Alcohol Consumption and Gastric Cancer Risk: A Meta-Analysis

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Background: We sought to determine by meta-analysis the relationship between drinking alcohol and the risk of gastric cancer.

Material/Methods: A systematic Medline search was performed to identify all published reports of drinking alcohol and the associated risk of gastric cancer. Initially we retrieved 2,494 studies, but after applying inclusion and exclusion criteria, only ten studies were found to be eligible for our meta-analysis.

Results: Our meta-analysis showed that alcohol consumption elevated the risk of gastric cancer with an odds ratio (OR) of 1.39 (95% CI 1.20–1.61). Additionally, subgroup analysis showed that only a nested case-control report from Sweden did not support this observation. Subgroup analysis of moderate drinking and heavy drinking also confirmed that drinking alcohol increased the risk of gastric cancer. Publication bias analysis (Begg's and Egger's tests) showed p values were more than 0.05, suggesting that the 10 articles included in our analysis did not have a publication bias.

Conclusions: The results from this meta-analysis support the hypothesis that alcohol consumption can increase the risk of gastric cancer; suggesting that effective moderation of alcohol drinking may reduce the risk of gastric cancer.

MeSH Keywords: Alcohol Drinking • Case-Control Studies • Meta-Analysis • Stomach Neoplasms

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Background

Gastric cancer, also known as stomach cancer, is one of the most frequent cancers in the world; almost two-thirds of gastric cancer cases and deaths occur in less developed regions such as China. The worldwide morbidity and mortality rate of gastric cancer has declined rapidly over the past few decades, likely due to the recognition of certain risk factors such as Helicobacter pylori and dietary and environmental risks factors [1]. However, the declining rate has been less dramatic in China compared with other countries. Although in China there is a lack of systematic national vital statistics, the results from retrospective sampling surveys of malignant tumors from 2004 to 2005 helped establish the mortality rate for gastric cancer in China, which ranked third in overall cancer mortality [2]. Interestingly, 42% of all gastric cancer cases worldwide are reported to occur in China [3].

It has been proposed that the development of gastric cancer is a multi-step process, although the exact influencing factors have not been elucidated. In the past, many researchers studying the cause of gastric cancer had contradictory hypotheses about the role of alcohol consumption in the development of gastric cancer. However, recent studies have confirmed that alcohol drinking can increase the risk of gastric cancer; and the main mechanism is likely related to the primary metabolites, acetaldehydes, that have a local toxic effect that increases the risk of gastric cancer [4–6].

However, it is still a matter of debate whether alcohol consumption elevates the risk of gastric cancer. We carried out this meta-analysis to explore the relationship between alcohol consumption and the development of gastric cancer. We retrieved studies published (both local and international) between 1995 and 2015, and then performed a comprehensive quantitative analysis to determine the relationship between alcohol consumption and gastric cancer. The aim of our study was to add to the understanding of and prevention of gastric cancer.

Material and Methods

Literature inclusion criteria and exclusion criteria

In this meta-analysis, we used the international PICOS format:

- **P:** The case group was patients with gastric cancer; gastric cancer was diagnosed by pathology.
- **I:** Alcohol drinking.
- **C:** The control group was those persons with non-gastric cancer or healthy persons.
- **O:** To explore whether drinking will increase the risk of stomach cancer or not.
- **S:** Case-control study

**Literature inclusion criteria:** 1) research method was a case-control study, 2) patients were diagnosed by histopathology, 3) study provided complete data, including loss data, 4) study was published between 1995 and 2015; 5) study controlled the main confounding factors, such as family history of cancer, race, height, smoking, and BMI.

**Literature exclusion criteria:** 1) study did not meet the inclusion criteria, 2) study had repetitive published data, duplicate data, or was a poor quality study, 3) raw data was not sufficient, and the case groups and the control groups total sample size was <80 cases, 4) same authors use the same case studies: only with the studies with the most samples and the latest published in the literature were used, and 5) animal experiments.

