RESEARCH ARTICLE

Association of Risk of Gastric Cancer and Consumption of Tobacco, Alcohol and Tea in the Chinese Population

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Abstract

This study aimed at summarizing epidemiological research findings on associations between tobacco, alcohol and tea consumption and risk of gastric cancer (GC) in the Chinese population. The review searched PubMed, Embase, China National Knowledge Infrastructure (CNKI) and China Biology Medicine (CBM) databases and reference lists of review papers for all studies published in English or Chinese languages. Information extracted, via two independent researchers, from retrieved articles included first author, year of publication, study design, sample size, source of controls and adjusted odds ratio (OR) or relative risk (RR) with the corresponding 95% confidence intervals (CIs) for each category. Statistical analyses used software STATA version 12.0. The systematic search found 89 articles containing 25,821 GC cases and 135,298 non-cases. The overall random effects in terms of pooled OR and 95%CI for tobacco, alcohol and tea consumption were 1.62 (95%CI: 1.50-1.74), 1.57 (95%CI: 1.41-1.76) and 0.67 (95%CI: 0.59-0.76) respectively; while the heterogeneity among included studies ranged from 80.1% to 87.5%. The majority of subgroup analyses revealed consistent results with the overall analyses. All three behavioral factors showed statistically significant dose-dependent effects on GC ($P<0.05$). The study revealed that tobacco smoking and alcohol drinking were associated with over 1/2 added risk of GC, while tea drinking conferred about 1/3 lower risk of GC in the Chinese population. However, these results should be interpreted with caution given the fact that most of the included studies were based on a retrospective design and heterogeneity among studies was relatively high.

Keywords: Tobacco - alcohol - tea - gastric cancer - Chinese population

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Introduction

Gastric cancer (GC) has become one of the most serious diseases threatening human health and life all over the world. GLOBOCAN 2008 reported that there were about 989 thousand new GC cases (including 640 thousand males and 349 thousand females) and 738 thousand GC deaths (including 464 thousand males and 273 thousand females) worldwide (Ferlay et al., 2010). The disease is also prevalent in China. It ranked the third most common cancer in Chinese population and estimated new cases of and deaths from GC were about 400 and 300 thousand respectively per year (Yang et al., 2005; Yang, 2006). Although it can be said that GC (like most other types of cancer) is a multi-factor-induced disease and is attributable to both genetic and environmental factors, our understanding of the causes of GC is generally limited (Guggenheim et al., 2013). H. pylor infection is perhaps the most widely recognized cause of GC (Uemura et al., 2001; Helicobacter and Cancer Collaborative Group, 2001; Wroblewski et al., 2010). Yet it accounts for only a small proportion of all GC cases. And there are evidences that subjects infected with helicobacter pylori do not necessarily progress to GC (Peek et al., 2002). This has generated great momentum researching into the contributions of other possible factors. As a result, articles documenting links between GC and behaviors have been mounting.

Worldwide, tremendous efforts have been invested on associations between tobacco, alcohol and tea consumption and GC and other types of cancers. For tobacco consumption, it is reported that as many as 60 components in cigarette smoke are considered to be carcinogens including polycyclic aromatic hydrocarbons, nitrosamines, aromatic amine, trace metals, as well as nicotine (Shin et al., 2005). Ladeiras-Lopes and colleagues' review of 42 cohort studies showed relative risk (RR) of GC were 1.62 in male smokers (95% confidence intervals (CI): 1.50-1.75) and 1.20 in female smokers (95%CI: 1.01-1.43) compared with those who had never smoked (Ladeiras-Lopes et al., 2008). With regard to alcohol drinking, some researchers believe that it is an important

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risk factor for numerous cancers worldwide, including cancer of the oral cavity and pharynx, esophagus, stomach, larynx, colorectum, central nervous system, pancreas, breast and prostate (Boffetta et al., 2006; de Menezes et al., 2013). Others have demonstrated that the first metabolite (acetaldehyde) of alcohol is a local carcinogen in humans (Salaspuro, 2003). And a recently published meta-analysis reported that, compared with nondrinkers, the pooled RR of GC was 1.07 (95%CI: 1.01-1.13) for alcohol drinkers and 1.20 (95%CI: 1.01-1.44) for heavy alcohol drinkers (≥4 drinks per day) (Tramacere et al., 2012). Turning to tea consumption, several animal experiments have suggested that green tea, which contains abundant polyphenols and catechins, specifically epigallocatechin-3-gallate (EGCG)5, might have a protective effect against cancers (Ahmad et al., 1999; Lambert, 2013; Yu et al., 2014). Gao et al's research showed that tea consumption was significantly associated with decreased risk of breast cancer in Chinese females, and the OR was 0.79 (95%CI: 0.65-0.95) (Gao et al., 2013). Zhou et al's systematic review revealed that green tea consumption was not associated with the risk of GC in both males and females with pooled odds ratio (OR) of 1.10 (95%CI: 0.76-1.60) and 0.99 (95%CI: 0.64-1.51) respectively (Zhou et al., 2008).

