

July 13, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (18431-Revised manuscript.docx).

Title: Gastric cancer risk in relation to tobacco use and alcohol drinking in Kerala, India
-- Karunagappally Cohort Study

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 18431

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated.
2. The informed consent statement, Conflict of interest statement and Data sharing statement have been added to the manuscript. (Clinical trial registration statement was not applicable to our study as it is an observational cohort study.)
3. The “Comments” section was added to the manuscript.
4. The language of the manuscript has been edited by a professional language editing company and revised accordingly. Language and format corrections are indicated by changing font colour to red in the manuscript.
5. Revisions have been made according to the suggestions of the reviewers. The detailed responses to the reviewer’s comments are included in the following pages of this document p.3-7. The revised parts are yellow-highlighted in the manuscript.
6. Table 5 was revised, as mentioned in the response to comment no. 5.

Thank you again for considering our manuscript for publication in the *World Journal of Gastroenterology*.

Sincerely yours,



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“In the present retrospective cohort study, Authors analyzed tobacco smoking and alcohol intake as risk factors for gastric cancer (GC). “

1. “The main limitation is that it has been conducted on a population with a wide variety in socio-economic conditions.”

Response: In this study, religion, income level, occupation and education were used as indicators of socioeconomic status (SES), and their associations with gastric cancer risk were analysed (results are presented in table1). Based on this analysis we identified occupation and education as the potential confounding SES related variables and we adjusted for their confounding effect by stratifying our data by the categorical variables of occupation and education, in addition to age and calendar time.

2. “Moreover, the type of smoking (bidi) and alcoholic beverage (toddy and arrack) are widespread only in India, and their preparation may change according to the city where the recipe was formulated. “

Response: Bidi smoking is common in many other Asian countries such as Pakistan, Afghanistan and Bangladesh. Bidi smoking has become popular even in US especially among young people because they are less expensive and wrongly perceived as less harmful. Bidi is made of sun dried flaked tobacco rolled into a conical shape in a dried rectangular piece of temburni leaf (*Diospyros melanoxylon*) and a thread securing the roll. As bidis are hand-rolled, the length and amount can vary but the difference is not large and on average it contains 0.15-0.25 g of tobacco leaves in Karunagappally taluk, our study area. Regarding toddy and arrack, the recipes can be different from area to area. However, the recipes are almost the same in the entire Karunagapally taluk. On average, toddy contains 5-10% of alcohol and arrack contains 25-45% of alcohol.

We revised the related parts in the introduction section, accordingly.

3.” There is no mention about the histopathology of GC. Indeed, it is known that diffuse-type and intestinal-type may show different risk factors. For example, diffuse-type is less influenced by *H. pylori* and more influenced by genetical factors. “

Response: We do not have any information regarding gastric cancer pathology; therefore, we could not distinguish the intestinal and diffuse types. However, the diffuse type is considered only weakly related to lifestyle-related factors such as smoking and dietary habits. Thus, the relations between bidi smoking and gastric cancer observed in this study were primarily from the associations with the intestinal type. However, we cannot tell whether-bidi smoking increased the risk of both subtypes, although to different magnitudes, or only increased the risk of the intestinal type.

We added sentences to that effect to the discussion section (limitation).

4. “Authors did not provide any data about *H. pylori* status in enrolled patients. This is a relevant drawback, since this bacterium is considered the most important gastric carcinogen. This omission may have interfered with the results provided in the present study. “

Response: *H. pylori* infection is the most important risk factor of gastric cancer and is known to trigger a consequence of pathological changes leading to gastric cancer. Risk factors such as tobacco use and alcohol drinking can modify the risk of gastric cancer induced by *H. pylori*. The evidence showing that tobacco smoking remains a risk factor among individuals infected with *H. pylori* supports this notion. However, studies in India have not shown a strong association between gastric cancer risk and *H. pylori* infection, although its prevalence is high. The high prevalence of *H. pylori* infection in India, despite relatively low gastric cancer incidence, is known as the Indian enigma. Taken together, in the results of the present study suggests that bidi smoking increases the risk of *H. pylori*-related gastric cancer. However, we cannot deny the possibility that

bidi smoking also increases *H. pylori*-unrelated gastric cancer risk because we do not have any information on *H. pylori* infection in the present study population.

We added a paragraph to that effect to the discussion section (limitation).

