Author's response to reviews

Title: Alcohol consumption is associated with an increased risk of erosive esophagitis and Barrett's epithelium in Japanese men

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Version: 2 Date: 8 September 2008

Author's response to reviews: see over
Dear Reviewers and Editors,

Thank you for your comments regarding our manuscript.

We would like to respond as follows:

**Title:** Alcohol consumption is associated with an increased risk of erosive esophagitis and Barrett’s epithelium in Japanese men

**Version:** 1  **Date:** 10 June 2000

**Reviewer:** Piers Gatenby

**Reviewer’s report:**

Abstract background - “the roles~are less well defined~” The authors must explain what the roles are less well defined than or in another way amend this sentence which is currently incomplete.

As you pointed out, this sentence needs to be amended.

The Background section of the Abstract was revised as follows:

Evidence regarding the association between alcohol consumption and the gastro-esophageal reflux disease (GERD) spectrum has been conflicting. We examined the association between alcohol consumption and erosive esophagitis and Barrett’s
epithelium in Japanese men.

Abstract results - the 95% confidence intervals stated for the >50g/day groups are incorrect for the odds ratios for both erosive esophagitis and Barrett’s esophagus in the abstract and throughout the manuscript. The odds ratios stated do not lie within the 95% confidence intervals. Furthermore the p values for the odds ratios should be stated in the abstract. The trend for the dose response relationship is not sufficiently clearly described in the abstract or later in the main body of the manuscript.

As you pointed out, the 95% confidence intervals for the odds ratios of the > 50 g/day alcohol consumption groups for both the erosive esophagitis and Barrett’s esophagus groups are incorrect in the abstract and throughout the manuscript. The Abstract and the Results sections were revised as follows:

Results. Compared with never drinkers, light drinkers (less than 25.0 g ethanol per day), moderate drinkers (25.0 to 50.0 g per day), and heavy drinkers (more than 50.0 g per day) had ORs for erosive esophagitis of 1.110 (95% CI: 0.553 – 2.228, p=0.7688), 1.880 (95% CI: 1.015 – 3.484, p=0.0445) and 1.988 (95% CI: 1.120 – 3.534, p=0.0190), respectively. These groups had ORs for Barrett’s epithelium of 1.278 (95% CI: 0.752 – 2.170, p=0.3643), 1.458 (95% CI: 0.873 – 2.433, p=0.1500), and 1.912 (95% CI: 1.185 – 3.086, p=0.0079), respectively. The odds ratios / grams (alcohol) / day of dose
response trends for erosive esophagitis and Barrett’s epithelium were: 1.015 (95% CI: 1.004-1.026, p=0.0066) and 1.012 (95% CI: 1.003-1.0021, p=0.0079), respectively.

Abstract conclusion - the results appear to demonstrate a trend for an association, no causal role or statistical difference. The conclusion drawn is not valid based upon the results stated.

As you pointed out, a significant difference was not demonstrated in the present study.

The conclusion in the Abstract has been revised as follows:

These findings suggest that alcohol consumption in Japanese men tends to be associated with an increased risk of erosive esophagitis and Barrett’s epithelium.

Background – suggest reference to recent article Barrett’s columnar-lined oesophagus: demographic and lifestyle associations and adenoma risk.


As you pointed out, this more recent article should be cited. The reference was added as follows:

Methods - paragraph 1 - explain why cases were excluded “because their profiles were unsatisfactory”, what the inclusion criteria were and the indications for endoscopy if these formed part of the inclusion criteria.

As you pointed out, our explanation of the inclusion and exclusion criteria was insufficient. The total study population underwent endoscopies as part of health checkups at our hospital between August 2005 and July 2006. Cases were excluded, if their complete profiles could not be obtained from their medical records, if they refused to participate in the present study, or if they had previously undergone an upper digestive tract operation.

