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Wan Chai, Hong Kong, China

ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 5610

Title: Association between esophageal cancer risk and EPHX1 polymorphisms : a meta-analysis

Reviewer code: 00004678

Science editor: Zhai, Huan-Huan

Date sent for review: 2013-09-17 18:04

Date reviewed: 2013-09-17 22:08

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

Well written meta-analysis on role of EPHX1 in esophageal cancer. Since in the tables results of Adenocarcinoma and Squamous cell carcinoma are given, the manuscript is very interesting. I have only one single suggestion: please state in the discussion that results from Adenocarcinoma and Squamous cell carcinoma were pooled and discuss whether this has any impact on the results.



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 5610

Title: Association between esophageal cancer risk and EPHX1 polymorphisms : a meta-analysis

Reviewer code: 00001114

Science editor: Zhai, Huan-Huan

Date sent for review: 2013-09-17 18:04

Date reviewed: 2013-09-27 18:10

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

This study showed EPHX1 polymorphisms might have nothing to do with developing esophageal cancer using the meta-analysis method. I'm really interested in this paper. I have the following comment - As well known, patients with esophageal cancer have a very poor prognosis, but detection at earlier stages could improve clinical outcome. The detection of environmental and genetic factors is important for prevention on an individual basis. About esophageal squamous cell carcinoma, it is reported that ADH1B and/or ALDH2 risk alleles had a significant interaction with alcohol consumption. I assume that these polymorphisms are clinically important to predict developing esophageal cancer. Please introduce other genetic polymorphisms to predict developing esophageal cancer.



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 5610

Title: Association between esophageal cancer risk and EPHX1 polymorphisms : a meta-analysis

Reviewer code: 02460000

Science editor: Zhai, Huan-Huan

Date sent for review: 2013-09-17 18:04

Date reviewed: 2013-09-30 05:52

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

This is a meta-analysis of several papers on the association between EPHX1 and esophageal cancer. Overall, in the meta-analysis of polymorphisms and health outcomes I would prefer to see the results of a group of related genes (rather than a single gene) if a single outcome is investigated, or a group of health outcomes if a single gene is studied. Otherwise, we will have tens of meta-analyses that could have a lot of similarities in the information they provide regarding carcinogenesis. Anyway, assuming that the current format could be acceptable, I have several comments. Also, there is another very recent meta-analysis on the same topic [PMID 23681797].

1. Please provide a flowchart for literature research, including the number of articles identified in each of the databases, the number of excluded articles in each step, the number of duplicate studies and so on. Also, the authors say "We preliminarily identified 13 studies based on the search terms." If the total number of retrieved article in the initial search is only 13, then there is major concern about the efficiency of their search terms for identifying potentially eligible articles, which is a major concern.
2. The authors say in the inclusion criteria "(iii) The paper should clearly describe the sources of cases and controls." I wonder what they did with the articles that did not clearly describe the source of cases and controls.
3. The authors say "population-based (PB) case-control study was defined as controls from healthy people." In many population-based studies, all controls may not be healthy. These controls are selected from the general population and not from hospitals and clinics, and this is the difference between these two groups of controls. Population-based controls do not have the outcome of interest and perhaps some other medical conditions depending on the study design, but they do not need to be totally healthy.
4. The Discussion part can be better organized. The authors can also reduce the amount of the repetition of their results in the Discussion. Please also add a paragraph on the association



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between polymorphisms in this gene and risk of a few other cancers reported in other meta-analyses. This is a meta-analysis of several papers on the association between EPHX1 and esophageal cancer. Overall, in the meta-analysis of polymorphisms and health outcomes I would prefer to see the results of a group of related genes (rather than a single gene) if a single outcome is investigated, or a group of health outcomes if a single gene is studied. Otherwise, we will have tens of meta-analyses that could have a lot of similarities in the information they provide regarding carcinogenesis. Anyway, assuming that the current format could be acceptable, I have several comments. Also, there is another very recent meta-analysis on the same topic [PMID 23681797].