China has also witnessed numerous survey studies investigating the relationships between GC and tobacco, alcohol and tea consumption. Yet findings of these researches are seldom used by international researchers due to language and perhaps cultural barriers. This review aims at comprehensively summarizing the epidemiological evidences about the associations between risks of GC and tobacco smoking, alcohol drinking and tea intake derived from Chinese population in a hope to facilitate application, by international community, of research findings by Chinese researchers.

Materials and Methods

Data sources and search strategy

We utilized two approaches to locate as many relevant papers as possible. First, we searched the English literatures available by March 1th, 2014 via PubMed and Embase using the following search terms "(alcohol OR tea OR tobacco OR cigarette OR smoking) AND (gastric OR stomach) AND (cancer OR oncology OR tumor OR tumour OR malignan* OR carcinoma OR neoplasm*) AND (China OR Chinese)", where * represents wildcard characters. Meanwhile, we searched the Chinese literatures from China National Knowledge Infrastructure (CNKI) and China Biology Medicine (CBM) database via the same search terms. Second, we examined the bibliographies of relevant review papers for additional articles. This process was conducted iteratively until no new papers were identified.

Inclusion criteria

The inclusion criteria were paper: 1) written in English or Chinese; 2) belong to cohort or case-control (≥100 GC cases) study investigating the relationships between GC and behavioral factors that include tobacco smoking, alcohol or tea consumption; and 3) with ORs/ RRs and the corresponding 95%CIs or adequate original data for calculating them.

Data extraction

Extraction of descriptive data about the included studies utilized a data-extract form consisting first author, year of publication, study design, sample size, source of controls and adjusted OR/ RR with the corresponding 95%CI for each category (e.g. gender, subtype of exposure, duration of exposure, dose of exposure, anatomical subtype of GC) of tobacco smoking, alcohol and tea drinking. Two researchers performed the data extraction independently and discrepancies were solved by consensus.

Statistical analysis

Given that absolute risk of GC was low and that the RR in cohort studies approximated OR (Greenland, 1987), the study used OR to measure the associations of the three behavioral factors and GC risk. Pooled ORs with 95%CIs derived by pooling study-specific effect sizes using a random effects model. For dose-response analyses, studies included must provide the following data: number of GC case and non-case, median exposure (i.e. tobacco smoking, alcohol and tea drinking) dose and OR with 95%CI for each category of exposure.

If a study did not report the median exposure dose of a given category, we assigned a value for such dose by calculating the midpoint between the lowest and highest bound exposure doses. When the highest category was open-ended, we assumed the dose as 1.5 times the lowest bound of this category. Computation of trend from the correlated log OR estimates across categories of exposure employed a two-stage random-effects dose-response meta-analysis (Orsini et al., 2012) which took into account the between-study heterogeneity. More specifically, we established a restricted cubic spline model with four knots at the 5th, 35th, 65th, and 95th percentiles (Durrleman et al., 1989) of exposure using generalized least-square regression (GLST), taking into account the correlation between estimates for different expose categories to compute study-specific slopes (linear trends) (Orsini et al., 2006). *P* value for nonlinearity derived by testing the null hypothesis that the coefficient of the second spline equals zero (Greenland et al., 1992) and two-sided P value of less than 0.05 defined statistically sufficient to refuse the null hypothesis. All statistical analyses utilized software STATA version 12.0 (Stata Corporation, College Station, TX, USA).

Quality assessment

Assessment of methodological quality of the included studies used Newcastle-Ottawa Scale (NOS) (Wells et al., 2000). The scale provides a comprehensive score system with three broad aspects including selection of study groups, comparability between groups and ascertainment of exposure or outcome for both case-control and cohort studies. Total score came out from adding up the points awarded to each item. Only studies scored 7 or higher were considered as of high methodological quality.

