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Original Article

Association of alcohol consumption before a meal with the risk of gastric adenocarcinoma and esophageal squamous cell carcinoma: a case-control study

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Abstract: This study aimed to investigate the effects of alcohol consumption before a meal at mealtime on the risk of non-cardia gastric adenocarcinoma (GA), gastric cardia adenocarcinoma (GCA), and esophageal squamous cell carcinoma (ESCC). A hospital-based case-control study was performed in Shandong, China, which consisted of a total of 488 male cases (159 non-cardia GA, 175 GCA, and 154 ESCC) and 160 healthy male controls matched by age. A total of approximate 160 pairs of each cancer cases and controls were matched successfully. Conditional logistic regression was used to calculated odds ratio (OR) and 95% confidence intervals (CIs), adjusting for potential confounders. The adjusted ORs (aORs) of non-cardia GA for subjects drinking before a meal at mealtime were 7.65 (95% CI: 2.83-20.69, *P*<0.001) compared with eating and drinking alcohol at the same time. Whereas, no significant association was found in GCA (aOR=2.32, 95% CI: 0.83-6.45) or ESCC (aOR=1.76, 95% CI: 0.71-4.39) risk. Furthermore, the heavy drinkers with alcohol consumption before meal at mealtime experienced higher non-cardia GA (aOR=13.60, 95% CI: 3.72-49.72, *P*<0.001) and ESCC risk (aOR=3.61, 95% CI: 1.02-12.99, *P*<0.05). Heavy drinking only showed a higher ESCC risk (aOR=1.79, 95% CI 1.07-3.02) than never drinking, with risk estimated significantly higher (*P* <0.05). This study is the first to assess the association of alcohol consumption before a meal with GA and ESCC risk. Alcohol consumption before a meal at mealtime is a clinically useful biomarker of susceptibility to non-cardia GA risk, but not to GCA and ESCC risk.

Keywords: Alcohol consumption, gastric cancer, gastric cardia adenocarcinoma, esophageal cancer, mealtime, case-control study

Introduction

Gastric cancer (GC) is a major subgroup of common malignancies, and the mortality rate of GC is the third highest of cancer-related deaths throughout the world [1]. GC consists of variable histological carcinomas and approximately 90% are adenocarcinomas. Diffuse-type gastric adenocarcinoma (GA) is one of the cancers with the most unfavorable prognosis [2-4]. Exposure to *Helicobacter pylori* infection and other environmental factors probably account for much of the variations seen in the incidence of GC [5, 6]. Esophageal cancer (EC) ranks the sixth cause of cancer-related death worldwide each year [7]. Esophageal squamous cell carcinoma (ESCC) is the major type in China. Tobacco smoking, alcohol drinking, and special dietary habits are recognized risk factors for ESCC [8]. Because of the high mortality and poor response to treatments of GA and EC, early intervention on behavioral and environmental risk factors seems to be imperative.

Alcohol consumption has been established as an important risk factor for cancers of the upper aero-digestive tract [9], including ESCC [10]. Early meta-analysis indicated a positive association between heavy alcohol drinking and non-cardia GC, rather than gastric cardia adenocarcinoma [11]. The different categories of alcoholic drinking are also related to the

increased risk of GC [12]. Additionally, drinkers of alcohol outside of meals suffered significantly higher death incidence from particular cancers [13], including GC and EC. However, there are some drinkers who consume alcohol at mealtime developing GC and EC, which suggests that other factors may play potential roles in the etiology of this disease.

Therefore, to investigate the impact of alcohol drinking before meal at mealtime, drinking outside mealtime, and lifetime alcohol consumption on the development of GC and ESCC, a hospital-based case-control study was conducted in China. Additionally, it was a goal to elucidate the association of several drinking habits with GC and ESCC.

Materials and methods

Subjects

Between February 2016 and February 2017, 488 newly diagnosed and pathologically proven male patients (154 with non-cardia GA, 175 GCA and 159 with ESCC) were recruited from Shandong Cancer Hospital in Shandong Province, China. A total of 160 male controls, with frequency matched by age greater than 10 years, were recruited on about 1:1 control ratio from inpatients and outpatients without a diagnosis of cancer. The subjects in control group included (1) healthy population; (2) upper respiratory tract diseases; (3) trauma; (4) skin and subcutaneous tissue disorders. The study subjects were restricted to males because of the low alcohol consumption rate in Chinese women [14]. The proportion of rejection in this study was less than 5%. All participants provided written informed consent.

