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SYSTEMATIC REVIEWS

Sex as an effect modifier in the association between alcohol intake and gastric cancer risk

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Abstract

BACKGROUND

The results of previous meta-analyses evaluating the association between the alcohol intake and gastric cancer risk have reported that a statistical significance only for men.

AIM

To investigate the different association between alcohol intake and gastric cancer risk between men and women.

METHODS

The selection criteria included a prospective cohort study for evaluating alcohol intake and gastric cancer risk, with relative risks adjusted for potential confounders. Adjusted relative risk (RR) for the potential confounders and its 95% confidence interval (CI) in the highest *vs* lowest level were extracted from each study and a random-effects meta-analysis was conducted. Subgroup analyses by region, level of adjustment for smoking status, adjusting for body mass index, and year of publication were conducted.

RESULTS

A meta-analysis of all 27 cohorts showed that alcohol intake increased the risk of gastric cancer (summary RR = 1.13, 95%CI: 1.04-1.23, I^2 = 58.2%). Further, 13 men's cohorts had higher summary RR while maintaining statistical significance, and only seven women's cohorts had no statistical significance.

CONCLUSION

The present review suggests that alcohol consumption increases the risk of gastric cancer in men. These findings showed that the sex variable in the association between alcohol intake and gastric cancer risk seemed to be an effect modifier with an interaction term. It is necessary to re-estimate follow-up outcomes after stratifying for sex.

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Core Tip: The present review suggests that alcohol consumption increases the risk of gastric cancer, especially in men. These findings showed that the sex variable in the association between alcohol intake and gastric cancer risk seemed to be an effect modifier with an interaction term. It is necessary to re-estimate follow-up outcomes after stratifying for sex.

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INTRODUCTION

Global cancer statistics 2018 reported that gastric cancer was the fifth most frequently diagnosed cancer and the third leading cause of cancer-related death[1]. As gastric cancer is known to be a multifactorial disease[2], modifiable risk factors such as *Helicobacter pylori* and Epstein–Barr virus infection, diet, smoking status, and alcohol intake have been identified[3-6].

Table 1 summarizes the results of three meta-analyses published in 2017, that evaluated the association between alcohol intake and gastric cancer risk[7-9]. All summary relative risk (sRR) was over 1, but the results of statistical significance conflicted with each other. Interestingly, all meta-analyses reported that the 95% confidence interval (CI) of sRR in men did not involve 1. This indicates a statistically significant association between alcohol intake and gastric cancer risk in men. However, women did not have statistical significance in any of the meta-analyses. In addition, He *et al*[8] reported that light alcohol intake was associated with a reduction in gastric cancer in women (sRR = 0.74, 95%CI: 0.57-0.98).

Based on these findings, the author hypothesized that alcohol intake's association with gastric cancer risk may differ between men and women. Thus, the aim was to investigate the suggested hypothesis targeting three meta-analyses in Table 1 and Tramacere *et al*[10]'s study by performing a meta-epidemiological review[11].

MATERIALS AND METHODS

Selection strategies

The selection criterion for this meta-epidemiological study was as follows: A prospective cohort study for evaluating alcohol intake and gastric cancer risk showing RR adjusted for potential confounders.

Of the cohort studies selected for conducting meta-analysis by four existing systematic reviews[7-10], a total of 18 studies met the selection criteria[12-29]. Since the latest year of publication, of the 18 studies, was 2015[29], cohort studies published until July 31, 2020 were needed. The articles that cited the 18 selected studies was listed using the "cited by" option on PubMed[30]. From this, additional cohort studies meeting the selection criteria were secured. After checking for duplication of cohort participants among the selected cohort studies, a study with more gastric cancer patients was selected between duplicate studies.

