Author's response to reviews

Title: Statins and risk of gastric cancer in diabetes patients

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Author's response to reviews: see over
Reviewer's report

Title: Statins and risk of gastric cancer in diabetes patients
Version: 2 Date: 18 January 2012
Reviewer: Patricia Coogan

Reviewer's report:
Second review, Statins and risk of gastric cancer in diabetes patients. While this manuscript describes a strong study design and analysis, and the results are important, it still does not meet the standards of scientific reporting. My reasons for stating this are as follows:

1. The paper still contains many confusing statements and redundancies. I believe this is due to the fact that the authors' first language is not English. I reproduce here advice from another Journal website:

   Non-native speakers of English
   Authors who are not native speakers of English who submit manuscripts to international journals often receive negative comments from referees or editors about the English-language usage in their manuscripts, and these problems can contribute to a decision to reject a paper. To help reduce the possibility of such problems, we strongly encourage such authors to take at least one of the following steps:
   • Have your manuscript reviewed for clarity by a colleague whose native language is English.
   • Use a service such as one of those listed below. An editor will improve the English to ensure that your meaning is clear and identify problems that require your review. Note that the use of such a service is at the author's own expense.

   Nature Publishing Group Language Editing (http://languageediting.nature.com)
   American Journal Experts (https://www.journalexperts.com/?rcode=NATURE)
   Inter-Biotec (http://www.inter-biotec.com)
   Inter-Biotec also provides a free online writing course (http://www.inter-biotec.com/biowc/biowc.html) to help biomedical scientists whose first language is not English to write and publish their papers in English-language journals.
   SPI Professional Editing Services (http://www.prof-editing.com)
   Write Science Right (http://www.writescienceright.com)

   ➔ As recommended by the reviewer, the manuscript was edited extensively by an English Editing Service.

2. There should be a paragraph in the discussion about the potential confounding by low LDL. This is a classic case of whether the effect is due to the drug or is due to confounding by indication – LDL level. This point was raised by one reviewer but not addressed adequately. There should be a sentence or two about the role of LDL (regardless of statin use) in gastric cancer etiology and a statement about how the potential for confounding by indication may have influenced the observed results.

   ➔ As recommended by the reviewer, the following sentence was added in Discussion:

   In addition, our observation that lower incidence of gastric cancer in statin users might be confounded by LDL cholesterol. Several epidemiological studies have
reported that low plasma LDL cholesterol levels are associated with an increased risk of cancer.[25-28] Therefore, patients who were prescribed of statins might have higher LDL cholesterol level, which might be associated with decreased cancer risk.

3. There are two misstatements in the paper that need to be corrected; both were pointed out in my initial review: 1) the last sentence of the first paragraph of the discussion states that, in these data, “There was no significant correlations between gastric cancer risk and prescriptions for aspirin.” This is contradicted by table 2, where there is a significantly reduced OR for aspirin use in both univariate and multivariable analyses. B) The end of the first sentence of the discussion is not true: “. . . the risk of gastric cancer has not been evaluated in association with statin use” . The authors themselves, in their introduction, refer to a meta-analysis that calculated a RR for gastric cancer. See the review (Browning and Martin, 2006. Int J Ca 120:833-43) which refers to at least 2 studies (one in the General Practice Research Database and a Dutch record linkage study) that showed results for gastric cancer. In addition, a nested case control study by Vinogradova et al, BMC Cancer Sept 2011 (online publication) reported an OR of 0.86 (95% CI 0.72-1.02) for stomach cancer based on 1992 cases and 8279 controls. (I understand that the last publication listed was not available upon initial submission of the article but has been available since September and should now be included.) I believe what the authors meant to say was that there was not large case-control study specifically of gastric cancer yet conducted, which is true. Thus the sentence should be stated this way.

As recommended by the reviewer, we have deleted the sentence. Also, we added the following sentence in Introduction:

A nested case control study reported an odds ratio of 0.86 (95% CI, 0.72 – 1.02) for stomach cancer based con 1,992 cases and 8,279 controls.[10]

4. My previous comment #7 was apparently not understood because it was not addressed. Was statin use in the 6 months prior to diagnosis included in the analysis? One sentence in the manuscript implied that this was so. (p. 7, first sentence under 3.3": “…99 patients had statin therapy >6 months prior the the diagnosis of gastric cancer”. This is an ambiguous sentence; I think now it means patients used statins for a duration of more than 6 months, and this use occurred prior to the cancer diagnosis.

As recommended by the reviewer, the sentence was modified as the following:

Among the 983 cases with gastric cancer, 99 patients had begun statin therapy > 6 months prior to the diagnosis of gastric cancer.

5. It is clear that somehow information on statin use outside the Samsung Medical Center was ascertained. However this paragraph describing how (top of page 5) is not understandable.

we have revised the manuscript accordingly as follows:
In the cases of statin prescribed before visiting Samsung Medical Center, we utilized the electronic drug identification system at our center, which identifies the drug and dosage to hospital pharmacists upon consultation. As a routine practice, we consult all of the outside prescription drugs with hospital pharmacists to verify identification of drugs.

6. End of first full paragraph on page 9, discussion potential bias in using diabetes patients from the large tertiary hospital. Since both cases and controls were diabetes patients from the same hospital, this bias will not operate in this study.

As recommended by the reviewer, we have deleted the sentence in the revised manuscript.

In conclusion, this important study deserves to be published but the authors first must improve the writing to meet current standards for scientific publication. I offer this advice most respectfully.

Reviewer's report
Title: Statins and risk of gastric cancer in diabetes patients
Version: 2 Date: 23 January 2012
Reviewer: Jung Hun kang

Reviewer's report:
The manuscript is further improved and nearly all my questions have been answered properly.

Thank you for the comments.

Reviewer's report
Title: Statins and risk of gastric cancer in diabetes patients
Version: 2 Date: 14 January 2012
Reviewer: Shoji Shimoyama

Reviewer's report:
Major Compulsory Revisions
The numbers here correspond to those itemized in the initial comments.
1. The authors did not respond to the major comment #1. Since all gastric cancer patients were diagnosed at the author's institution, the authors could analyze the frequency of routine examination to detect gastric cancer.

As recommended by the reviewer, the following sentence was added:

The median time for routine endoscopic examination was 2 years.

2 and 3 and 5. The authors should perform uni- and multivariate analyses again using the patients who have a full data set of all background factors. Indeed, Helicobacter pylori status was known among over 80% of patients. I mean ALL confounding factors potentially related to gastric cancer or gastric cancer aggressiveness presented in Table 4, such as smoking, histology, etc., and the results should be presented irrespective of positive or negative p-value. The results of these analyses should be stated at least in the text.

We did perform the analyses again using the full data set of background factors.
As stated in the revised manuscript, none of the variables were statistically significant. We hope the following sentence is acceptable to the reviewer and the editor:

We performed a further association analysis to characterize the clinical features of statin users among gastric cancer patients (Table 4). Statin use was not significantly associated with smoking status, Lauren classification, location, or the presence of *Helicobacter pylori*.

4. **MEAN or MEDIAN length between date of registry and date of gastric cancer diagnosis should be presented.**

   ➔ As recommended by the reviewer, the following sentence was added:

   The mean duration between the date of entry into the diabetes cohort and the date of gastric cancer index was 673 days.

6. **The authors did not respond to the major point #6.**

   ➔ As recommended by the reviewer, the following sentence was added:

   Lastly, the incidence of gastric cancer in DM patients should be compared to that in the statin users.