Data collection

Face to face interviews were conducted by well-trained interviewers with the structured questionnaire, regarding alcohol consumption before meal at mealtime, alcohol consumption outside mealtime, body mass index (BMI), drinking habits, smoking habits, dietary habits, and upper digestive disease. Participants were instructed to report their habits before they were diagnosed with the disease. Alcoholic drinkers were defined as those who reported drinking white spirits, beer or wine more than once a week for at least half a year [15]. A person who had smoked more than 10 cigarettes a week for at least half a year in a lifetime was defined as cigarette smoker [15]. Lifetime alcohol consumption (g-year) was calculated by multiplying the amount of alcohol consumed per day (the concentration (g/ml) of alcohol multiplied by the beverage volume (ml)) by drinking years. The categories of moderate and heavy drinkers or smokers were classified by the median cut-off point. The median cut-off point for lifetime alcohol consumption among controls in the study was 1200 g-year. Lifetime smoking (pack-year) was calculated by multiplying the number of packs/day by smoking years. The median cut-off point for cigarette smoking among the controls was 14 pack-year. When drinking alcohol at mealtime, the participants reported that they drank alcohol before eating something in most cases, they were defined as alcohol consumption before meal at mealtime. When participants reported that drink alcohol outside meal in most cases, they were defined as alcohol drinking outside mealtime. The special dietary habits were defined as eating moldy food, fried food, scalding hot food, or pickled vegetables on a daily basis.

Data analysis

Categorical variables and numerical variables in cases and controls were compared by Chi-square test and Student's t-test statistic, respectively. Conditional multiple logistic regression analysis was performed to calculate odds ratio (OR) and 95% confidence interval (95% CI). OR and 95% CI were used as measures of association for the risk of GA and ESCC, matched for age (<50, 50-59, 60-69 and ≥70 years). The adjusted ORs were calculated in a multivariate model, includin drinking alcohol before meal at mealtime, drinking outside mealtime, BMI, drinking habits, smoking habits, dietary habits, and upper digestive disease before diagnosis. Statistical assessment of variables interaction was based on a multiple model including an interaction term as well as variables and confounding factors. All p values were two-sided and a p value <0.05 was considered significant. The data were analyzed using the STATA statistical package, version 12 (STATA Corporation, College Station, TX, USA).

Results

Characteristics of the study subjects

The general characteristics of 488 cases and 160 controls are shown in **Table 1**. The study

Table 1. Selected characteristics of non-cardia GA, GCA and ESCC cases and controls

Variable	Non-cardia GA (n=154)	GCA (n=175)	ESCC (n=159)	Controls (n=160)	*P*-Value (GA vs. Cs)	*P*-Value (GCA vs. Cs)	*P*-Value (ESCC vs. Cs)
Age (years)	63.4 ± 8.3	66.8 ± 9.0	62.2 ± 10.0	61.0 ± 7.8			
Education (years)	9.4 ± 3.0	9.4 ± 4.1	9.1 ± 3.0	9.5 ± 2.9	0.412	0.062	0.104
BMI before disease (kg/m^2)	24.3 ± 2.4	24.1 ± 2.6	24.6 ± 3.2	25.2 ± 2.9	<0.05	<0.05	0.07
Drinking habit	88 (57.1%)	105 (60.0%)	111 (69.8%)	75 (46.9%)	0.069	<0.05	<0.001
Alcohol consumption (g-year)	863.0 ± 1135.3	872.0 ± 1039.5	860.1 ± 934.7	498.4 ± 754.3	<0.001	<0.001	<0.001
Drink before meal at mealtime	24 (15.1%)	44 (25.1%)	19 (12.4%)	10 (6.2%)	<0.05	<0.05	0.077
Liquor drinking	67 (76.1%)	80 (45.7%)	84 (75.7%)	60 (80.0%)	0.278	0.128	<0.05
Smoking habits	103 (66.9%)	99 (56.6%)	121 (76.1%)	95 (59.4%)	0.168	0.604	<0.001
Cigarette smoking (pack-year)	24.2 ± 25.3	16.7 ± 20.7	23.8 ± 20.2	24.5 ± 26.0	0.07	<0.001	<0.001
Special dietary habits	79 (51.3%)	98 (56.0%)	99 (62.3%)	45 (28.1%)	<0.001	<0.001	<0.001
Upper digestive disease	57 (37.0%)	52 (29.7%)	54 (34.0%)	43 (26.9%)	0.054	0.565	0.169

GA gastric adenocarcinoma, GCA gastric cardia adenocarcinoma, ESCC esophageal squamous cell carcinoma, BMI body mass index. Values are mean ± standard deviation or frequency (%).