Statistical analysis

Adjusted RR for potential confounders and its 95%CI in the highest *vs* lowest level were extracted by sex from each study. As the reference group of Buckland *et al*[27] was the moderate/high-intake group, the adjusted RR of the study was taken by the reciprocal of the adjusted RR of the no/low-intake group. The level of adjustment for

Table 1 Summary of previous systematic reviews for evaluating the association between alcohol intake and gastric cancer risk

Ref.	Searching	Selected studies (Cohort)	Group	Summary relative risk (95% confidence interval)	I^2 (%)
Han *et al*[7], 2017	Dec-16	23	Both, HLL	1.17 (1.00-1.34)	79.6
		7	Men, HLL	1.18 (1.06-1.30)	0
		1	Women, HLL	1.13 (0.79-2.25)	0
Wang *et al*[9], 2017	Dec-16	17	Both, HLL	1.19 (1.06-1.34)	37.6
		34	Men, HLL	1.21 (1.06-1.37)	68.2
		12	Women, HLL	1.18 (0.95-1.47)	26.2
He *et al*[8], 2017	Apr-17	22	Both, HLL	1.03 (0.99-1.08)	21.9
			Men, heavy	1.13 (1.06-1.22)	28.1
			Women, heavy	1.33 (0.79-2.24)	2.4

HLL: Highest versus lowest level.

smoking status and the adjustment for body mass index in each cohort study were evaluated. A high level of smoking status was defined as ≥ 3 in the definition suggested by Thomas and Hodges[31]. They defined three levels as adjustments with less than four categories based on smoking status and intensity.

The level of heterogeneity among cohorts was evaluated using the I-squared value, and a random-effects model meta-analysis was performed[32]. In addition, subgroup analyses by region, level of adjustment for smoking status, adjusting for body mass index, and year of publication were conducted to evaluate the effects of potential confounders. The level of statistical significance was set at $P < 0.05$.

RESULTS

Final selection

The list made using the "cited by" option on PubMed on July 31, 2020 contained a total of 411 articles. Five cohort studies meeting the selection criteria were obtained from the list[33-37]. While checking for duplication of cohort participants, the author found that three studies of the Honolulu Heart Program[12,15], two of the European Prospective Investigation into Cancer and Nutrition cohort[13,27], and two of the NIH-AARP diet and health cohort[14,36] had the same cohort participants, respectively. Thus Nomura *et al*[12], Duell *et al*[13], and Freedman *et al*[14] were excluded based on the number of gastric cancer patients. Finally, 20 cohort studies with a total of 26864280 participants were selected (Figure 1)[15-29,33-37]. There were 10 Asian, 7 European, and 3 American studies in the regional distribution. They consisted of 27 cohorts by sex: 13 men's, 7 women's, and 7 adjusted for sex.

Summary effect size

A meta-analysis of all 27 cohorts showed that alcohol intake increased the risk of gastric cancer (sRR = 1.13, 95%CI: 1.04-1.23, I^2 = 58.2%) (Figure 2). When subgroup analysis by sex was performed, the 13 men's cohorts had higher sRR while maintaining statistical significance (sRR = 1.18, 95%CI: 1.06-1.32, I^2 = 55.5%), but the seven women's cohorts (sRR = 1.07, 95%CI: 0.96-1.19, I^2 = 0.0%) and seven cohorts adjusted for sex (sRR = 1.05, 95%CI: 0.83-1.33, I^2 = 61.6%) had no statistical significance.

The subgroup analysis of the 13 men's cohorts showed that there was statistical significance in Asians, in the group with a high level of adjustment for smoking status, in the group with the adjustment for body mass index, and in more recently published studies (Table 2). These results were not found in the seven women's cohorts.

Table 2 Subgroup analysis by potential confounders[1]