The methods were revised as follows:

A total of 463 male subjects (median age, 67 years; age range, 31 – 91 years) who had undergone an upper endoscopy at the Gastroenterology Division of Yokohama City University Hospital between August 2005 and July 2006 were enrolled in the present study. The total study population had undergone endoscopies as part of health checkups, and the majority of these subjects were outpatients. Cases were excluded if their complete profiles could not be obtained from their medical records, if they refused to participate in the present study, or if they had previously undergone an upper digestive tract operation.
Methods paragraph 3 – quantify how smoking habit was examined for the purposes of analysis. Please also explain what “shochu” is for non-Japanese readers. Please also quantify how g of alcohol compares to number/volume of drinks and their alcohol percentage.

“Smoking habit” in the study means current regular smoker. “Shochu” is a clear liquor commonly distilled from sweet potatoes, rice, or buckwheat. We calculated the amount of ethanol (in grams) consumed per day according to the standard ethanol percentages: sake (15%), shochu (25%), beer (5%), whisky (40%), and wine (15%). The Methods were revised as follows:

Complete patient information, including age, sex, body mass index (BMI), regular drinking habit, and smoking habit, at the time of the initial diagnosis was obtained from each patient’s medical records.

“Regular drinking habit” was defined in this study as a current regular drinker. Regular drinkers were asked about the frequency of their drinking habit (once or twice per week, three or four times per week, or five times or more per week), the amount drunk on each occasion, and the types of beverage usually consumed (sake, shochu, beer, whisky, wine, or others). “Shochu” is a clear liquor commonly distilled from sweet potatoes, rice, or buckwheat. From these data, we calculated the amount of ethanol (in grams) consumed
per day according to the standard ethanol percentage: sake (15%), shochu (25%), beer (5%), whisky (40%), and wine (15%). The study population was then classified into four groups: never drinkers, light drinkers (less than 25.0 g of ethanol per day), moderate drinkers (25.0 to 50.0 g of ethanol per day), and heavy drinkers (more than 50.0 g of ethanol per day). “Smoking habit” was defined in this study as a current regular smoker.

Methods ethics - please state that patients consented to be involved in the study.

As you pointed out, the section regarding medical ethics was insufficient. The ethics section in the Methods was revised as follows:

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Yokohama City University Hospital. All the patients provided their written informed consent.

Methods statistical analysis - state the type of regression analysis used. Also expand on the linear regression of the logistic regression analysis for analysis of dose-response trends with validation for this analysis.

The Methods section of the Abstract was revised as follows:

A linear regression of the logistic regression analysis was used to analyze the dose-response trends.
Results and discussion - state the definition of long and short-segment Barrett’s esophagus (what’s the cut-off?).

As you pointed out, our explanation of SSBE and LSBE was insufficient. The Discussion section was revised as follows:

The present study demonstrated that 45.6% of the total study population was diagnosed as having Barrett’s epithelium, based on the Prague C & M Criteria [17]. These cases consisted of 45.1% with short-segment Barrett’s esophagus (SSBE), the circumferential (C) extent of which was less than 3 cm, and 0.4% with long-segment Barrett’s esophagus (LSBE), the C extent of which was 3 cm or more (Table 1). These figures are consistent with those of a previous Japanese report that concluded that the incidence of SSBE was higher in Japan than in the United States and Western Europe, whereas LSBE was much rarer (Table 1) [20].

Results and discussion - the authors should comment on the British Society of Gastroenterology guidelines that the histological detection of specialized intestinal metaplasia is not pre-requisite for the diagnosis of columnar metaplasia of the esophagus as its absence on one set of biopsies may be solely due to sampling error and the tissue still has an increased neoplastic potential compared to squamous-lined
esophagus.

As you pointed out, our discussion, regarding the diagnosis of columnar metaplasia of the esophagus, was insufficient. The Discussion was revised as follows:

The frequency of Barrett’s epithelium might be affected by whether its definition requires the histological confirmation of specialized intestinal metaplasia. The British Society of Gastroenterology guidelines have shown that the histological evidence of specialized intestinal metaplasia is not necessary for the diagnosis of Barrett’s esophagus, as its absence on one set of biopsies may be solely due to a sampling error, and the tissue may still have an increased neoplastic potential compared with squamous-lined esophagus [21]. This conclusion is regarded as being valid. In western countries except U.K., however, the confirmation of intestinal metaplasia of the esophagus based on biopsy results is thought to be essential for the diagnosis of Barrett’s epithelium [22], as it is considered a risk factor for esophageal adenocarcinoma [23]. In the present study, Barrett’s epithelium was diagnosed endoscopically based on the Prague C & M Criteria [17], without requiring histological confirmation; thus, the patients in this study were actually diagnosed as having endoscopic Barrett’s epithelium.