Results

Studies included

Total English articles retrieved from PubMed and Embase accounted for 523, of which 484 articles were excluded on the basis of title and abstract and another 18 were excluded after more detailed evaluation of full-texts. Examination of reference lists identified additional 6 articles and 27 English papers finally met the inclusion criteria. Similarly, total Chinese papers retrieved from CNKI and CBM and papers excluded by title, abstract and full text screening were 1046 and 987 respectively. After adding 3 papers from reference tracking, a total of 62 Chinese articles met inclusion criteria. Putting papers published in both languages together, this review finally included a total of 89 articles.

Descriptive analyses

The 89 articles documented 5 cohort, 21 hospital-based case-control and 63 population-based case-control studies containing 25821 GC cases and 135298 non-cases. The sample sizes of case-control and cohort studies ranged from 202 to 2987 and 943 to 40508 respectively. The most frequently studied behaviors were tobacco smoking (n=74), followed by alcohol consumption (n=61) and tea drinking (n=33). The NOS scores of individual studies ranged from 6 to 9 with a mean score of 7.35.

Tobacco smoking and GC

The ORs of GC for tobacco smoking documented in included studies ranged from 0.82 (95%CI: 0.57-1.24) to 20.74 (95%CI: 5.82-73.89) with a pooled OR of 1.62 (95%CI: 1.50-1.74) and a heterogeneity among the included studies as high as I^2=87.5% (P<0.001). Subgroup analysis revealed pooled ORs of hospital-based case-control, population-based case-control and cohort designed studies as 1.85 (95%CI: 1.51-2.28; I^2 =88.5%, P<0.001), 1.61 (95%CI: 1.46-1.77; I^2 =87.8%, P<0.001) and 1.46 (95%CI: 1.13-1.89; I^2 =69.9%, P=0.01) respectively (Figure 1).

Significant associations were observable in various categories of subgroups including anatomical subtype of cancer (cardia: pooled OR=1.56, 95%CI: 1.07-2.27; non-cardia: pooled OR=1.22, 95%CI: 1.02-1.47), study quality (NOS score ≥7: pooled OR=1.65, 95%CI: 1.52-1.80; NOS score <7: pooled OR=1.62, 95%CI: 1.51-1.74), sample size (<300 GC cases: pooled OR=1.63, 95%CI: 1.50-1.78; ≥300 GC cases: pooled OR=1.55, 95%CI: 1.38-1.74), publication language (Chinese: pooled OR=1.64, 95%CI: 1.50-1.79; English: pooled OR=1.58, 95%CI: 1.39-1.80) and publication year (<2000: pooled OR=1.32, 95%CI: 1.17-1.49; ≥2000: pooled OR=1.79, 95%CI: 1.61-1.99) (Table 1). For gender subgroups, both male (pooled OR=1.30, 95%CI: 0.92-1.83) and female (pooled OR=1.82, 95%CI: 0.81-4.08) did not show significant association with risk of GC. For subgroups of tobacco smoking type and duration, positive association was only detectable in categories of cigarette smoking (pooled OR=1.61, 95%CI: 1.44-1.81) and smoking ≥20 years (pooled OR=1.53, 95%CI: 1.28-1.82).

Table 1. Summary Statistics for the Association between Tobacco Smoking and Gastric Cancer

Subgroups	No. of [a]datasets	[b]OR (95% CI)	Heterogeneity test		
			Q	[c]*P*	I^2 (%)
Overall	73	1.62 (1.50-1.74)	574.01	<0.001	87.5
Study design					
Cohort	5	1.46 (1.13-1.89)	13.3	0.01	69.9
Case-control	68	1.63 (1.51-1.76)	553.47	<0.001	87.9
Population-based	50	1.61 (1.46-1.77)	402.34	<0.001	87.8
Hospital-based	18	1.85 (1.51-2.28)	148.06	<0.001	88.5
Gender of subjects					
Male	4	1.30 (0.92-1.83)	12.45	0.006	75.9
Female	3	1.82 (0.81-4.08)	3.25	0.197	38.4
Anatomical subtype of cancer					
Cardia	6	1.56 (1.07-2.27)	32.57	<0.001	84.6
Non-cardia	5	1.22 (1.02-1.47)	0.78	0.942	0
Tobacco smoking type					
Cigarette	38	1.61 (1.44-1.81)	310.48	<0.001	88.1
Pipe	3	1.18 (0.83-1.66)	6.9	0.032	71
Cigarette and pipe	4	1.12 (0.93-1.34)	6.04	0.11	50.3
Duration of smoking (yrs)					
<20	5	1.09 (0.89-1.34)	5.22	0.266	23.3
≥20	22	1.53 (1.28-1.82)	113.5	<0.001	81.5
Study quality					
NOS score ≥7	67	1.65 (1.52-1.80)	516.27	<0.001	87.2
NOS score <7	6	1.62 (1.51-1.74)	33.65	<0.001	85.1
Sample size					
<300 cancer cases	47	1.63 (1.50-1.78)	338.36	<0.001	86.4
≥300 cancer cases	26	1.55 (1.38-1.74)	109.28	<0.001	77.1
Publication language					
Chinese	46	1.64 (1.50-1.79)	376.33	<0.001	88
English	27	1.58 (1.39-1.80)	142.23	<0.001	81.7
Publication year					
<2000	16	1.32 (1.17-1.49)	106.71	<0.001	85.9
≥2000	57	1.79 (1.61-1.99)	443.48	<0.001	87.4

