

## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology

**ESPS manuscript NO:** 13317

**Title:** Prevention of hepatocellular carcinoma by correction of metabolic

**Reviewer's code:** 01220634

**Reviewer's country:** France

**Science editor:** Xue-Mei Gong

**Date sent for review:** 2014-08-18 14:01

**Date reviewed:** 2014-08-18 19:09

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input checked="" type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	PubMed Search:	<input checked="" type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Duplicate publication	publication
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	language polishing	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

Excellent review. The figure 1 could be improved using regular squares instead of "hand-drawn" lines and putting in note the entire names of abbreviated factors.

## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology

**ESPS manuscript NO:** 13317

**Title:** Prevention of hepatocellular carcinoma by correction of metabolic

**Reviewer's code:** 02530754

**Reviewer's country:** Spain

**Science editor:** Xue-Mei Gong

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**Date reviewed:** 2014-08-28 02:10

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	PubMed Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Duplicate publication	publication
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor	language polishing	<input type="checkbox"/> No	<input type="checkbox"/> Minor revision
	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

## COMMENTS TO AUTHORS

The present review by Ampuero and Romero-Gómez comprehensively summarized the available evidence concerning the role of statins as chemopreventive agents against hepatocellular carcinoma. The manuscript is pertinent, informative and reads well. However there are some minor considerations that may improve the paper if appropriately addressed: - Whenever odd ratios (OR), relative risks (RR) or hazard ratios (HR) are shown they should be accompanied by their corresponding "p" value and/or 95% confidence interval. It would make easier the interpretation of data for the reader. - As the authors have pointed out several studies reported a protective effect of metformin against HCC when compared with other anti-diabetics and insulin. However these studies are neither randomized, nor controlled, and most of them with a retrospective design. The risk of bias is extremely increased as diabetic patients taking metformin may not be comparable with those taking insulin or other oral anti-diabetics. In addition the dosage and duration of metformin therapy is not controlled as a possible confounding factor in most studies. The heterogeneity of the studies, the lack of randomization and the increased risk of reporting bias prevent from any reliable conclusion when pooled analyses are performed. These limitations should be highlighted and further



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discussed in the text. - It would be helpful to add a table summarizing the studies evaluating metformin as a chemopreventive agent of HCC. The study design, number of patients included, doses and duration of metformin therapy, median follow-up and results may be included in the table.

- The English requires minor polishing

## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Hepatology

**ESPS manuscript NO:** 13317

**Title:** Prevention of hepatocellular carcinoma by correction of metabolic

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**Science editor:** Xue-Mei Gong

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	PubMed Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Duplicate publication	publication
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
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		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

This is an exhaustive review regarding the role of metabolic abnormalities in inducing HCC; the Authors also addressed the issue of the clinical impact of metformin and statins in preventing HCC. I think there is still room for improvement of this second part of the review. The Authors correctly report that the chemopreventive role of metformin and statins was studied in observational studies; the great majority of them support the protective role of these two drugs on HCC. On the other hand, they report only one randomised controller trial regarding statins showing no impact of such drug on HCC incidence. What about metformin? I think that this part should be stressed: if no randomized controlled study using metformin was performed to date, a prospective randomized study should be strongly encouraged but meanwhile the indirect evidences of metformin usefulness should be taken into account. In particular, the Authors should approach the use of widespread use of insulin therapy by diabetologists (and concomitant metformin withdrawal) in cirrhotic patients, irrespective of their Child status. Insulin seems (Donadon, Liver Int 2010) to enhance HCC risk, metformin is very likely to reduce such risk. Why suspend an useful drug and introduce a potentially harmful drug? The safety issue of metformin in well compensated cirrhotic patients is



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really a problem or (more probably) a legend ? I think that this point deserves a more detailed analysis.