**Literature retrieval strategies**

We searched CBM, CNKI, Wanfang, VIP, PubMed, and Web of Science with MeSH terms “gastric cancer”, “alcohol drinking”, “case-control studies” following the Meta-analysis Of Observational Studies in Epidemiology guidelines to identify relevant studies in the published literature. The searched was performed for articles published between 1995 and 2015.

**Material selection and extraction**

The selection of the initial eligible studies and data extraction of eligible studies was performed independently by two authors (ZB and MK). A consultation with a third researcher was performed when a dispute occurred. All three researchers had expertise in clinical epidemiological methodology and related domain knowledge.

**Extracting information, Excel spreadsheet, and fetching information:** 1) General information extracted was: title, first author, publication date, and region. 2) The characteristics of the research were: research type, number of cases and control group, crowd source, and distribution (proportion) of men and women. 3) Data characteristics were: capacity for alcohol, unit measure of alcohol consumption, relative risk (RR) and 95% confidence interval (CI) or odds ratio (OR) and 95% CI. If comparative data was not provided within the literature, it was obtained by statistical software.

Study participants were divided into three groups: 1) no drinking, 2) moderate drinking, and 3) heavy drinking.

Moderate drinking for women was defined as one standard cup of alcohol per day or 15 grams of alcohol per day. Moderate drinking for men was defined as two standard cups of alcohol per day or 30 grams of alcohol per day. The definition of a standard cup for drinking was 118 mL of beer or 355 mL of
Heavy drinking was defined as a man or woman who drinks more than two standard cups a day (standard cup of alcohol content of about 15 grams of alcohol). Because units for alcohol consumption varied by study, we standardized the alcohol unit to grams per day, and converted all study data into grams per day for comparisons.

Statistical treatment

We used RevMan 5.0 and State 12.0 software to analyze the data, and to map forest and funnel plots. Data included: 1) alcohol consumption and gastric cancer risk, 2) non-alcohol consumption and gastric cancer risk, 3) the analysis of moderate alcohol consumption and gastric cancer, 4) the analysis of heavy alcohol consumption and gastric cancer, 5) heterogeneity test and subgroup analysis, 6) sensitivity analysis, 7) bias analysis, 8) the dose effect relationship of drinking and gastric cancer.

Results

In the literature

In total, 2,494 studies were retrieved; we excluded 2,484 studies by following the aforementioned exclusion and inclusion criteria. The eligible 10 case-control studies [8–17] including three studies from China, three studies from Sweden, one study from Brazil, one study from Korea, one study from Russia, and one study from the USA. A total of 19,302 persons were included in the 10 studies: case group (n=3,613) and control group (n=15,689). See Table 1. A flowchart depicting the study selection is shown in Figure 1.

Meta-analysis of drinking with gastric cancer

Alcohol drinking and gastric cancer risk: drinkers versus non-drinkers

Because the studies were case-control studies, we use an odds ratio (OR) value to measure the effect quantity. To ensure the accuracy of the results and because of the high heterogeneity of the studies, we used the random effects model (in statistics a random effect model, also known as variance component model, is a type of hierarchical linear model). We used the Mantel-Haenszel (M-H) method to calculate the combined effect quantity. The combined effect quantity for drinkers versus non-drinkers had an OR value of 1.39 with 95% CI (1.20, 1.61). This suggests that alcohol drinking can increase the risk for gastric cancer. This may be because alcohol can act as a solvent, assisting other harmful chemicals to enter the cells lining in the upper digestive tract more easily. Heterogeneity test showed chi-square=22.35 and $I^2=60\%$. The large heterogeneity suggests the data was original. In order to determine the difference between moderate drinking and the risk of gastric cancer and heavy drinking and the risk of gastric cancer, we divided the study participants into three groups: control group (no drinking), moderate drinking group, and heavy drinking group. The difference between the three groups is shown in Figure 2.