Note: [a]single study may has more than one dataset; [b]ORs generated form random-effects analysis; [c]P value of Q test for heterogeneity test; NOS=Newcastle-Ottawa Scale; OR=odds ratio.

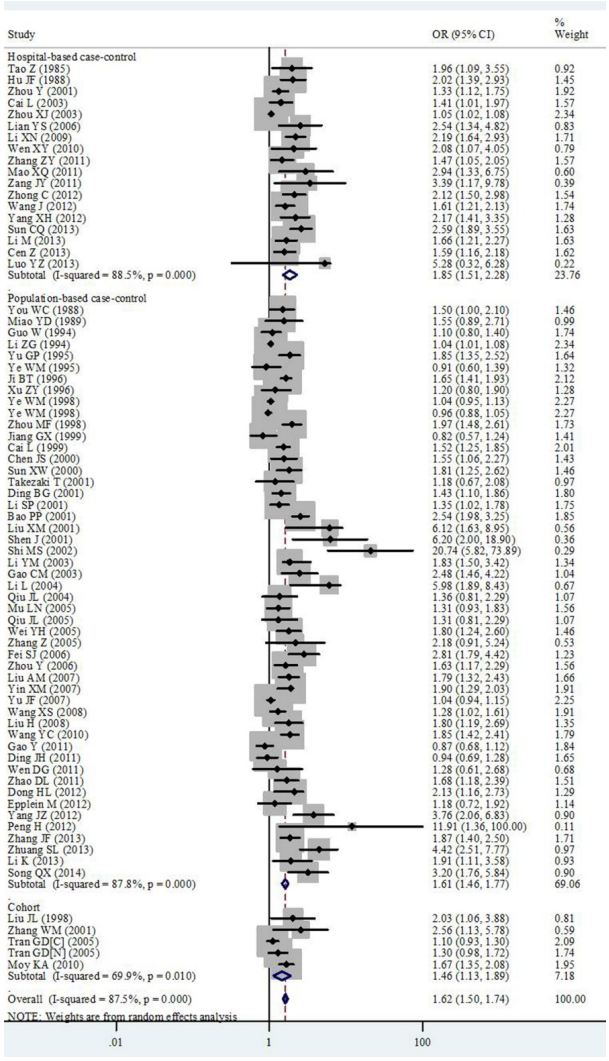

Figure 1. Adjusted Odds Ratios of Gastric Cancer for Smokers versus Nonsmokers. C=cardia; N=non-Cardia; OR=odds ratio

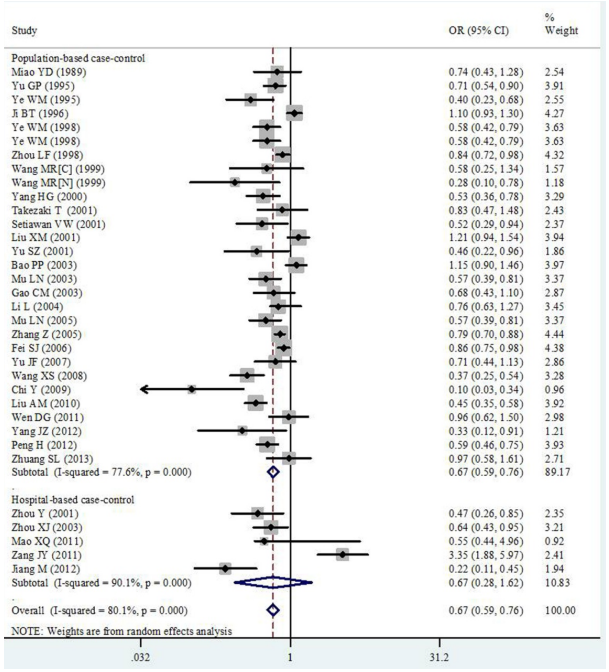

Figure 3. Adjusted odds Ratios of Gastric Cancer for Tea Drinkers Versus Non Drinkers. C=cardia; N=non-cardia; OR=odds ratio