	Men	Women	Both
All	1.18 (1.06-1.32) [13]	1.07 (0.95-1.19) [7]	1.13 (1.04-1.23) [27]
Region			
Asia	1.22 (1.09-1.36) [8]	1.09 (0.91-1.29) [3]	1.43 (1.02-1.28) [13]
Non-Asia	1.12 (0.83-1.50) [5]	1.07 (0.83-1.38) [4]	1.11 (0.99-1.24) [14]
Level of adjustment of smoking status			
Low	1.14 (0.91-1.41) [7]	1.07 (0.95-1.20) [5]	1.16 (1.06-1.27) [10]
High	1.19 (1.08-1.31) [6]	1.09 (0.84-1.43) [2]	1.12 (0.98-1.27) [17]
Adjustment of body mass index			
No	1.05 (0.83-1.34) [5]	1.48 (0.93-2.36) [2]	1.12 (0.92-1.36) [8]
Yes	1.22 (1.08-1.37) [8]	1.05 (0.96-1.17) [5]	1.13 (1.03-1.24) [19]
Year of publication			
Approximately 2005	1.08 (0.88-1.33) [4]	[0]	1.08 (0.89-1.33) [5]
2006-2010	1.07 (0.81-1.41) [3]	1.48 (0.93-2.36) [2]	1.14 (0.98-1.32) [8]
2011-	1.26 (1.02-1.56) [6]	1.05 (0.95-1.17) [5]	1.14 (1.00-1.29) [14]
Site			
Cardia	1.07 (0.79-1.44) [1]	1.30 (0.43-3.90) [1]	1.05 (0.81-1.35) [3]
Non-cardia	0.75 (0.53-1.06) [1]	0.66 (0.24-1.82) [1]	0.84 (0.65-1.08) [3]

[1]Summary relative risk (95% confidence interval) [number of cohorts].

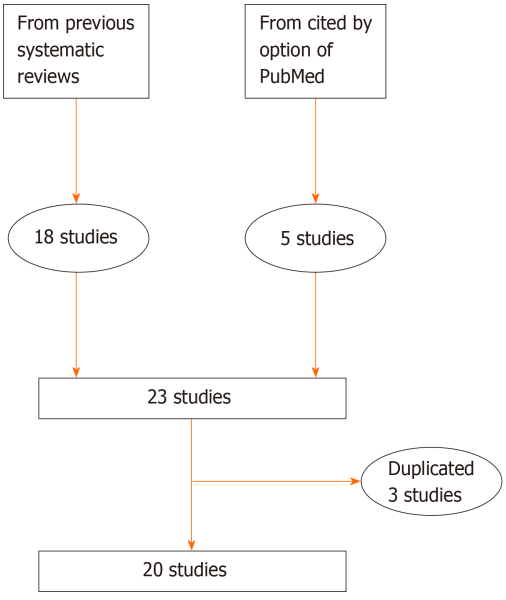

Figure 1 Flow chart of the final selection of prospective cohort studies.

DISCUSSION

Summary of the main finding

The results show that alcohol intake increased the risk of gastric cancer, especially in men. However, this association was not seen in women.

Differences between sex groups

Compared to the sRR of 1.21 in men's cohorts of Wang *et al*[9] in Table 1, the sRR of