Non-drinking: gastric cancer cases versus controls

We performed M-H analysis to determine the difference between the non-drinking with the gastric cancer-cases group and the control group. The combined effect quantity OR value was 0.71 (95% CI=0.61–0.84), suggesting that non-drinking was a protective factor for gastric cancer. There was substantial
Figure 1. The results of literature retrieval.

| Study or subgroup | Drinkers | Non-drinkers | Odds ratio M-H, random, 95% CI |
|-------------------|----------|--------------|-------------------------------|
|                  | Events   | Total        | Weight | M-H, random, 95% CI |
| 1.2.1 Case control|          |              |        |                        |
| Bao 2001         | 112      | 458          | 199    | 1332                   | 11.8% | 1.84 [1.42, 2.39] |
| Bu-Tian 1996     | 342      | 655          | 402    | 885                    | 13.8% | 1.31 [1.07, 1.61] |
| Cheol 2011       | 232      | 370          | 213    | 445                    | 11.2% | 1.83 [1.38, 2.43] |
| Hamada 2002      | 28       | 86           | 68     | 202                    | 5.4%  | 0.95 [0.56, 1.63] |
| He 2012          | 143      | 226          | 69     | 144                    | 7.4%  | 1.87 [1.23, 2.86] |
| Lagergren 2000   | 228      | 916          | 34     | 166                    | 7.8%  | 1.29 [0.86, 1.93] |
| Lindblad 2005    | 312      | 6093         | 210    | 4429                   | 14.6% | 1.08 [0.91, 1.30] |
| Ye 1999          | 398      | 1264         | 106    | 371                    | 12.0% | 1.15 [0.89, 1.48] |
| Zaridze 2000     | 327      | 714          | 123    | 347                    | 11.7% | 1.54 [1.18, 2.01] |
| Zhang 1996       | 47       | 134          | 20     | 65                     | 4.2%  | 1.22 [0.64, 2.29] |
| Subtotal (95% CI)| 10916    | 8386         |        | 100.0%                 | 1.39  [1.20, 1.61] |
| Total events     | 2169     | 1444         |        |                        |      |
| Heterogeneity:   |          |              |        | Tau²=0.03; Chi²=22.35, df=9 (P=0.008); I²=60% |
| Test for overall effect: Z=4.31 (P<0.0001) |
| Total (95% CI)   | 10916    | 8386         |        | 100.0%                 | 1.39  [1.20, 1.61] |
| Total events     | 2169     | 1444         |        |                        |      |
| Heterogeneity:   |          |              |        | Tau²=0.03; Chi²=22.35, df=9 (P=0.008); I²=60% |
| Test for overall effect: Z=4.31 (P<0.0001) |
| Test for subgroup differences: Not applicable |

Figure 2. Alcohol drinking and gastric cancer risk: drinkers versus non-drinkers.
Figure 3. Non-drinking with the gastric cancer: cases versus controls.

| Study or subgroup | Cases | Controls | Weight | Odds ratio M-H, random, 95% CI | Odds ratio M-H, random, 95% CI |
|-------------------|-------|----------|--------|--------------------------------|--------------------------------|
| Bao 2001          | 199   | 311      | 11.7%  | 0.54 [0.42, 0.70]               |                                |
| Bu-Tian 1996      | 402   | 74       | 13.4%  | 0.76 [0.62, 0.93]               |                                |
| Cheol 2011        | 213   | 445      | 11.1%  | 0.50 [0.37, 0.66]               |                                |
| Hamada 2002       | 68    | 96       | 5.8%   | 1.05 [0.61, 1.80]               |                                |
| He 2012           | 69    | 212      | 7.7%   | 0.53 [0.35, 0.82]               |                                |
| Lagergren 2000    | 34    | 262      | 8.1%   | 0.78 [0.52, 1.17]               |                                |
| Lindblad 2005     | 210   | 522      | 14.1%  | 0.92 [0.77, 1.10]               |                                |
| Ye 1999           | 106   | 504      | 11.9%  | 0.87 [0.67, 1.12]               |                                |
| Zaridze 2000      | 123   | 450      | 11.6%  | 0.65 [0.50, 0.85]               |                                |
| Zhang 1996        | 20    | 67       | 4.6%   | 0.82 [0.44, 1.55]               |                                |
| Total (95% CI)    | 3613  | 15689    | 100.0% | 0.71 [0.61, 0.84]               |                                |

