Reviewer's report

**Title:** No influence of the MDM2 SNP309 on early onset lung cancer in a Caucasian population

**Version:** 2 **Date:** 21 February 2008

**Reviewer:** Nandita Mitra

**Reviewer's report:**

- **Major Compulsory Revisions**

Mittelstrass et al. conduct a large, well-designed case-control study of the association between SNP309 in the promoter region of the MDM2 gene and early onset lung cancer. The statistical analyses are well written and correctly conducted. The authors also uniquely use propensity scores to evaluate differences in the two case populations. On the whole, the results are also clearly presented. However, Table 4 which shows subgroup characteristics, should also present odds ratios and 95% confidence intervals (or p-values from chi-squared of Fisherâ##'s exact test) comparing the genotypes between the cases (two cases groups separately and combined) and controls within subgroups. These results would clearly reveal the gender specific associations that Reviewer 2 (Dr. Gareth Bond) very importantly points out. I agree with Dr. Bond that these subgroup analyses are counter to the overall conclusion of the paper that the MDM2 SNP309 locus is not associated with early onset lung cancer in this population. However, I do not believe that the results of the paper should be ignored based on the results of one post-hoc subgroup analysis. Instead, the authors should emphasize that, overall, after controlling for gender and other characteristics no association was found in the combined analysis. The authors should then go on to explain that in their subgroup analysis of gender, among only those from the HLC study, was a gender specific association found. Some explanations or theories should be provided as to why this may be the case. Is this an erroneous result due only to chance? Why was this result found in the HLC study but not in the LUCY study? What ascertainment differences could lead to such conclusions? Although the authors compare the HLC and LUCY study groups on several patient characteristics, there could always be unmeasured variables that differ between the study populations that may affect outcome. They should also suggest that further studies be conducted to explicitly study these gender-specific effects in an independent cohort as the primary hypothesis rather than as a hypothesis-generating exercise.

- **Minor Essential Revisions**

1. Were haplotypes comprised of SNPs in proximity of SNP309 investigated? A brief discussion should be provided with regards to the utility of haplotypes in this study.
2. On page 5, when describing the KORA study, the sentence “With respect to genotyped polymorphisms to date, a major population stratification between KORA and two other cohorts from Northern Germany could not be detected in a genomic control approach.” This sentence is confusing and needs to be reworded. I presume that the authors mean to say that genomic control methods were used to test for population stratification in a population comprised of Southern and Northern Germans and that no such population stratification was found.

**What next?:** Accept after minor essential revisions

**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.