Table 2. Odds ratio of Non-cardia GA according to alcohol consumption, drink habits and other risk factors

Subjects	Non-cardia GA	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Alcohol consumption (g-year)	n=154	n=160		
Never drinker	66 (42.9%)	85 (53.1%)	1.00	1.00
Moderate drinker (<1200)	12 (7.8%)	30 (18.8%)	0.52 (0.25-1.08)	0.22 (0.52-1.02)
Heavy drinker (≥1200)	76 (49.3%)	45 (28.1%)	2.16 (1.33-3.55)	1.61 (0.9-3.29)
Alcohol drinking habit 1	n=88	n=75		
Drink at mealtime	61 (69.3%)	67 (89.3%)	1.00	1.00
Drink outside mealtime	27 (30.7%)	8 (10.7%)	3.71 (1.57-8.78)	4.96 (1.82-13.51)
Alcohol drinking habit 2	n=88	n=75		
Drink and eat at the same time	58 (65.9%)	63 (84.0%)	1.00	1.00
Drink before meal at mealtime	30 (34.1%)	12 (16.0%)	2.72 (1.27-5.80)	7.65 (2.83-20.69)
Type of alcoholic beverage	n=88	n=75		
Liquor	67 (76.1%)	60 (80.0%)	1.00	1.00
Other alcoholic drinks	21 (23.9%)	15 (20.0%)	1.25 (0.59-2.65)	1.57 (0.61-4.06)
Cigarette smoking (pack-year)	n=154	n=160		
Never smoker	51 (33.1%)	65 (40.6%)	1.00	1.00
Moderate smoker (<14)	16 (10.4%)	15 (9.4%)	1.36 (0.61-3.01)	0.85 (0.37-1.97)
Heavy smoker (≥14)	87 (56.5%)	80 (50.0%)	1.39 (0.86-2.23)	0.81 (0.33-1.98)
Special dietary habits	n=154	n=160		
No	75 (48.7%)	117 (73.1%)	1.00	1.00
Yes	79 (51.3%)	43 (26.9%)	2.87 (1.79-4.59)	5.98 (2.06-17.40)
Upper digestive disease	n=154	n=160		
No	97 (63.0%)	115 (71.9%)	1.00	1.00
Yes	57 (37.0%)	45 (28.1%)	1.50 (0.93-2.42)	0.93 (0.42-2.07)

GA gastric adenocarcinoma, OR odds ratio, CI confidence interval. [a]Adjusted for BMI, alcohol consumption, alcohol categories, smoking, special dietary habits and upper digestive diseases before diagnosis.

included 154, 175, and 159 male cases of non-cardia GA, GCA, and ESCC, respectively, and 160 male controls. Cases and controls were similar in the distribution of age, education and upper digestive disease (P<0.05). There were higher pre-diagnostic BMI (P<0.05), lifetime alcohol consumption (P<0.001) and special dietary habits rate (P<0.001) in non-cardia GA and GCA cases compared with those among controls. ESCC cases and controls sig-

Table 3. Odds ratio of GCA according to alcohol consumption, drinking habits, and other risk factors

