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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 4670
Title: Association between RASSF1A promoter methylation and hepatocellular carcinoma: a meta‑analysis
Reviewer code: 00051753
Science editor: Gou, Su-Xin
Date sent for review: 2013-07-16 10:56
Date reviewed: 2013-07-17 08:43

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[Y] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

The authors present a meta-analysis evaluating the performance characteristics of RASSF1A in assessing for hepatocellular carcinoma in at risk patients. As was pointed out, HCC is leading cause of morbidity and mortality, and current screening and surveillance tools leave much to be desired. The need for novel diagnostic biomarkers are needed, and the current paper presents a meta-analysis evaluating one of these potential tools. While the overall meta-analysis was clearly described and followed started algorithms for performing a meta-analysis study, my main concerns reside in the heterogeneity of the studies included. Given that this is a novel biomarker, extreme care is needed not to conclude a false association when one does not exist. The studies that were included in the current meta-analysis had sensitivities ranging from 0.27 - 0.94 and specificities ranging from 0.38 - 0.95. This represents huge variation, and extreme caution is needed when interreting pooled values that incorporate such wide variations from studies that have relatively small sample sizes. Furthermore, the "control groups" of the different studies included are not entirely comparable. The different cohorts include HBV, HCV, cirrhosis, and presumably non-cirrhotic, although this is not clear in the study. It is possible that RASSF1A may perform differently in the setting of HBV, HCV, cirrhosis, and this should be addressed by the authors. Despite these major concerns, I think the idea of this paper in novel and important as we continue to evaluate novel potential biomarkers for the early diagnosis of HCC. Minor comments: 1. In the study characteristics section of the results, it currently indicates that Taiwan is a region that is part of China. While this may reflect the opinion/perspective of the authors, the World J Gastroenterology targets an international audience, where Taiwan is recognized as a separate country. Thus, this should be corrected. 2. Review of the

manuscript for language assessment is needed, as there are minor English language stylistic/grammatical items that need to be corrected prior to publication

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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 4670
Title: Association between RASSF1A promoter methylation and hepatocellular carcinoma: a meta‐analysis
Reviewer code: 00070577
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[Y] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
The authors showed that RASSF1A methylation in body fluids on HCC patients can improve HCC diagnostic accuracy using meta-analysis. The results are potential important, but I have some concerns about this paper. 1. Makers for HCC such as AFP levels are very different depending on the tumor differentiation and/or tumor sizes and/or number (stage). In this paper the authors did not show the data of tumor differentiation and/or tumor sizes and/or number (stage). Thus it is very difficult to say RASSF1A methylation is really useful compared to the AFP levels. I think this point is the weak point of this paper. 2. The author showed the sensitivity of AFP, but did not show the specificity. The authors should show more data from literature. How was the sensitivity and specificity if the HCC was diagnosed by combination of AFP and PIVKA-II. 3. Published papers usually mention the usefulness of a certain things, thus the paper having negative data often have not been published. Therefore it is possible the authors collected only papers that have only good data. The author should mention about this.

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ESPS Peer-review Report
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[Y] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
The methods of statistical analysis seem relevant. The authors proposed methylation of RASSF1A promoter is used as a diagnostic marker of HCC. Before the application to clinic, methylation of RASSF1A promoter should be discussed in the manuscript and understood by readers. Why is it possible to analyze promoter methylation with fluid samples? Traditionally, promoter methylation was analyzed with surgically resected tumor samples (J Gastroenterol 48, 132-143, 2012). Is DNA isolated from the fluid samples? Biological significance of detection of methylation of RASSF1A promoter with serum samples should be discussed. Does that mean patient DNA already methylated? Or HCC tumor cells are circulating in the blood flow? Mohamed et al report that RASSF1A promoter is methylated in 10 % of control (reference 19). Does this mean false positive? If so, blood or fluid samples harbors false positive. The discussion about false positive would be desirable. Is methylation of RASSF1A promoter specific to HCC? If so, the methylation would be a marker of HCC. If not, is the methylation a marker of various type of cancers? How did the author conclude methylation of RASSF1A promoter was a marker of HCC? Sensitivity and specificity vary depending on the publication. Some describe below 50 %. This phenomenon is common. How did the authors think about weight?