

February 14, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: **HAMA_7979_140214.doc**).

Title: Current issues and future perspectives of gastric cancer screening

Author: Chisato Hamashima

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 7979

I appreciate all the constructive comments of the reviewers and the opportunity to submit a revised version of my manuscript entitled, “**Current issues and future perspectives of gastric cancer screening**”.

I carefully revised my manuscript in accordance with all the comments raised. My point-by-point responses to the reviewers’ comments are shown below. The corresponding changes in the revised paper are underlined. To clarify evidence and for clarity, references were added. In addition, the results of the meta-analysis related to targeting the high risk group were added in Figure 1.

The revised manuscript was also thoroughly checked and edited by a native English-speaking medical editor with specialist knowledge in this field to meet the language standards required by leading English language publications.

I hope that the revisions made have satisfactorily answered all the comments raised and that our paper is now suitable for publication in the *World Journal of Gastroenterology*.

Thank you in advance for considering our revised paper for publication. I look forward to hearing from you at your earliest convenience.

Yours sincerely

Chisato Hamashima MD, DrMedSc

Cancer Screening Assessment and Management Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji Chuo-ku, Tokyo 104-0045, Japan

Phone: +81-3-3547-5305

Fax: +81-3-3547-8587

E-mail: chamashi@ncc.go.jp

PONIT-BY-POINT RESPONCE

The manuscript has been carefully revised in according with the suggestions of the reviewers as follows:

1 Format has been updated

The author contribution was added.

The abstract was revised to an unstructured abstract within 200 words.

A short summary was added as CORE TIP.

2 Revision has been made according to the suggestions of the reviewer

Reviewer 00183445

Somewhat greater accuracy requires a description of endoscopic and histological procedures ie what markers are taken into account in addition to atrophy.

Response

Thank you for helpful comment. We cited a Korean study which reported the sensitivity and specificity of population-based screening. A detail explanation was added on the base of a Korean and Japanese study as follows (Page 8-9):

“A comparison of the sensitivity of endoscopic and radiographic screenings has been reported^[22, 23]. In a Korean study, the sensitivity of endoscopic screening was reported as 69.4% (95%CI: 66.4-72.4) for the first round and 66.9% (95%CI: 59.8-74.0) for the subsequent round^[23]. On the other hand, the sensitivity of radiographic screening was reported as 38.2% (95%CI: 35.9-40.5) for the first round and 27.3% (95%CI: 22.6-32.0) for the subsequent round^[23]. Although the definition of interval cancer was different between Korea and Japan, the sensitivity of endoscopic screening was always higher than that of radiographic screening. However, there are possibilities of an increase in the frequency of overdiagnosis by endoscopic screening because it can detect cancer earlier than radiographic screening. Although the detection method is commonly used to measure the sensitivity of the screening method, it cannot exclude cases of overdiagnosis. The incidence method was developed to calculate sensitivity, avoiding cases of overdiagnosis^[24]. Screening for breast, lung, and colorectal cancers has been evaluated using the incidence method^[25-27]. In a Japanese study, the sensitivities of endoscopic and radiographic screening were calculated by both methods^[22] (**Table 2**). By the detection method, it was found that the sensitivity of endoscopic screening was higher than that of radiographic screening in both rounds (prevalence screening: $p = 0.255$, incidence screening: $p = 0.043$). By the incidence method, the sensitivity of endoscopic screening for prevalence and incidence screenings was also higher than that of radiographic screening (prevalence screening: $p = 0.626$, incidence screening: $p = 0.117$). Even if the incidence method is used, the sensitivity.”

The outcome measure of gastric cancer screening is gastric cancer mortality. Atrophy is a surrogate outcome of gastric cancer even if it can be predicated. The effectiveness of cancer screening can be based on the final outcomes reported in this article. In addition, the biomarkers for targeting the high-risk group are limited to serum pepsinogen and *H.pylori* antibody.

**Abstract should be revised and references should be omitted.*

Response

Thank you for your helpful comment. The abstract was revised into an unstructured abstract within 200 words and the references were removed as follow (Page 2-3).

“Gastric cancer remains the second leading cause of cancer death worldwide. About half of the incidence of gastric cancer is observed in East Asian countries, which show a higher mortality than other countries. The effectiveness of 3 new gastric cancer screening techniques, namely, upper gastrointestinal endoscopy, serological testing, and screen and treat method were extensively reviewed. Moreover, the phases of biomarker development for cancer screening were analyzed on the basis of the development road map. Several observational studies have reported the effectiveness of endoscopic screening in reducing mortality from gastric cancer. On the other hand, serologic testing has mainly been used for targeting the high-risk group for gastric cancer. To date, the effectiveness of new techniques for gastric cancer screening has remained limited. However, endoscopic screening is presently in the last trial phase of development before their introduction to population-based screening. To effectively introduce new techniques for gastric cancer screening in a community, incidence and mortality reduction from gastric cancer must be initially and thoroughly evaluated by conducting reliable studies. In addition to effectiveness evaluation, the balance of benefits and harms must be carefully assessed before introducing these new techniques for population-based screening.”