Subjects	GCA	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Alcohol consumption (g-year)	n=175	n=160		
Never drinker	70 (40.0%)	85 (53.1%)	1.00	1.00
Moderate drinker (<1200)	35 (20.0%)	30 (18.8%)	1.42 (0.79-2.53)	0.23 (0.87-0.59)
Heavy drinker (≥1200)	70 (40.0%)	45 (28.1%)	1.89 (1.16-3.08)	0.57 (0.24-1.36)
Alcohol drinking habit 1	n=105	n=75		
Drink at mealtime	44 (41.9%)	67 (89.3%)	1.00	1.00
Drink outside mealtime	61 (58.1%)	8 (10.7%)	11.6 (5.07-26.61)	9.17 (3.17-26.56)
Alcohol drinking habit 2	n=105	n=75		
Drink and eat at the same time	41 (39.0%)	63 (84.0%)	1.00	1.00
Drink before meal at mealtime	64 (61.0%)	12 (16.0%)	8.20 (3.94-17.03)	2.32 (0.83-6.45)
Type of alcoholic beverage	n=105	n=75		
Liquor	80 (76.2%)	60 (80.0%)	1.00	1.00
Other alcoholic drinks	25 (23.8%)	15 (20.0%)	1.25 (0.61-2.57)	1.77 (0.74-4.25)
Cigarette smoking (pack-year)	n=175	n=160		
Never smoker	76 (43.4%)	65 (40.6%)	1.00	1.00
Moderate smoker (<14)	29 (16.6%)	15 (9.4%)	1.65 (0.82-3.35)	2.16 (0.83-5.62)
Heavy smoker (≥14)	70 (40.0%)	80 (50.0%)	0.75 (0.47-1.19)	0.41 (0.21-0.78)
Special dietary habits	n=175	n=160		
No	75 (42.9%)	117 (73.1%)	1.00	1.00
Yes	100 (57.1 %)	43 (26.9%)	3.63 (2.29-5.75)	2.73 (1.49-5.00)
Upper digestive disease	n=175	n=160		
No	125 (71.4%)	115 (71.9%)	1.00	1.00
Yes	50 (28.6%)	45 (28.1%)	1.02 (0.64-1.65)	0.84 (0.42-1.67)

GCA gastric cardia adenocarcinoma, OR odds ratio, CI confidence interval. [a]Adjusted for BMI, alcohol consumption, alcohol categories, smoking, special dietary habits and upper digestive diseases before diagnosis.

nificantly differed in lifetime alcohol consumption, lifetime cigarette smoking, and special dietary habits rate (all $P<0.001$). Rates of drinking alcohol before meal at mealtime among non-cardia GA, GCA, and ESCC were 15.1%, 25.1%, and 12.4%, respectively, and both non-cardia GA and GCA patients significantly higher than controls (all $P<0.05$).

Association of alcohol consumption before meal with the GA, GCA, and ESCC

The crude odds ratios (ORs), adjusted ORs (aORs), and 95% confidence intervals (CIs) of non-cardia GA, GCA and ESCC according to lifetime alcohol consumption, alcohol drinking at meal time, alcohol consumption before meals and other risk factors are shown in **Tables 2**-**4**. When compared with never drinkers in a multiple-adjusted model, both moderate and heavy drinkers did not experience a significantly increased non-cardia GA and GCA risk. However, significantly higher ESCC risk was observed in heavy drinkers than non-drinkers (aOR=1.79; 95% CI: 1.07-3.02, P<0.05). The subjects reporting alcohol drinking outside of mealtime had a 4.96- (95% CI: 1.82-13.51), 9.17- (95% CI: 3.17-26.56) and 6.04- (95% CI: 1.98-18.41) fold adjusted risk to develop non-cardia GA, GCA, and ESCC (all P<0.001), respectively, compared with those reporting drink at mealtime. When compared with eating and drinking alcohol at the same time, only non-cardia GA risk was significantly associated with the habit of alcohol consumption before eating something at mealtime (aOR=7.65; 95% CI: 2.83-20.69, $P<0.001$). The subjects reporting alcohol consumption before eating something at mealtime did not have a significant risk of GCA and ESCC, the aORs were 2.32 (95% CI: 0.83-6.45) and 1.76 (95% CI: 0.71-4.39), comparing eating and drinking alcohol at the same time.

Associations of other factors with the GA, GCA, and ESCC

After adjustment for potential confounders, lifetime smoking was not significantly associated with higher risk of non-cardia GA, GCA, and ES-

Table 4. Odds ratio of ESCC according to alcohol consumption, drinking habits, and other risk factors

