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315-321 Lockhart Road, Wan Chai, Hong Kong, China

ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 9161

Title: Lower serum folate is associated with development and invasiveness of gastric cancer

Reviewer code: 00011431

Science editor: Qi, Yuan

Date sent for review: 2014-01-24 10:56

Date reviewed: 2014-02-18 15:49

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input 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)		BPG Search:	<input checked="" 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

1. In the Core Tip, the authors wrote that this is a case-control study, but from the other part of the ms, it seems a nested case-control study. Since the author did not indicate in the Material and Methods when the blood samples were collected in this study, it is not clear whether this is a case-control study or nested case-control study. Please state the experiment design clearly.

2. the authors reported that low serum folate level is associated with increased gastric cancer risk. This is consistent with a previous Chinese study, but contrary to a European study. The authors considered that this discrepancy could be resulted from the timing of blood collection. Is there any other factors such as the different SNP genotype of folate metabolic enzymes between Chinese and European populations may be involed?

3. The authors should indicate the parameters which have been adjusted for when estimating the OR in table 3 and 4.

4. To access the association between serum folate levels and invasiveness of gastric cancer, the authors set a cutoff value (?2.61) to divide the study subjects into two groups. Did they ever compare the mean level of serum folate between the patients with invasive and non-invasive gastric cancer ?



ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 9161

Title: Lower serum folate is associated with development and invasiveness of gastric cancer

Reviewer code: 00054951

Science editor: Qi, Yuan

Date sent for review: 2014-01-24 10:56

Date reviewed: 2014-02-19 00:42

Table with 4 columns: CLASSIFICATION, LANGUAGE EVALUATION, RECOMMENDATION, CONCLUSION. It lists various grades (A-E) and their corresponding evaluation and recommendation options.

COMMENTS TO AUTHORS

This is a nested case-control study conducted in Taiwan on the association between serum folate and gastric cancer risk. Apparently, authors followed patients for some 10 years, but no mention on the follow-up and the longitudinal study is available in the Methods section. Authors found that serum folate may be the key indicator for gastric cancer, a precise "biomarker of gastric cancer" and, also, that it may represent an important prognostic factor for patients with gastric cancer. These findings are "not consistent", or "only partially in agreement", with the current overall evidence on the issue, which is in line with a "possible (weak) association between serum folate and gastric cancer risk. Given that the present study has a number of limitations, including the low sample size, the selection of controls (systematically older than cases), the lack of allowance in the models for selected potentially important covariates, I strongly suggest authors to derive "softer conclusions". The following major points should be addressed by authors: * Given the number of limitations of the present study, authors should interpret more cautiously their findings. For example, several future studies should confirm the present findings before authors can conclude that serum folate is an important biomarker for gastric cancer. * Description of methods lacks of important data, including the period of enrolment of both cases and controls, how cases and controls were selected (are those all consecutive patients?), etc. * Follow-up and survival analysis should be carefully described in the methods section. * How is that h-pylori infection, the most important risk factor for gastric cancer, is not associated to the risk in this case-control study? This should be further discussed. * Given that serum folate is not a recognized biomarker for gastric cancer, it is a nonsense to evaluate the best cut-off to identify gastric cancer cases. I strongly suggest authors to avoid the use of ROC



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curves. Authors can show the association between serum folate and gastric cancer risk using the median value (or tertiles) of serum folate computed among controls or among the overall population of cases and controls.



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 9161

Title: Lower serum folate is associated with development and invasiveness of gastric cancer

Reviewer code: 00007096

Science editor: Qi, Yuan

Date sent for review: 2014-01-24 10:56

Date reviewed: 2014-02-21 11:13

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 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 is useful research which addresses an important topic. The work uses a NCC design from a cohort that the authors have previously used with success. The study design has important limitations, and the authors address these clearly and fairly. Their conclusions are not overstated. Though not likely available at the time of submission, it might be noted that their results appear to conflict with Xiao Q et al BJ Cancer Jan 2014. The authors may wish to address this manuscript as a minor revision.



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Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 9161

Title: Lower serum folate is associated with development and invasiveness of gastric cancer

Reviewer code: 00033061

Science editor: Qi, Yuan

Date sent for review: 2014-01-24 10:56

Date reviewed: 2014-02-22 01:55

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 type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input checked="" type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input checked="" 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 manuscript was aimed at describe the association between low level of folate and development and invasiveness of gastric cancer. This paper has important methodological and substantial weaknesses. Moreover it is not well structured nor clearly written. I think this case-control study (or better nested case-control study) can only suggest an association between low levels of folate and presence of gastric cancer, but it cannot demonstrate a cause/effect relationship. In fact, it could be possible that the low folate status could be secondary to gastric cancer-related malnutrition, instead of being the cause. Significant and important information are missing in the description of study population, as BMI that could give an idea on the nutritional study of cases as well as of controls. Moreover, H. Pylori status was not analyzed as a possible risk factor. ROC curves in this context (and obtained from a case-control study) seems inappropriate. In this study, a significant recall bias is present. The conclusions are inappropriate, in particular the conclusion regarding the association between serum folate and patients survival: the folate levels were already of borderline significance at the univariate analysis, but this lost any significance in multivariate analysis: the conclusion in this regard should be that it is not associated with survival.