Results and discussion - correct the odds ratio and 95% confidence intervals as above
and also in the table.

Table 3 was revised as follows:

<table>
<thead>
<tr>
<th>Endoscopic results</th>
<th>Never drinkers</th>
<th>Alcohol consumption (g/day)</th>
<th>Dose response trends</th>
<th>OR</th>
<th>(95%CI)</th>
<th>P value **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiatal hernia</td>
<td>1.00</td>
<td>0.672 (&lt; 25.0)</td>
<td>0.907 (25.0 – 50.0)</td>
<td>1.036</td>
<td>0.672 (0.372-1.213)</td>
<td>0.0.1872</td>
</tr>
<tr>
<td>Erosive esophagitis</td>
<td>1.00</td>
<td>1.110 (Referent) (0.553-2.228)</td>
<td>1.880 (1.015-3.484)</td>
<td>1.988</td>
<td>0.7688 (1.120-3.534)</td>
<td>0.0445</td>
</tr>
<tr>
<td>Barrett’s epithelium</td>
<td>1.00</td>
<td>1.278 (Referent) (0.752-2.170)</td>
<td>1.458 (0.873-2.433)</td>
<td>1.912</td>
<td>0.3643 (1.185-3.086)</td>
<td>0.0190</td>
</tr>
</tbody>
</table>

Table 3. Odds ratios (ORs) and 95% confidence interval (CI) of hiatal hernia, erosive esophagitis, and Barrett’s epithelium according to different alcohol consumption levels.


Results and discussion – correct the paragraph on alcohol consumption and risk of erosive esophagitis and hiatal hernia as only a trend has been demonstrated using a linear regression of the odds ratios. This should also be corrected further on in this
The paragraph in the results section on the relationship between alcohol consumption and the risks of hiatal hernia, erosive esophagitis, and Barrett’s esophagus has been corrected as follows:

Table 3 presents the odds ratios (ORs) and 95% confidence intervals (CIs) for hiatal hernia, erosive esophagitis, and Barrett’s epithelium according to the different alcohol consumption levels. Compared with never drinkers, light drinkers (less than 25.0 g ethanol per day), moderate drinkers (25.0 to 50.0 g per day), and heavy drinkers (more than 50.0 g per day) had ORs for erosive esophagitis of 1.110 (95% CI: 0.553 – 2.228, p=0.7688), 1.880 (95% CI: 1.015 – 3.484, p=0.0445) and 1.988 (95% CI: 1.120 – 3.534, p=0.0190), respectively. These groups had ORs for Barrett’s epithelium of 1.278 (95% CI: 0.752 – 2.170, p=0.3643), 1.458 (95% CI: 0.873 – 2.433, p=0.1500), and 1.912 (95% CI: 1.185 – 3.086, p=0.0079), respectively. The odds ratios / grams (alcohol) / day of dose response trends for erosive esophagitis and Barrett’s epithelium were 1.015 (95% CI: 1.004-1.026, p=0.0066) and 1.012 (95% CI: 1.003-1.0021, p=0.0079), respectively.

Discussion - comment on the low incidence of adenocarcinoma in the Japanese
population despite the high incidence of Barrett’s esophagus in the study population.