1. Please provide a flowchart for literature research, including the number of articles identified in each of the databases, the number of excluded articles in each step, the number of duplicate studies and so on. Also, the authors say "We preliminarily identified 13 studies based on the search terms." If the total number of retrieved article in the initial search is only 13, then there is major concern about the efficiency of their search terms for identifying potentially eligible articles, which is a major concern.
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Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 5610

Title: Association between esophageal cancer risk and EPHX1 polymorphisms : a meta-analysis

Reviewer code: 02471371

Science editor: Zhai, Huan-Huan

Date sent for review: 2013-09-17 18:04

Date reviewed: 2013-10-05 20:57

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
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COMMENTS TO AUTHORS

ESPS Manuscript NO: 5610 Title: Association between esophageal cancer risk and EPHX1 polymorphisms: a meta-analysis, by Li et al. This manuscript presented a well-performed meta-analysis assessing the effect of two EPHX1 polymorphisms on esophageal cancer risk. The authors clearly show that neither of EPHX1 substitutions p.Tyr113His and p.His139Arg is associated with esophageal cancer risk. Thereby, they cut short to controversy over the role of the variants in esophageal cancer risk. Overall, this study is well-presented. The analytical method used is correctly described and it is suitable for reaching the objectives well defined in the introduction. The interpretation of data seems appropriate and competent. A few corrections should be made however to improve the manuscript. A. From a formal point of view, a few sentences did not sound very clear to me, and English, which is good overall, could be improved in a few sentences by a slight proof-reading. A few examples: 1. in introduction, page 3, "The EPHX1 activity varies widely and inter-individual" could be replaced for instance by "The EPHX1 activity varies widely among individuals" or by "The EPHX1 activity displays a wide inter-individual variability"; 2. page 5, in the Material and methods section, the sentences "Major reasons for exclusion.../... duplicated studies" (see inclusion and exclusion criteria), and "For our analysis population-based (PB).../... hospitalized patients." are understandable, but they could be much clearer; 3. idem as 2., for sentence "However, one article by Wang et al. .../... Casson et al.", page 7 in the Results section (Characteristics of studies); 4. idem as for 2. for sentence "And hospital-based controls cannot represent.../... controls might have." in the discussion section, on page 10; 5. page 8, the sentence ".../...suggesting that the results were stability and credibility." should be corrected; 6. in the heading of Table 1, the authors wrote "Ethciny" instead of "Ethnicity". B. The nomenclature used for describing the polymorphisms



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is far too approximate, which is not a problem limited to the present study only, but which could be easily corrected. Thus, *EPHX1* in italics refers to the gene, and its related polymorphisms are c.337T>C (NM_000120.3) or rs1051740 and c.416A>G (NM_000120.3) or rs2234922. Tyr113His and His139Arg (which should actually be written p.Tyr113His and p.His139Arg) refer to amino acid substitutions of the protein, i.e., *EPHX1* not italicized. C. Redundancies could be avoided in the discussion. Most of the first paragraph (page 9) is almost a copy of the comments in the results section. Such a repetition does not seem necessary. Redundancies are also noted within the discussion section itself. For instance, the absence of publication bias is mentioned twice. The same remark is valuable for the analysis of subgroups defined by ethnicity. D. The discussion is interesting, but whenever possible, arguments would be strengthened by citations of previous and/or comparable studies. Not a single citation is made in the discussion, which may therefore appear “autocentric”, whereas it raises points which may be applied to case-controlled association studies in general not necessarily restricted to esophageal cancer. The question about the lack of significance due to the small size of the study populations has already been discussed much in other studies, which would deserve to be cited. The authors could point to the current tendency to develop consortia based on thousands of individuals for association studies. In the same way, the problem of the heterogeneity between cohorts/collections is a frequent topic of discussion. By the way, regarding the heterogeneity, the authors did not comment on the apparent heterogeneity observed also within the Asiatic populations included in their meta-analysis (see p for heterogeneity in table 2).