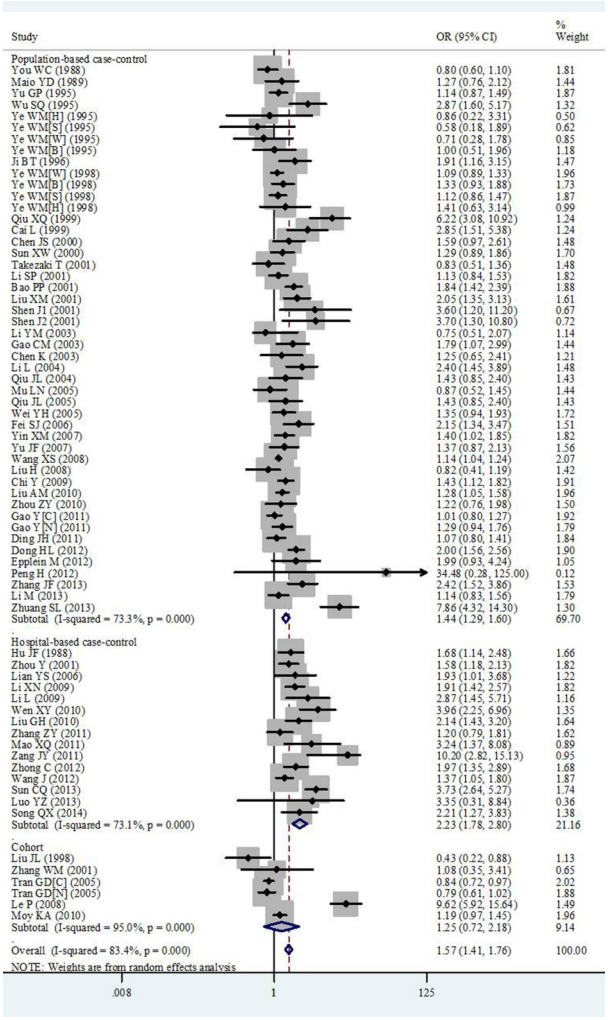

Figure 2. Adjusted Odds Ratios of Gastric Cancer for Alcohol Drinkers versus Non Drinkers. B=beer; C=cardia; H=hard distilled spirit; N=non-cardia; S=Soft distilled spirit; W=wine; OR=odds ratio

Alcohol drinking and GC

The ORs of GC due to alcohol drinking reported in the included studies ranged from 0.43 (95%CI: 0.22-0.88) to 34.48 (95%CI: 0.28-125.00) with pooled OR of 1.57 (95%CI: 1.41-1.76), 2.23 (95%CI: 1.78-2.80), 1.44 (95%CI: 1.29-1.60) and 1.25 (95%CI: 0.72-2.18) for overall, hospital-based case-control, population-based case-control and cohort studies respectively. Heterogeneity (I^2) of these analyses was 83.4%, 73.3%, 73.1% and 95.0% respectively (Figure 2).

Looking at subgroups, significant effect was observable for males (pooled OR=1.32, 95%CI: 1.03-1.69) and those who used to drink beer (pooled OR=1.24, 95%CI: 1.01-1.52) and hard distilled spirit (pooled OR=1.30, 95%CI: 1.08-1.55) and who had 20 or more years of drinking (pooled OR=1.32, 95%CI: 1.15-1.50). For subgroups of anatomical subtype of GC, both cardia (pooled OR=1.10, 95%CI: 0.79-1.52) and non-cardia (pooled OR=1.25, 95%CI: 0.74-2.10) did not show positive association of GC risk with alcohol consumption. When stratified by study quality, sample size, publication language and publication year, every category of these subgroups showed significantly increased risk of GC (P<0.05) (Table 2).

Table 2. Summary Statistics for the Association between Alcohol Drinking and Gastric Cancer