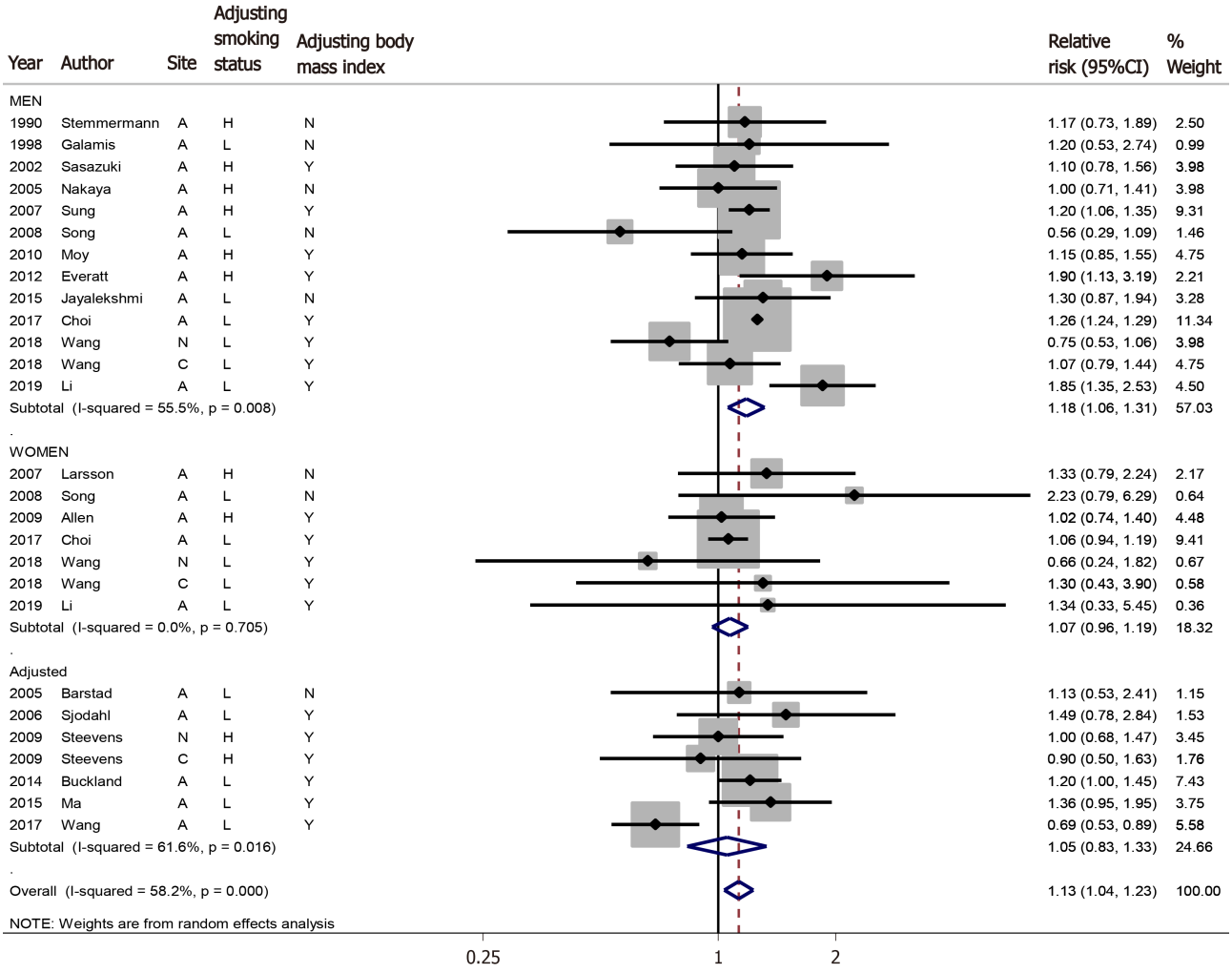

Figure 2 Forest plot of estimating the summary relative risk. A: All; C: Cardia; N: Non-cardia; H: High level; L: Low level; Y: Yes; N: No; CI: Confidence interval.

1.13 estimated from 13 cohorts was the almost the same level, but the CI was narrower. The sRR of men's cohorts published more recently was the highest and was statistically significant. Cumulative meta-analysis showed that the sRR converged as it moved from the past to the present (Figure 3).

However, the results of the women's cohorts showed that alcohol intake might not increase the risk of gastric cancer. This finding can be supported by the results of He *et al*[8], who reported that light alcohol intake was associated with a reduction in gastric cancer in women (sRR = 0.74, 95%CI: 0.57-0.98). In addition, incidence rates are two-fold higher in men than in women[1]. Thus, the sex variable in the association between alcohol intake and gastric cancer risk seems not to be a simple confounder but be an effect modifier having an interaction term[38]. In other words, seven cohorts adjusted for sex need to re-estimate outcomes stratified by sex.

Inferences about subgroup analyses

The subgroup analysis of 13 men's cohorts indicated that there was statistical significance in Asians, in the group with the high level of adjustment for smoking status, and in the group adjusted for body mass index. Interestingly, the statistical significance was not shown in the group with a low level of adjustment for smoking status, and in the group not adjusted for body mass index. This is because a RR generally shifts to null as the potential confounder is strengthened. These phenomena strongly support the hypothesis that alcohol intake increases the risk of gastric cancer in men.