We have added a comment to the Discussion section regarding the low incidence of adenocarcinoma in the Japanese population as follows:

The low incidence of adenocarcinoma in the Japanese population, despite the high incidence of Barrett’s epithelium in the study population, is an unusual phenomenon. The frequency of Barrett’s epithelium might be affected by whether its definition requires the histological confirmation of specialized intestinal metaplasia. The British Society of Gastroenterology guidelines have shown that the histological evidence of specialized intestinal metaplasia is not necessary for the diagnosis of Barrett’s esophagus, as its absence on one set of biopsies may be solely due to a sampling error, and the tissue may still have an increased neoplastic potential compared with squamous-lined esophagus [21]. This conclusion is regarded as being valid. In western countries except U.K., however, the confirmation of intestinal metaplasia of the esophagus based on biopsy results is thought to be essential for the diagnosis of Barrett’s epithelium [22], as it is considered a risk factor for esophageal adenocarcinoma [23]. In the present study, Barrett’s epithelium was diagnosed endoscopically based on the Prague C & M Criteria [17], without requiring histological confirmation; thus, the patients in this study were actually diagnosed as having
endoscopic Barrett’s epithelium. In addition, as the prevalence of esophageal adenocarcinoma is not as high among non-Caucasians in the United States as it is among Caucasians [24], large ethnic differences in the pathogenesis process of esophageal adenocarcinoma may exist.

Discussion - I would recommend that the authors discuss the role of physiological studies to examine differences in patients who consume alcohol and the absence of these data from the cohort.

We agree that physiological studies examining the differences among patients who consume alcohol are necessary to investigate the role of alcohol consumption in the etiology of erosive esophagitis and Barrett’s epithelium.

Consequently, we have revised the Discussion section as follows:

Further physiological studies examining differences among patients who consume alcohol are necessary for investigating the influence of alcohol consumption on the mechanism of erosive esophagitis and Barrett’s epithelium.

Conclusions - see comments on the abstract.

The Conclusions section was revised as follow:
Our data suggests that alcohol consumption in Japanese men tends to be associated with an increased risk of erosive esophagitis and Barrett’s epithelium. From a public health perspective, further studies are needed to clarify the role of alcohol consumption in the etiology of erosive esophagitis and Barrett’s epithelium.

Table 1 – clarify smoking habit.

We defined “smoking habit” as current smokers in this manuscript. We have revised Table 1 and Table 2 accordingly.

Table 2 – the p-value column is empty and smoking habit requires definition.

Table 2 was revised as follows:

<table>
<thead>
<tr>
<th>Lifestyle characteristics</th>
<th>Never drinkers n=187 Number (%)</th>
<th>Regular drinkers n=276 Number (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age median; range (years)</td>
<td>66 (31-91)</td>
<td>67 (31-86)</td>
<td>0.2307</td>
</tr>
<tr>
<td>Body mass index &gt; 25</td>
<td>46 (24.6)</td>
<td>63 (22.8)</td>
<td>0.6591</td>
</tr>
<tr>
<td>Current smoking habit</td>
<td>94 (50.3)</td>
<td>170 (61.6)</td>
<td>0.0157</td>
</tr>
</tbody>
</table>

Table 2. Lifestyle characteristics of never drinkers or regular drinkers

Table 3 – correct the odds ratio and 95% confidence intervals as above.

Table 3 was revised as follows:
<table>
<thead>
<tr>
<th>Endoscopic results</th>
<th>Never drinkers</th>
<th>Alcohol consumption (g/day)</th>
<th>Regular drinkers</th>
<th>Dose response trends</th>
<th>OR (95%CI)</th>
<th>P value **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiatal hernia</td>
<td>1.00 (Referent)</td>
<td>Light* &lt; 25.0</td>
<td>0.672 (0.372-1.213)</td>
<td>1.001 (Referent)</td>
<td>0.672 (0.372-1.213)</td>
<td>0.1872</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate* 25.0 – 50.0</td>
<td>0.907 (0.525-1.567)</td>
<td>0.907 (0.525-1.567)</td>
<td>0.8121</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heavy* &gt; 50.0</td>
<td>1.036 (0.629-1.709)</td>
<td>1.036 (0.629-1.709)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erosive esophagitis</td>
<td>1.00 (Referent)</td>
<td>Light* &lt; 25.0</td>
<td>1.110 (0.553-2.228)</td>
<td>1.001 (Referent)</td>
<td>1.110 (0.553-2.228)</td>
<td>0.7688</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate* 25.0 – 50.0</td>
<td>1.880 (1.015-3.484)</td>
<td>1.880 (1.015-3.484)</td>
<td>0.0445</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heavy* &gt; 50.0</td>
<td>1.988 (1.120-3.534)</td>
<td>1.988 (1.120-3.534)</td>
<td>0.0190</td>
<td></td>
</tr>
<tr>
<td>Barrett’s epithelium</td>
<td>1.00 (Referent)</td>
<td>Light* &lt; 25.0</td>
<td>1.278 (0.752-2.170)</td>
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<td>0.3643</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate* 25.0 – 50.0</td>
<td>1.458 (0.873-2.433)</td>
<td>1.458 (0.873-2.433)</td>
<td>0.1500</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heavy* &gt; 50.0</td>
<td>1.912 (1.185-3.086)</td>
<td>1.912 (1.185-3.086)</td>
<td>0.0079</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.001</td>
<td>1.001</td>
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<td></td>
</tr>
</tbody>
</table>