Subgroups	No. of [a]datasets	[b]OR (95% CI)	Heterogeneity test		
			Q	[c]*P*	I^2 (%)
Overall	69	1.57 (1.41-1.76)	408.45	<0.001	83.4
Study design					
Cohort	6	1.25 (0.72-2.18)	100.39	<0.001	95
Case-control	63	1.60 (1.44-1.77)	278.62	<0.001	77.7
Population-based	48	1.44 (1.29-1.60)	175.9	<0.001	73.3
Hospital-based	15	2.23 (1.78-2.80)	52.04	<0.001	73.1
Gender of subjects					
Male	7	1.32 (1.03-1.69)	14.45	0.025	58.5
Female	2	1.12 (0.32-3.87)	5.69	0.017	82.4
Anatomical subtype of cancer					
Cardia	4	1.10 (0.79-1.52)	11.77	0.008	74.5
Non-cardia	3	1.25 (0.74-2.10)	13.37	0.001	85
Alcohol consumption type					
Beer	4	1.24 (1.01-1.52)	4.55	0.208	34
Wine	4	1.09 (0.95-1.26)	1.31	0.726	0
Hard distilled spirit	8	1.30 (1.08-1.55)	12.08	0.098	42
Soft distilled spirit	2	1.04 (0.70-1.55)	1.14	0.285	12.6
Duration of drinking (yrs)					
<20	3	0.89 (0.71-1.11)	0.66	0.717	0
≥20	11	1.32 (1.15-1.50)	10.78	0.375	7.2
Study quality					
NOS score ≥7	63	1.55 (1.38-1.74)	392.87	<0.001	84.2
NOS score <7	6	1.74 (1.42-2.12)	6.49	0.262	22.9
Sample size					
<300 cancer cases	46	1.69 (1.44-1.98)	199.91	<0.001	77.5
≥300 cancer cases	23	1.42 (1.21-1.65)	179.5	<0.001	87.7
Publication language					
Chinese	41	1.70 (1.45-1.99)	231.82	<0.001	82.7
English	28	1.44 (1.23-1.68)	168.94	<0.001	84
Publication year					
<2000	17	1.33 (1.06-1.67)	67.55	<0.001	76.3
≥2000	52	1.66 (1.46-1.88)	338.27	<0.001	84.9

Note: [a]single study may has more than one dataset; [b]ORs generated form random-effects analysis; [c]*P* value of Q test for heterogeneity test; NOS=Newcastle-Ottawa Scale; OR=odds ratio.

Table 3. Summary statistics for the Association between Tea Drinking and Gastric Cancer

Subgroups	No. of [a]datasets	[b]OR (95% CI)	Heterogeneity test		
			Q	[c]*P*	I^2 (%)
Overall	34	0.67 (0.59-0.76)	165.57	<0.001	80.1
Study design					
Population-based	29	0.67 (0.59-0.76)	125.03	<0.001	77.6
Hospital-based	5	0.67 (0.28-1.62)	40.37	<0.001	90.1
Gender of subjects					
Male	3	0.85 (0.66-1.09)	3.31	0.191	39.6
Female	3	0.73 (0.55-0.98)	0.17	0.917	0
Anatomical subtype of cancer					
Cardia	3	0.63 (0.35-1.13)	3.2	0.201	37.6
Non-cardia	4	0.54 (0.31-0.95)	9.22	0.027	67.5
Tea consumption type					
Green tea	19	0.62 (0.52-0.74)	83.52	<0.001	78.4
Duration of drinking (yrs)					
<20	8	0.64 (0.53-0.77)	5.64	0.583	0
≥20	5	0.52 (0.42-0.64)	1.57	0.814	0
Study quality					
NOS score ≥7	26	0.76 (0.66-0.86)	113.52	<0.001	78
NOS score <7	8	0.40 (0.30-0.54)	14.22	0.047	50.8
Sample size					
<300 cancer cases	29	0.67 (0.59-0.77)	105.39	<0.001	73.4
≥300 cancer cases	5	0.66 (0.51-0.87)	31.55	<0.001	81
Publication language					
Chinese	26	0.65 (0.55-0.76)	135.27	<0.001	81.5
English	8	0.74 (0.61-0.91)	24.37	<0.001	71.3
Publication year					
<2000	9	0.68 (0.54-0.85)	33.96	<0.001	76.4
≥2000	25	0.67 (0.57-0.79)	129.99	<0.001	81.5

Note: [a]single study may has more than one dataset; [b]ORs generated form random-effects analysis; [c]*P* value of Q test for heterogeneity test; NOS=Newcastle-Ottawa Scale; OR=odds ratio.

Putting together, habitual tea drinking significantly decreased the risk of GC (overall pooled OR=0.67, 95%CI: 0.59-0.76); while dividing into subgroups by study design, the pooled effect was only statistically significant for the population-based case-control studies (OR=0.67, 95%CI: 0.59-0.76) but not for the 5 hospital-based case-control studies (OR=0.67, 95%CI: 0.28-1.26) (Figure 3). Tea consumption showed statistically significant associations with GC for all the subgroups categorized by duration of drinking, study quality, sample size, publication language and publication year (P<0.05) (Table 3). It demonstrated a 27% risk reduction for females (pooled OR=0.73, 95%CI: 0.55-0.98) but no significant effect for males (pooled OR=0.85, 95%CI: 0.66-1.09); a 46% risk reduction for non-cardia (pooled OR=0.54, 95%CI: 0.31-0.95) but not cardia GC. The result of green tea (pooled OR=0.62, 95%CI: 0.52-0.74) but other types of tea was consistent with that of the overall analysis.