** Figure 1 should be omitted. **

Response

Figure 1 (Trends of incidence of gastric cancer) was removed.

The manuscript must be extensively edited for the grammar and meaning. Author can find some corrections at attached file.

Response

I appreciate your valuable comments. In accordance with your suggestion, I carefully revised the manuscript and the paper was also thoroughly checked and edited by a native English-speaking medical editor with specialist knowledge in this field to meet the language standards required by leading English language publications.

** Table 1: What is the meaning of “rate of diagnostic test”?*

Response

Thank you for pointing this out. It means ‘participant rate for diagnostic examination’. In order to avoid confusion with participation rate of primal screening, ‘participant rate’ was used for ‘screening rate’.

** Table 2: What is the meaning of “sensitivity by incidence method”? The incidence rates are equal, even higher than prevalence rates!*

Response

Thank you for pointing this out. ‘Incidence method’ is the original name of the method used to calculate sensitivity which was developed by Day NE (Day NE. Estimating the sensitivity of a screening test. J Epidemiol Community Health 1985; 39: 364-6.). The incidence method was developed to evaluate the sensitivity of a screening method that avoids overdiagnosis and length bias. Screening for breast, lung, and colorectal cancers has been evaluated using the incidence method. These explanations of the incidence method were added in the revised manuscript as follows (Page 9):

“The incidence method was developed to calculate sensitivity, avoiding cases of overdiagnosis^[24]. Screening for breast, lung, and colorectal cancers has been evaluated using the incidence method^[25-27]. In a Japanese study, the sensitivities of endoscopic and radiographic screening were calculated by both methods^[22] (**Table 2**). By the detection method, it was found that the sensitivity of endoscopic screening was higher than that of radiographic screening in both rounds (prevalence screening: $p = 0.255$, incidence screening: $p = 0.043$). By the incidence method, the sensitivity of endoscopic screening for prevalence and incidence screenings was also higher than that of radiographic screening (prevalence screening: $p = 0.626$, incidence screening: $p = 0.117$). Even if the incidence method is used, the sensitivity of endoscopic screening was always higher than that of radiographic screening in both rounds.”

** What is the meaning of “grade 4 risk of gastric cancer”?*

Response

I apologize for the mistake. This sentence was removed.

Reviewer 00039434

In this paper the authors extensively reviewed the effectiveness of 3 new gastric cancer screening techniques, namely, endoscopic screening, serological testing, and screen and treat method. The paper is well structured, but authors reported data on the screening of gastric cancer limited to Japan and Korea's population, without European studies' population.

Response

Thank you for your insightful comments. European studies related to targeting the high-risk group were discussed and cited in the revised manuscript, including problems these studies encountered as follows (Page 10-12):

“Although several studies have been reported from European countries, their outcomes were mainly for chronic atrophic gastritis which is a surrogate endpoint even if it can be a precursor of gastric cancer^[33-35]. Lomba-Viana et al. previously reported the results of a 5-year follow-up study of the serum pepsinogen test for the early detection of gastric cancer in a European country. The constraint of that study was that the subjects were limited only to 2% of the primary subjects who were screened by the serum pepsinogen test^[36]. For the successful introduction of a screening procedure for population-based screening, a direct evaluation of the reduction in gastric cancer incidence is required. Therefore, a long-term follow-up for the whole target population is needed to evaluate the possibility of predicting the incidence of gastric cancer.”

Some typing errors are present and English language could be improved.

Response

I appreciate your valuable comments. In accordance with your suggestion, I carefully revised the paper and the revised manuscript was thoroughly checked and edited by a native English-speaking medical editor with specialist knowledge in this field to meet the language standards required by leading English language publications.

Reviewer 00074961

I would not mention that the lung cancer mortality rate has increased and that the colorectal cancer mortality rate has increased (last paragraph of Introduction); this is not the subject of your manuscript.

Response

Thank you for your suggestion. The description related to lung cancer mortality rate and colorectal cancer screening mortality rate were removed, and the Introduction section was shortened.

-You forgot the space in Table1 (second line of the first paragraph of “Current status of gastric cancer screening in Japan).

Response

This was corrected accordingly, thank you.

-I would delete the text of Figure 1. It is too long and it is written in Introduction.

Response

In accordance with your comment, Figure 1 was removed. Both mortality and incidence of gastric cancer were revised based on the new data of GLOBOSCAN2012.

3 References and typesetting were corrected