Subjects	ESCC	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Alcohol consumption (g-year)	n=159	n=160		
Never drinker	48 (30.2%)	85 (53.1%)	1.00	1.00
Moderate drinker (<1200)	37 (23.3%)	30 (18.8%)	2.18 (1.20-3.97)	1.21 (0.24-6.15)
Heavy drinker (≥1200)	74 (46.5%)	45 (28.1%)	2.91 (1.75-4.86)	1.79 (1.07-3.02)
Alcohol drinking habit 1	n=111	n=75		
Drink at mealtime	81 (73.0%)	67 (89.3%)	1.00	1.00
Drink outside mealtime	30 (27.0%)	8 (10.7%)	3.10 (1.33-7.22)	6.04 (1.98-18.41)
Alcohol drinking habit 2	n=111	n=75		
Drink and eat at the same time	85 (76.6%)	63 (84.0%)	1.00	1.00
Drink before meal at mealtime	26 (23.4%)	12 (16.0%)	1.61 (0.75-3.43)	1.76 (0.71-4.39)
Type of alcoholic beverage	n=111	n=75		
Liquor	84 (75.7%)	60 (80.0%)	1.00	1.00
Other alcoholic drinks	27 (24.3%)	15 (20.0%)	1.28 (0.62-2.64)	1.87 (0.77-4.56)
Cigarette smoking (pack-year)	n=159	n=160		
Never smoker	38 (23.9%)	65 (40.6%)	1.00	1.00
Moderate smoker (<14)	32 (20.1%)	15 (9.4%)	3.65 (1.75-7.59)	2.44 (0.36-16.46)
Heavy smoker (≥14)	89 (56.0%)	80 (50.0%)	1.90 (1.15-3.14)	0.78 (0.18-3.42)
Special dietary habits	n=159	n=160		
No	60 (37.7%)	117 (73.1%)	1.00	1.00
Yes	99 (62.3%)	43 (26.9%)	4.49 (2.79-7.21)	4.99 (2.40-10.39)
Upper digestive disease	n=159	n=160		
No	105 (66.0%)	115 (71.9%)	1.00	1.00
Yes	54 (34.0%)	45 (28.1%)	1.31 (0.82-2.12)	0.61 (0.28-1.31)

ESCC esophageal squamous cell carcinoma, OR odds ratio, CI confidence interval. [a]Adjusted for BMI, alcohol consumption, alcohol categories, smoking, special dietary habits and upper digestive diseases before diagnosis.

CC, compared with non-smoking. Subjects with a special dietary habit (daily eating of scalding hot food, fried food, moldy food, or pickled vegetable, etc.) experienced a 5.98-fold (95% CI: 2.06-17.40, $P<0.001$), 2.73-fold (95% CI: 1.49-5.00, $P<0.05$), and 4.99-fold (95% CI: 2.40-10.39, $P<0.001$) risk to develop non-cardia GA, GCA, and ESCC, respectively. Upper digestive disease before cancer diagnosed, including gastroesophageal reflux disease, gastric ulcer, gastritis, etc., did not influence the risk of non-cardia GA, GCA, and ESCC in this study.

Combination of alcohol consumption and drinking before meal at mealtime

After matching for age and adjusted for other confounding factors, the combined effect of drinking habit and alcohol consumption was estimated on non-cardia GA, GCA, and ESCC risk (**Table 5** and **Figure 1**). Moderate drinkers were used who eat and drink alcohol at the same time as the reference category. Both heavy drinkers with (aOR=12.39; 95% CI: 2.71-56.75) and without (aOR=13.60; 95% CI: 3.72-49.72) the habit of alcohol consumption before meal at mealtime experienced a high adjusted risk (all $P<0.001$) to develop non-cardia GA. While only heavy drinkers who drink alcohol before a meal at mealtime experienced significantly higher ESCC risk (aOR=3.61; 95% CI: 1.02-12.99, $P<0.05$), compared with moderate drinkers who eat and drink at the same time. Additionally, the combination of lifetime alcohol consumption and drinking before meal at mealtime did not increase the risk of GCA.

Discussion

In this hospital-based case-control study, alcohol consumption before a meal at mealtime was a significant risk factor for non-cardia GA, but not for GCA and ESCC. We further found that, when combined with heavy alcohol drinking, alcohol consumption before a meal at mealtime significantly increases the non-cardia GA and ESCC risk. Additionally, alcohol consumption outside mealtime and special dietary habits showed a significantly higher non-cardia GA, GCA, or ESCC risk.

