

Format for ANSWERING REVIEWERS



March 25, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8531-review.doc).

Title: Acetylcholine Receptor Pathway in Lung Cancer: New Twists to an Old Story

Author: Xiaomin Niu, Shun Lu

Name of Journal: *World Journal of Clinical Oncology*

ESPS Manuscript NO: 8531

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) Studies have shown that the genetic variations of these genes more likely affect smoking behaviors and nicotine dependence, which may subsequently modify lung cancer risk. The authors need to add this component and discuss how the two interplay and lead to lung cancer.

Q: adding contents

1.3 Interplay of smoking behaviors, nAChR cluster and lung cancer risk

Evidence that nAChR cluster on 15q25 locus is associated with smoking status and nicotine dependence and with the risk of lung cancer is inconsistent in different populations. The region of nAChR cluster has been confirmed to be associated with a number of smoking-related traits, including nicotine dependence, cigarettes smoked per day, and heavy smoking, in some lung cancer GWA studies, and in some genome-wide meta-analyses in Caucasian populations. For example, the Caucasian population with variant rs1051730 SNP on nAChR cluster were related with lung cancer risk and nicotine dependence, approximately smoking one and two more cigarette per day than those without variant rs1051730 SNP. Some other study demonstrates further that association signals in the nAChR cluster affecting early smoking behaviors may be different from those affecting the mature nicotine dependence.

Surprisingly, a Japanese case-control study reported associations between the selected SNPs on nAChR cluster and risk of lung cancer and found that associations among never and ever smokers were similar. The association was consistent among non-smokers and smokers in our study. These studies might argue for a role of the nAChR cluster in lung cancer that is independent of smoking behavior in Asians.

These findings in different populations suggest a role for racial differences in the association between smoking behaviors, nAChR cluster, and risk of lung cancer. Reasons underlying the racial difference in the genotype with smoking associations are unclear. This discrepancy may be due to differences in genetic and environmental backgrounds. Alternatively, other factors that have not been taken into account, such as food intake and passive smoking, differentiate the mode of contribution of the nAChR cluster in non-smokers.

(2) The manuscript contains quite some grammatical errors or hard-to-understand sentences that need to be carefully corrected or professionally edited. Just a few examples:

a. "The first functional evidence of SNP rs8023462 in CHRNA3/CHRNA4 intergenic region associated with lung cancer risk, could influence gene CHRNA3/CHRNA4 expression by interacting with GATA transcription factors [20]" on page 3. Here the "evidence" can not have an action of "influence".

Q: Thank you for your careful review. The revision is "The first functional evidence of SNP rs8023462 in CHRNA3/CHRNA4 intergenic region associated with lung cancer risk, could interfere gene CHRNA3/CHRNA4 expression by interacting with GATA transcription factors".

b. What does this sentence really mean on page 4? "it is stringent to perform meta-analyses of existing genetic data on nAChR gene cluster to better discover additional disease loci harboring common variants associated with lung cancer risk".

Q: Sorry for the unclear expression. Should this sentence be better as "it is stringent to perform meta-analyses of existing genetic data on nAChR gene cluster to better understand disease loci harboring common variants associated with lung cancer risk"?

c. On the same place: "A total 12 qualified articles between 2008 and 2011 screening from 40 potentially relevant researches were selected...". "screening" should be "screened".

Q: thank you. It has been revised as "screened".

d. On page 4, "For rs1051730-G/A, carriers of A allele had a 36% increased risk for lung cancer (95%CI: 1.27-1.46; P<0.0005) without heterogeneity or publication bias in all population [34]." The authors need to explain what "without heterogeneity or publication bias in all population" means in this context.

Q: First sorry for my confusive expression.

Considering this analyses were a meta-analyses for existing 12 qualified articles between 2008 and 2011, including 16 studies with 9 in Caucasians, 4 in East Asians, 2 in African-Americans, and 1 in mixed (Caucasian, African-American and Hispanic) populations, the final meta-analyses results maybe eliminate racial differences to the great degree. So the sentence was expressed as "without heterogeneity or publication bias in all population".

To reduce the misunderstanding, the sentence will be revised as "without heterogeneity in all population" in the new version.

e. Page 9, "which was the first study associated the downregulation of α 4nAChRs with PAC"

Q: Indeed, this sentence put here will cause confusion. So the sentence will be deleted in the new version.

f. On the top of page 10, "...is the prognostic effect for resected early stage NSCLC [62]." "is" is not correct here.....

Q: Thank you. "is" will be revised as "was".

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Clinical Oncology*.

Sincerely yours,

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