ANSWERING REVIEWERS

October 5, 2015

Dear Editor,

Thank you for receiving your positive letter about our manuscript" GSTM1 Polymorphism and Esophageal Cancer Risk: An updated meta-analysis based on 37 studies ". We have revised the paper according to the comments of reviewers and editors. Besides, we have marked the revisions in yellow highlight.

Please find enclosed the edited manuscript in Word format (file name: 17966-Revised manuscript)

Title: GSTM1 Polymorphism and Esophageal Cancer Risk: An updated meta-analysis based on 37 studies

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 17966

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.

Reviewer #1
Reviewer's code: 00052339
Reviewer's country: Japan
(1) Major point; This study analyzed the effect of GST1 polymorphism on esophageal

cancer risk, but the study conducted the conclusion without considering histological difference. I think EADC in Asian population is less than 10% and more than 40% in Caucasian population in all esophageal carcinoma. In Table2, Caucasian group did not show the statistically significant difference in odds ratio (OR 1.02, p=0.97) and EADC also showed no significant difference (OR 0.98, p=0.93). These data suggested that EADC popular in Caucasian people did not relate to GST1 polymorphism. Hence, the authors should analyze data according to ESCC in Asian and Caucasian population, EADC in Asian and Caucasian population.

Answers, Thanks for your attention. Considering that only one study (including 14EADC and137 ESCC) reported the association between GSTM1 polymorphism and EADC in Asian population, we did not conduct the subgroup analysis according to ESCC and EADC in Asian population. However we analyzed data according to ESCC and EADC in Caucasian population, founding no statistically significant association between GSTM1 polymorphism and ESCC (OR=1.15,95%CI=0.91-1.45)or EADC(OR=0.98, 95%CI=0.81-1.18)

(2) Minor point: What is the ratio of homozygous deletion of GST1 gene in Asian and Caucasian general population?

Answers, Thanks. The ratio of homozygous deletion of GSTM1 gene in Asian and Caucasian general population is 56-70% and 40–60%, respectively[1, 2].

(3) The last 4 line in page4, is the phrase that "The homozygous deletions of GSTM1 may modify their enzymatic activity in the detoxification of carcinogens and consequently confer the host's risk for some cancers" correct? If the homozygous deletion of the gene may occur its biological function is completely lost. Why do the homozygous deletions of GSTM1 not loose but modify their activity?

Answers, thanks for your valuable suggestions. After reading relevant articles[3-6], we found that it is not proper, therefore we have correct the statement using the following words: "Homozygous deletions of GSTM1 have been associated with the loss of enzymatic activity for the detoxification of carcinogens"

Reviewer #2

Reviewer's code: 00053419

Reviewer's country: Spain

Comments: The manuscript describes the results of a meta-analysis aimed to define the association of GSTM1 deficiency and esophageal cancer. The authors conclude that the proposed association exist in Asian population but this do not seem to be the case for Caucasian population. The methods are clearly described and there is interest in the reported results. However, there are some concerns for the authors' consideration:

(1) If there is an homozygous deletion of GSTM1, the enzymatic activity will be modified, as no active enzyme is expected to be expressed. Therefore, the first sentence on page 6 is not well understood.

Answer, Thanks for your attention. After reading relevant study[7] and thinking carefully, we have changed the sentence to "Therefore, individuals variation in Phases II enzyme activity may contribute to varying susceptibility to esophageal

cancer progression."

(2) How the reported observations match with data produced in massive cancer sequencing and genotyping programs such as TCGA, for instance? What is the association found in other databases such as disgenet?

Answer, Thanks. In our study, we found that GSTM1 null polymorphism might be associated with an increased risk for esophageal cancer in Asian but not in Caucasian populations, which is consistent with the found in DisGenent data base: the top 5 cancers associated with GSTM1 null genotype are: lung neoplasms, squamous cell carcinoma, hepatocellular carcinoma, leukemia, and urinary bladder neoplasms, respectively. Besides, GSTM1 null genotype is the fourth most common gene associated with esophageal cancer[8].

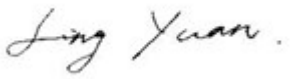
(3) Text for figure5 axes titles is too small.

Answer, Thanks. We have enlarged the text for figure axe titles.

3 References and typesetting were corrected

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

Sincerely yours,



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8 Group IBI. DisGenet. 2015