Table 5. Impact of the combination of alcohol consumption and drinking habit on cancer

Subjects	Cases	Controls	Adjusted OR (95% CI)[a]	*P*-Value
Non-cardia GA	n=88	n=75		
Moderate drinker and A[b]	3 (3.4%)	28 (37.3%)	1.00	
Moderate drinker and B	9 (10.2%)	7 (9.3%)	1.50 (0.10-23.07)	0.77
Heavy drinker and A	55 (62.5%)	35 (46.7%)	12.39 (2.71-56.75)	<0.001
Heavy drinker and B	21 (23.9%)	5 (7.7%)	13.60 (3.72-49.72)	<0.001
GCA	n=105	n=75		
Moderate drinker and A	29 (27.6%)	28 (37.3%)	1.00	
Moderate drinker and B	40 (38.1%)	7 (9.3%)	1.82 (0.42-7.97)	0.425
Heavy drinker and A	13 (12.4%)	35 (46.7%)	0.38 (0.13-1.14)	0.084
Heavy drinker and B	23 (21.9%)	5 (7.7%)	0.97 (0.26-3.69)	0.963
ESCC	n=111	n=75		
Moderate drinker and A	27 (24.3%)	28 (37.3%)	1.00	
Moderate drinker and B	9 (8.1%)	7 (9.3%)	0.55 (0.13-2.25)	0.40
Heavy drinker and A	58 (52.3%)	35 (46.7%)	2.40 (0.97-5.88)	0.057
Heavy drinker and B	17 (15.3%)	5 (6.7%)	3.61 (1.02-12.99)	<0.05

GA gastric adenocarcinoma, GCA gastric cardia adenocarcinoma, ESCC esophageal squamous cell carcinoma, OR odds ratio, CI confidence interval. [a]Adjusted for BMI, alcohol categories, smoking, special dietary habits and upper digestive diseases before diagnosis. [b]A=eat and drink alcohol at the same time, B=drink alcohol before meal at mealtime.

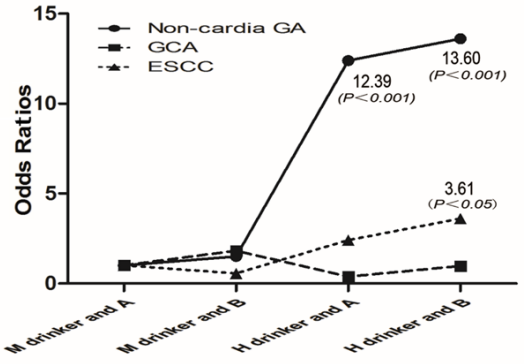

Figure 1. Impact of the combination of drinking habits and alcohol consumption on cancer. M drinker=moderate drinker, H drinker=heavy drinker, A=eat and drink alcohol at the same time, B=drink alcohol before meal at mealtime.

In several meta-analyses, there is an absence of association between lifetime alcohol drinking and risk of gastric cardia (relative risk (RR)=0.87; 95% CI: 0.74-1.01) or esophageal adenocarcinoma (RR=0.89; 95% CI: 0.76-1.03), which is partly consistent with our results [11, 16]. Our study revealed that heavy alcohol consumption (≥1200 g-year) significantly increases the ESCC risk, which is biologically plausible but without definite evidence. Drinking on an empty stomach maybe an important risk factor for GC and ESCC risk and mortality. Drinking outside mealtime experienced an increased stomach cancer risk and higher death incidence from cancers [13, 17]. Those who usually drink vodka before breakfast have a significantly elevated GC risk (RR=2.98, 95% CI 1.60-5.53) which was also present in all the subgroups investigated in Poland [18]. This study also identified the positive effect of drinking outside mealtime on the risk of GC and ESCC (all *P*<0.001).

However, some drinkers who consume alcohol at mealtime also suffer from GC and ESCC. Alcohol consumption before a meal at mealtime in some GC and ESCC patients was observed by our team, and this habit on alcohol related cancer risk has not been previously studied in non-cardia GA, GCA, and ESCC. After adjustment of covariates and analysis of the data, drinkers who consume alcohol before a meal at mealtime experienced a significantly increased non-cardia GA risk, while those reporting eating and drinking alcohol at the same time did not. This result may indicate a new alcohol-related risk factor for non-cardia GA patients who drink at mealtime.

Although alcohol consumption before meal at mealtime is on an empty stomach, this habit is different form drinking outside mealtime. Subsequent food taking will influence the process of alcohol absorption by an empty stomach. Additionally, the habit of drinking outside meal-

time always combined with heavier alcohol consumption, which also related to a higher rate of gastroesophageal reflux disease. Our result did not find higher GCA and ESCC risk in drinkers who consume alcohol before meal at mealtime, but in drinkers outside mealtime. This result also certified the potential difference between alcohol consumption before a meal at mealtime and drink outside mealtime or on an empty stomach.

