Reviewer’s report

Title: Characterization of the association between 8q24 and colon cancer: gene-environment exploration and meta-analysis

Version: 2 Date: 12 July 2010

Reviewer: Elias Zintzaras

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The WHI and DALS studies cannot be combined in the context of a general linear model due to different design settings. Thus, only separate analysis for each study should be shown.

The genotype distribution of each variant should be presented and an analysis based on contrasts of genotypes (dominant, recessive, additive, co-dominant) should be performed. The analysis based on the allele contrasts always increases the chance of significant results. An additional analysis based on the generalized OR may reveal masked significant associations, especially for the tumor stage analysis (see Zintzaras E. The generalized odds ratio as a measure of genetic risk effect in the analysis and meta-analysis of association studies. Stat Appl Genet Mol Biol. 2010;9(1):Article21.).

In the WHI and DALS studies, there are 126 and 139 non-whites, respectively, but the populations were in HWE, an explanation is needed for this result.

The significant results of the subgroup analysis might be data driven since the study protocol was not designed to investigate these specific subgroups. Furthermore, the study was not designed to investigate gene-environment interaction. All risk factors can be used to adjust the genetic risk effect.

The analysis and presentation of the mass subgroup results corresponding to risk factors raises the need for multiple testing adjustment.

Haplotypes frequencies should be estimated and the haplotypes of cases and controls should be compared.

The significance of the association results should be adjusted be the number of examined variants.

A high LD in HapMap does not justify the switchability between two variants.

In the meta-analysis use the RE model.

The Egger’s test and the funnel plot do not really investigate publication bias (see Zintzaras and Lau 2088 J Clin Epidemiol).

A meta-analysis that includes the WHI and DALS studies plus other published studies should be performed for all 11 variants (whenever published studies with these variants exist).
In Table 1, P-values should be provided.

**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'