Dose-response analyses

As shown in Figure 4, risk of GC increased stably as the dose of tobacco smoking rose from 0 to 30 cigarettes per day, while the risk decreased slightly when the dose was higher than 30 cigarettes a day. Similarly, the risk of GC increased sharply as the dose of alcohol drinking rose from 0 to 30 g/day; then the OR kept stable as the dose of alcohol drinking increased from 30 to 60 g/day; and when the dose became higher than 60 g/day, the OR began to increase again though at a much lower velocity. As for tea drinking, the OR remained stable at a relatively high level when the dose was less than 60 g/month; then the OR decreased consistently at a moderate speed as the dose increased. All the associations of GC with tobacco smoking, alcohol consumption, and tea drinking tested with statistical non-linearity.

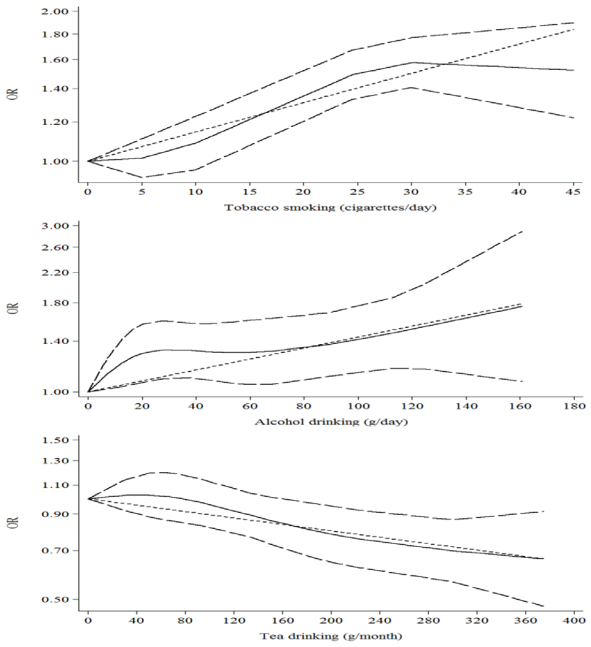

Figure 4. Dose-Response Relations between Tobacco Smoking, Alcohol and Tea Drinking and Risk of Gastric Cancer. The plots were generated from random-effects dose-response model; solid lines and the long dash lines represent the estimated odds ratio and its 95% confidence interval of the nonlinear relationship; short dash lines represent the linear relationship

Discussion

To our knowledge, this is the first review to summarize the associations between tobacco smoking, alcohol drinking, tea drinking and the risk of GC in Chinese population with literatures published in Chinese and English languages. Our findings indicated that tobacco smoking was associated with 1.62-fold higher risk of GC (95%CI: 1.50-1.74) compared with nonsmokers in Chinese population. This is consistent with a previous review based on international cohort studies, which reported a pooled RR of 1.53 (95%CI: 1.42-1.65) and a meta-analysis of international case-control studies with a pooled OR of 1.48 (95%CI: 1.28-1.71) (Ladeiras-Lopes R et al., 2008; La Torre et al., 2009).

Our review showed that alcohol drinking was associated with 1.57-fold risk of GC (95%CI: 1.41-1.76). This is a little lower than that of a previous reported pooled risk based on international case-control studies (pooled OR=1.77, 95%CI: 1.46-2.15) by Mahjub et al but apparently higher than the result documented in a recently published review which reported pooled RR of 1.07 (95%CI: 1.01-1.13) for alcohol drinkers and 1.20 (95%CI: 1.01-1.44) for heavy alcohol drinkers (Mahjub et al., 2007; Tramacere et al., 2012). These discrepancies may partly be attributed to differences in composition of studies reviewed by different authors. The majority (8 out of 11) of studies included in Mahjub and colleagues' review were hospital-based case-control studies; while Tramacere et al's review included as many as 16 cohort studies; and the bulk of our review consisted of population-based case-control studies. As our and other studies indicate (Table 1-3), ORs derived from hospital-based case-control studies tends to be higher than that from population-based case-control studies, which in turn tend to be higher than that from cohort studies.