The effect of alcohol consumption before a meal at mealtime on particular cancer risk may reflects the metabolic characteristics and carcinogenic mechanism of alcohol. After drinking, ethanol has a direct impact on the digestive system due to its contact with mucosal lining and interference with digestive functions [19]. Ethanol is first metabolized into acetaldehyde, primarily by alcohol dehydrogenase (ADH). Acetaldehyde is considered to play a causal role in alcohol-associated cancers development, because of its potential oncogenicity observed. Acetaldehyde is subsequently metabolized by aldehyde dehydrogenase 2 (ALDH2) into acetate in the body [20]. Several recent studies have suggested that ALDH2-deficient individuals may suffer from higher risk of non-cardia GA development [21, 22]. Alcohol consumption before meal at mealtime means drinking on an empty stomach before taking food, more ethanol will contact with and stimulate the mucosal lining. Additionally, before mixing with food, more ethanol may be absorbed by digestive tract fast and direct, compared with drinking and eating something at the same time. The enzyme systems of ADH and ALDH suffer from overloading, which may result in the accumulation of acetaldehyde in human body. Excess acetaldehyde plays a crucial role in the development of non-cardia GA. In this study, compared with moderate drinker who eat and drink alcohol at the same time, significantly higher ESCC risk was only found in heavy drinker drinking before meal at mealtime. The esophagus may be affected slightly by the direct stimulation and absorption of ethanol, comparing with stomach. Overall, the potential mechanisms suggested explaining these findings remain to be clarified.

Among the 7 million cancer-related deaths worldwide in 2001, there have been an estimated 2.43 million deaths attributable to nine main behavioral and environmental risk factors [23]. Identification lifestyle and environmental risk factors and primary prevention through corresponding interventions may greatly reduce the burden of cancers. This study demonstrates a new possible behavioral risk factor of non-cardia GA: alcohol consumption before meal at mealtime, which can be corrected by appropriate intervention. For alcohol drinkers, especially for heavy drinkers, eating and drinking alcohol at the same time may help to prevent non-cardia GA. However, to further confirm alcohol consumption before meal at mealtime as a new behavioral risk factor for non-cardia GA, large-scale, prospective studies are needed.

The current study also has several limitations. First, the retrospective design of this study limited the accuracy of the collected information, which was based on recalls of the subjects. Second, the relatively small number of cancer patients and controls may render some estimates not reliable, but the major results were highly significant and consistent throughout the analysis. Third, all subjects were recruited from only one hospital, selection bias should be concerned. However, participation rates were high and all eligible subjects were based on strict criteria, which may reduce the possibility of selection bias. Therefore, large-scale prospective studies are required to confirm these drinking habits as risk factors of non-cardia GA, GCA, and ESCC.

In conclusion, this hospital-based case-control study is the first to demonstrate the significant association of alcohol consumption before a meal at mealtime with non-cardia GA risk, especially combined with heavy alcohol drinking. Additionally, alcohol consumption before a meal at mealtime did not experience higher GCA and ESCC risk. Our study suggests that alcohol consumption before a meal at mealtime may serve as a hazard biomarker of non-cardia GA, especially for heavy drinkers, which may help clinicians with their decisions in the future.

Disclosure of conflict of interest

None.

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References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87.

[2] Saito H, Takaya S, Fukumoto Y, Osaki T, Tatebe S and Ikeguchi M. Clinicopathologic characteristics and prognosis of gastric cancer in young patients. Yonago Acta Medica 2012; 55: 57.

[3] Marqués-Lespier JM, González-Pons M and Cruz-Correa M. Current perspectives on gastric cancer. Gastroenterol Clin North Am 2016; 45: 413-28.

[4] Mita MT, Marchesi F, Cecchini S, Tartamella F, Ricco' M, Abongwa HK and Roncoroni L. Prognostic assessment of gastric cancer: retrospective analysis of two decades. Acta biomed 2016; 87: 205.

[5] Zhang RG, Duan GC, Fan QT and Chen SY. Role of helicobacter pylori infection in pathogenesis of gastric carcinoma. World J Gastrointestinal Pathophysiology 2011; 7: 97.

