Reviewer's report

Title: Polymorphism +17 C/G in Matrix Metalloprotease MMP8 decreases lung cancer risk

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Reviewer: Jun Yokota

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Gonzalez-Arriaga et al. performed a hospital-based case-control and case-case studies for the association of MMP1, MMP8 and MMP13 polymorphisms with lung cancer risks and with lung cancer patients’ prognosis, respectively. The results indicate that MMP8 SNPs are associated with a decreased lung cancer risk and a higher survival rate. The results of case-control studies may contain some useful information; however, the results of case-case studies for patients’ survival are still incomplete and may be negative. Thus, I don’t think this paper is acceptable in the present form, and extensive revisions will be required for publication. Specific comments are as follows.

1. Table 8: MMP8 polymorphisms showed statistically significant association with lung cancer risk in males, smokers, and in individuals with family history of lung cancer. Associations were significant for squamous cell carcinoma (SQC) and small cell carcinoma (SCC), but not for adenocarcinoma (ADC). Since males, family history of lung cancer, SQC and SCC are usually strongly associated with smoking history, the authors should further analyze what is the most significant variable associated with MMP8 polymorphisms. A kind of multivariate analysis would be applicable for this purpose.

2. Figures 1-3: The results of Kaplan-Meier analyses should be shown with the number of each group and p-value. In my impression, none of these three polymorphisms would be associated with patient survivals.

3. Prognosis of patients with lung cancer is known to be different among three major histological types, ADC, SQC and SCC. Clinical stages as well as pathological stages are also important and critical prognostic indicators. In several statistical studies, gender and smoking history themselves are also judged as being prognostic factors. Therefore, Kaplan-Meier analyses of all the patients according to the MMP1, MMP8 and MMP13 polymorphisms would not give us any useful information. Stratified analysis as well as multivariate analysis should be performed to obtain more informative data.

4. In “Summary”, the MMP1 2G genotype is not a borderline independent poor prognostic factor, because the p-value in Table 5 is 0.153.

My judgement for this paper is "not acceptable in the present form, and major revision required for possible acceptance".