The current review also revealed that tea drinking was associated with decreased risk of GC in Chinese population (overall: pooled OR=0.67, 95%CI: 0.59-0.76; green tea: pooled OR=0.62, 95%CI: 0.52-0.74). Previous review papers reported inconsistent results. Myung et al's review showed an adjusted pooled risk for green tea as 0.82 (95%CI: 0.70-0.96), 0.73 (95%CI: 0.64-0.83) and 1.04 (95%CI: 0.93-1.17) for overall, case-control and cohort studies respectively (Myung et al., 2009). Kang and colleagues' meta-analysis indicated a reduced risk of GC with intake of green tea (pooled OR=0.86, 95%CI: 0.74-1.00) (Kang et al., 2010). However, another meta-analysis concluded that green tea consumption was not associated with the risk of GC in both males (OR=1.10, 95%CI=0.76-1.60) and females (OR=0.99, 95%CI=0.64-1.51) (Zhou et al., 2008). Yu et al's dose-response meta-analysis of prospective studies also did not find any inverse association between tea consumption and risk of five major cancers including GC (Yu et al., 2014).

Given the high heterogeneity in the overall pooled

analyses (I^2=87.5%, 83.4% and 90.1% for tobacco smoking, alcohol drinking and tea drinking respectively, P<0.001), we performed comprehensive subgroup analyses to identify potential contributing factors to the differences. In the analysis of tobacco smoking on risk of GC, dividing subjects into subgroups by gender (female: OR=1.82, 95%CI: 0.81-4.08; I^2=38.4%), anatomical subtype of GC (non-cardia: OR=1.22, 95%CI: 1.02-1.47; I^2=0%) and duration of smoking (<20 years: OR=1.09, 95%CI: 0.89-1.34; I^2=23.3%) partly reduced the heterogeneity. With respect to the analysis of alcohol drinking on risk of GC, the heterogeneity all reduced to less than 50% by stratifying the datasets by alcohol type and duration of drinking. It seemed that duration of drinking (I^2=0% in both categories) may be the most important factor causing heterogeneity in the analysis of tea drinking on risk of GC, followed by gender of subjects (male: OR=0.85, 95%CI: 0.66-1.09; I^2=39.6% and female: OR=0.73, 95%CI: 0.55-0.98; I^2=0%) and anatomical subtype of GC (cardia: OR=0.63, 95%CI: 0.35-1.13; I^2=37.6).

Compared with previous reviews, our paper has several strengths: a) our analysis included almost all of the epidemiological studies carried out in Chinese population investigating the association between GC risk and tobacco, alcohol and tea consumption, involving as many as 25821 GC cases and 135298 non-cases; b) it comprised quite comprehensive subgroup analyses with 9 factors including study design, gender of subjects, anatomical subtype of GC, subtype of exposure, duration of exposure, study quality, sample size, publication language and publication year; and c) it included dose-response analyses for quantitatively assessing the non-linearity relationships between exposure dose and GC risk. Of course, our results should also be interpreted with caution for several limitations. First, the majority of the studies included were based on retrospective design which is prone to recall bias. Second, unpublished studies and papers published in languages other than English and Chinese, as well as articles did not provide ORs/RRs and the corresponding 95%CIs or adequate original data for calculating them were excluded in this review. Third, although major potential confounding factors had been adjusted in most studies, some unknown or residual factors could also result in exaggeration or underestimation of risk estimates. Last, the heterogeneity for the overall and part of the subgroup analysis were quite high (I^2>50%) in our review and thus damages the validity of results.

The study revealed that tobacco smoking and alcohol drinking were associated with over 1/2 added risk of GC while tea drinking, about 1/3 lower risk of GC in Chinese population. Given that these three behaviors are very common in China, they merit special attention for related researchers and policy-makers. Future studies in this regard should:1) pursue larger sample size and more rigorous (e.g. cohort or population-based) studies with ample attention be paid to methodology quality; 2) emphasize the importance of adopting a consistent definition of exposures (e.g. alcohol drinking) and using uniform grouping criteria for exposure dose, duration and frequency so as to reduce the grouping bias and to determine the dose-effect relationships between them; 3) focus on identifying other factors that may affect the correction between tobacco, alcohol, tea and GC including behavioral factors (e.g. coffee consumption, dietary factors) and medical history (e.g. chronic atrophic gastritis, peptic ulcer); and 4) conduct more comprehensive and sophisticated analyses on the risk of GC to build multi-variable risk prediction models (e.g. regression models, score systems).

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