[6] Ohba R and Iijima K. Pathogenesis and risk factors for gastric cancer after helicobacter pylorieradication. World J Gastrointest Oncol 2016; 8: 663.

[7] Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International Journal of Cancer Journal International Du Cancer 2010; 127: 2893-2917.

[8] Schweigert M, Dubecz A and Stein HJ. Oesophageal cancer--an overview. Nat Rev Gastroenterol Hepatol 2013; 10: 230.

[9] Baan R, Straif K, Grosse Y, Secretan B, El GF, Bouvard V, Altieri A and Cogliano V. Carcinogenicity of alcoholic beverages. Lancet Oncology 2007; 8: 292.

[10] Brown LM and Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. Surg Oncol Clin N Am 2002; 11: 235.

[11] Tramacere I, Negri E, Pelucchi C, Bagnardi V, Rota M, Scotti L, Islami F, Corrao G, Vecchia CL and Boffetta P. A meta-analysis on alcohol drinking and gastric cancer risk. Ann Oncol 2012; 23: 28-36.

[12] Barstad B, Sørensen TI, Tjønneland A, Johansen D, Becker U, Andersen IB and Grønbaek M. Intake of wine, beer and spirits and risk of gastric cancer. Eur J Cancer Prev 2005; 14: 239.

[13] Trevisan M, Conti S, Schisterman E, Mennotti A and Farchi G. Drinking pattern and mortality: the italian risk factor and life expectancy pooling project. Ann Epidemiol 2001; 11: 312-9.

[14] Cochrane J, Chen H, Conigrave KM and Hao W. Alcohol use in China. Alcohol Alcohol 2003; 38: 537-42.

[15] Chen YJ, Chen C, Wu DC, Lee CH, Wu CI, Lee JM, Goan YG, Huang SP, Lin CC, Li TC, Chou YP, Wu MT. Interactive effects of lifetime alcohol consumption and alcohol and aldehyde dehydrogenase polymorphisms on esophageal cancer risks. Int J Cancer 2006; 119: 2827-2831.

[16] Tramacere I, Pelucchi C, Bagnardi V, Rota M, Scotti L, Islami F, Corrao G, Boffetta P, La Vecchia C and Negri E. A meta-analysis on alcohol drinking and esophageal and gastric cardia adenocarcinoma risk. Ann Oncol 2012; 23: 287-297.

[17] Hu JF, Zhang SF, Jia EM, Wang QQ, Liu SD, Liu YY, Wu YP and Cheng YT. Diet and cancer of the stomach: a case-control study in China. Int J Cancer 1988; 41: 331-335.

[18] Jedrychowski W, Boeing H, Wahrendorf J, Popiela T, Tobiasz-Adamczyk B and Kulig J. Vodka consumption, tobacco smoking and risk of gastric cancer in Poland. Int J Epidemiol 1993; 22: 606-613.

[19] Federico A, Cotticelli G, Festi D, Schiumerini R, Addolorato G, Ferrulli A, Merli M, Lucidi C, Milani S, Panella C, Domenico M, Vantini I, Benini L, Ubaldi E, Romano M, Loguercio C. The effects of alcohol on gastrointestinal tract, liver and pancreas: evidence-based suggestions for clinical management. Eur Rev Med Pharmacol Sci 2015; 19: 1922-40.

[20] Song Q, Hu P, Wang J, Jia Y, Zhang G, Lv L, Liu Y and Cheng Y. Association between gastric cardia adenocarcinoma risk and alcohol flushing response, but not alcohol consumption. Med Oncol 2014; 31: 1-6.

[21] Shin CM, Kim N, Cho SI, Kim JS, Jung HC and Song IS. Association between alcohol intake and risk for gastric cancer with regard to ALDH2 genotype in the Korean population. Int J Epidemiol 2011; 40: 1047-55.

[22] Matsuo K, Oze I, Hosono S, Ito H, Watanabe M, Ishioka K, Ito S, Tajika M, Yatabe Y and Niwa Y. The aldehyde dehydrogenase 2 (ALDH2) Glu504Lys polymorphism interacts with alcohol drinking in the risk of stomach cancer. Carcinogenesis 2013; 34: 1510-5.

[23] Danaei G, Vander HS, Lopez AD, Murray CJ and Ezzati M. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet 2005; 366: 1784-93.