5. “A direct comparison in risk evaluation between bidi smoking and classical cigarette smoking is lacking. “

Response: In order to compare the effects of bidi smoking and cigarette smoking we did the following analysis:

Cigarette smoking	Bidi smoking	Person Years	Gastric Cancer cases	RR	95% CI
Never	Never	267320	23	1	Reference
Never	Current	99803	30	2.2	1.3-4.0
Current	Never	139294	7	0.7	0.3-1.6
Current	Current	246681	32	1.3	0.7-2.3

Those findings are added to the result section of the manuscript.

6. “The cumulative effect of smoking and drinking has not been analyzed.”

Response: As requested by the reviewer we analysed the effect of cumulative smoking and drinking and the results are as follows:

Table. Gastric cancer risk in relation to cumulative amount of bidi smoking, cigarette smoking and arrack drinking

Cumulative amount	Person years	Gastric cancer cases	RR	95% CI	P-value*
Bidi number/day x duration(year)					0.017
Never smoker	485787	39	1	Reference	
<400	244041	29	1.3	0.8-2.1	
400-799	112844	28	1.7	1.0-2.9	
>=800	58049	20	1.8	1.0-3.3	

Cigarette number/day x duration(year)					>0.5
Never smoker	441568	59	1	Reference	
<400	422306	49	0.9	0.6-1.4	
>=400	36847	8	1.1	0.5-2.3	
Arrack consumption(ml/day) x duration(year) **					0.377
Never drinker	454152	51	1	Reference	
<1000	17227	4	2.2	0.8-6.2	
1000-2999	18655	4	2.4	0.9-6.7	
>=3000	26910	5	1.1	0.4-2.8	
Unknown	383776	52	1.1	0.8-1.7	

*P for trend**Regarding drinking, we limited the analysis of alcohol drinking to subjects who drink or used to drink arrack only, because it is the most common liquor (with high alcohol content) among our study population.

Those findings are added to the results section of the manuscript.

We omitted the results about the amount of alcohol consumption from table 5. We did so because we came to realise that we did not have sufficient information to calculate the accurate amount of alcohol consumed a day for each of a wide variety of alcohol types. Instead we added the results of the analysis restricted to only-arrack-drinkers, shown in the following table, to the results section.

Table. Gastric cancer risk in relation to arrack drinking

Arrack	Person years	Gastric cancer cases	RR	95% CI	P-value
Never drinker	454152	51	1		0.107
former	11132	3	1.5	0.5-4.9	
current	60956	12	1.7	0.9-3.2	
Daily arrack consumption (ml)					
Never	454152	51			0.098
Former	11132	3	1.5	0.5-4.9	
-70 ml/day	12355	2	1.3	0.3-5.3	
+70 ml/day	42140	8	1.6	0.8-3.5	

7. “Another factor that strongly influences GC is the diet, but in the present study an alimentary survey is lacking.”

Response: Our questionnaire included questions about the weekly consumption of vegetarian and non-vegetarian food items and fruits. However, food item categories were broad. For example, vegetables were leafy vegetables, roots/tubers, tapioca and the other vegetables. In the case of non-vegetarian food items the categories are egg, fish (dry and fresh), mutton, beef, chicken and others. The amounts of consumption were not asked. In the case of stomach cancer, salt intake is the most important dietary risk factor. We cannot calculate the accurate amount of salt consumption based on our questionnaire, because our questionnaire was described as before. However, a case-control study by Mathew *et al.*, conducted in Regional Cancer Centre, Trivandrum, South India gastric cancer risk was not associated with the consumption of dried fish, which is the main food item with a high concentration of salt in our study area. Moreover the consumption of dried fish was not common in the study population. The same study found that high consumption of rice (OR:3.9; 95%CI:1.6-10.0 for daily users), chilli (OR:7.4; 95%CI:4.0-13.5) and high temperature food (OR:7.0; 95%CI:3.7-12.9) was related to the risk of stomach cancer. The ORs for chilli and high temperature foods are relatively large in this study but their CIs are wide. In addition, those habits are not so common in the study area and therefore the percentage of stomach cancer cases related to those habits are expected to be small even though ORs are relatively high. In addition, the association of those factors with bidi smoking is unlikely to be large enough to be able to explain the association between bidi smoking and gastric cancer completely. However, the weak associations of cigarette smoking and alcohol drinking with gastric cancer risk may be explained by the associations with dietary habits. Regarding rice eating, this habit is so common that everybody eats it; the amount of rice consumption is unlikely to be strongly associated with bidi smoking. We added sentences to that effect to the discussion section (limitation).