Limitations

The main limitation is that the category of alcohol intake varies in each study, such as times *per* week, amount consumed *per* day, none/moderate/heavy, or never/

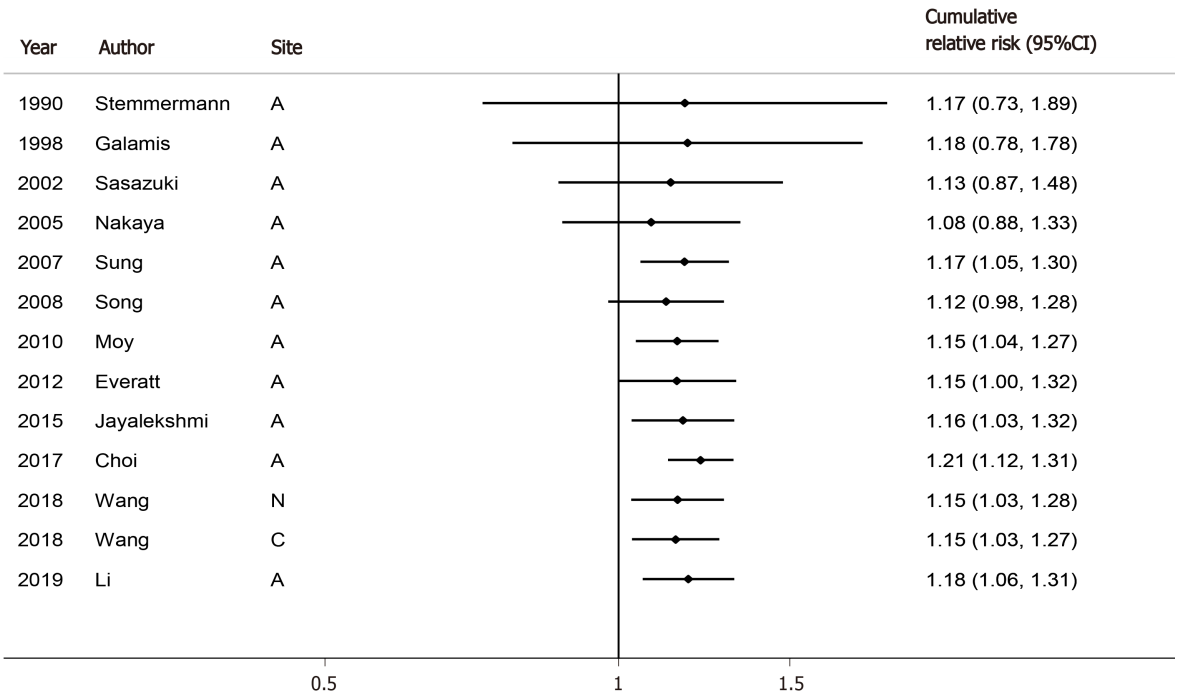

Figure 3 Cumulative meta-analysis for the risk of gastric cancer in men by alcohol intake. A: All; C: Cardia; N: Non-cardia; CI: Confidence interval.

former/current drinker. Therefore, the author extracted the results of the highest and lowest levels from each study and applied a random effect model. Another limitation is that the author could not perform subgroup analysis for cardia and non-cardia because only three cohorts were selected. Thus, the author could not evaluate the argument by sex that "intestinal non-cardia carcinoma was accompanied by heavy alcohol consumption"[3].

CONCLUSION

In conclusion, the present study suggests that alcohol consumption increases the risk of gastric cancer in men. It is necessary to re-estimate the follow-up outcomes by stratification for sex to determine whether there is a sex difference in the association between alcohol intake and gastric cancer risk.

ARTICLE HIGHLIGHTS

Research background

The previous systematic reviews showed a statistically significant association between alcohol intake and gastric cancer risk in men. However, women did not have statistical significance in any of the meta-analyses.

Research motivation

The author hypothesized that alcohol intake's association with gastric cancer risk may differ between men and women.

Research objectives

The aim was to investigate the suggested hypothesis targeting four previous meta-analyses by performing a meta-epidemiological review.

Research methods

After securing additional cohort studies meeting the selection criteria, updated meta-analysis and subgroup analysis by sex were conducted.

Research results

The subgroup analysis of the 13 men's cohorts showed that there was statistical significance in Asians, in the group with a high level of adjustment for smoking status, in the group with the adjustment for body mass index, and in more recently published studies. These results were not found in the seven women's cohorts.

Research conclusions

The present study suggests that alcohol consumption increases the risk of gastric cancer in men.

Research perspectives

It is necessary to re-estimate the follow-up outcomes by stratification for sex to determine whether there is a sex difference in the association between alcohol intake and gastric cancer risk.

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