Table 3. Odds ratios (ORs) and 95% confidence interval (CI) of hiatal hernia, erosive esophagitis, and Barrett’s epithelium according to different alcohol consumption levels.

1, There was no description of the reason that patients attended to the hospital and underwent an upper endoscopic examination. In Japan, most of patients with reflux esophagitis do not complain of typical GERD symptoms, including heartburn and regurgitation, whereas some patients without erosive gastritis have persistent heartburn. It is possible that heavy drinkers may be insensitive to gastroesophageal reflux of gastric acid, resulting in taking a greater amount of ethanol.

We have added a description of the reason why the patients underwent an upper endoscopic examination in the Methods section, as follows:

A total of 463 male subjects (median age, 67 years; age range, 31 – 91 years) who had undergone an upper endoscopy at the Gastroenterology Division of Yokohama City University Hospital between August 2005 and July 2006 were enrolled in the present study. The total study population had undergone endoscopies as part of health checkups, and the majority of these subjects were outpatients. Cases were excluded if their complete profiles could not be obtained from their medical records, if they refused to
participate in the present study, or if they had previously undergone an upper digestive tract operation.

2. Authors should describe the mean value of age, and BMI, and the rate of subjects with smoking habit in each group of regular drinkers (<25.0g, 25.0-50.0g, and >50.0g).

We have added the mean age, BMI, and the percentage of subjects with a smoking habit for each group of regular drinkers.

The Results section was revised as follows:

The patient profiles for each group of regular drinkers were as follows: never drinkers (n=187; mean age, 64 years; mean BMI, 22.8; smoking habit, 50.3%), light drinkers (n=80; mean age, 65 years; mean BMI, 22.4; smoking habit, 51.3%), moderate drinkers (n=87, mean age, 68 years; mean BMI, 23.0; smoking habit, 65.5%), and heavy drinkers (n=109, mean age, 65 years; mean BMI, 23.1, smoking habit, 66.1%).

3. Based on the results that alcohol consumption in Japanese men is associated with a statistically significant increased risk of erosive esophagitis and Barrett’s epithelium regardless of the presence of hiatal hernia, is alcohol consumption more likely to contribute to developing erosive esophagitis? The author had better describe this in the
We think that alcohol consumption is more likely to contribute to the development of erosive esophagitis than Barrett’s epithelium. The Discussion section was revised as follows:

Additionally, these findings suggest that alcohol consumption may be more likely to contribute to the development of erosive esophagitis than Barrett’s epithelium.

4. In Table 2, p-value is unwritten. The author should fill in a blank.

Table 2 was revised as follows:

<table>
<thead>
<tr>
<th>Lifestyle characteristics</th>
<th>Never drinkers</th>
<th>Regular drinkers</th>
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<td>Current smoking habit</td>
<td>94 (50.3)</td>
<td>170 (61.6)</td>
<td>0.0157</td>
</tr>
</tbody>
</table>

Table 2. Lifestyle characteristics of never drinkers or regular drinkers

Thank you very much for your comments for my work.

We correct some grammatical errors and spell errors.
Yours sincerely,

Masahiko Inamori, MD.

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E-mail : inamorim@med.yokohama-cu.ac.jp