using hospital controls and the implications. The authors also state that their control population was “similar to the general population in terms of the exposure of interest” and they cite a study from 1997. However, the exposures of interest here are the 8q24 SNPs, which were not evaluated in the cited study. Perhaps, it would be better to state that the controls were similar to the population on these select baseline characteristics if that is the authors point. Finally, the authors state that the lack of interaction with other factors “warrants the solidness of our findings concerning rs6983267”. However, this study is underpowered to examine interactions, so it is
not entirely clear how a lack of interaction would solidify the results.

Minor Essential Revisions

1. There are a number of typos that need to be corrected. Some of the typos I found are: 1) “rs698326” should be “rs6983267” in the abstract. 2) Page 7: “expected and observed haplotypes” should be “expected and observed genotypes”. 3) Page 8: “rs4693267” should be “rs6983267”. 4) The p-value for the recessive model for rs6983267 is not correct in Table 2 and does not match what is stated in the results. 5) The number of significant digits varies in Table 3.

2. Table 1 is missing from the submitted manuscript.

3. I believe there are a few additional studies (e.g. Curtin K et al) that have been published on 8q24 rs6983267. Table 4 should be updated to include these studies.

Discretionary Revisions

1. It would be helpful to show the odds ratio for the heterozygotes compared to the homozygous wildtype as well as the odds ratio for the homogygous variant compared to the homozygous wildtype for both SNPs in Table 2.

2. It would be helpful to see the number of cases and controls with each genotype in the stratified analyses in Table 3. The authors mention that the number of subjects with a positive family history is small, but the reader cannot tell how small this stratum is.

3. It would be helpful to clarify which estimates are for adenoma and which are for CRC in table 4. For some studies, it is not clear.

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.