Total events: 1444, 6950

Heterogeneity: Tau² = 0.04; Chi² = 25.38, df = 9 (P = 0.003); I² = 65%
Test for overall effect: Z = 4.17 (P < 0.0001)

Figure 4. The analysis of moderate alcohol drinking with gastric cancer: drinker versus non-drinkers.

| Study or subgroup | Drinkers | Non-drinkers | Weight | Odds ratio M-H, random, 95% CI | Odds ratio M-H, random, 95% CI |
|-------------------|----------|--------------|--------|--------------------------------|--------------------------------|
| 1.4.1 Case control |          |              |        |                                |                                |
| Bao 2001          | 43       | 199          | 9.7%   | 1.45 [1.00, 2.09]               |                                |
| Bu-Tian 1996      | 147      | 402          | 14.4%  | 1.34 [0.88, 1.81]               |                                |
| Cheol 2011        | 70       | 213          | 7.7%   | 1.91 [1.24, 2.93]               |                                |
| Hamada 2002       | 17       | 68           | 4.0%   | 1.02 [0.53, 1.95]               |                                |
| He 2012           | 63       | 69           | 6.4%   | 1.29 [0.79, 2.11]               |                                |
| Lagergren 2000    | 152      | 34           | 8.1%   | 1.16 [0.76, 1.76]               |                                |
| Lindblad 2005     | 306      | 210          | 19.6%  | 1.10 [0.92, 1.31]               |                                |
| Ye 1999           | 276      | 106          | 14.1%  | 1.21 [0.92, 1.58]               |                                |
| Zaridze 2000      | 225      | 123          | 13.0%  | 1.85 [1.39, 2.47]               |                                |
| Zhang 1996        | 20       | 65           | 3.0%   | 1.25 [0.59, 2.67]               |                                |
| Subtotal (95% CI) | 8706     | 8386         | 100.0% | 1.30 [1.13, 1.50]               |                                |

Total events: 1319, 1444

Heterogeneity: Tau² = 0.02; Chi² = 14.50, df = 9 (P = 0.11); I² = 38%
Test for overall effect: Z = 3.72 (P = 0.0002)

Test for subgroup differences: Not applicable

Total (95% CI) 8706 8386 100.0% 1.30 [1.13, 1.50]

Total events: 1319, 1444

Heterogeneity: Tau² = 0.02; Chi² = 14.50, df = 9 (P = 0.11); I² = 38%
Test for overall effect: Z = 3.72 (P = 0.0002)
Test for subgroup differences: Not applicable

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heterogeneity between case-control studies ($\chi^2 = 25.38, P = 65\%$) (Figure 3).

The analysis of moderate alcohol drinking with gastric cancer: drinkers versus non-drinkers

Based on alcohol consumption, we determined the risk of gastric cancer by comparing heavy drinkers with non-drinkers and observe whether heavy drinking could increase the risk of gastric cancer. We used the M-H method of analysis. The combined effect quantity OR value was 1.58 with 95% CI (1.21, 2.05), indicating that the risk of gastric cancer in heavy drinkers was higher than non-drinkers. The data suggest that heavy drinking have an increased risk of gastric cancer. The heterogeneity test showed chi-square = 35.13 and $I^2 = 74\%$. Because the heterogeneity was high, we also performed a sensitive analysis (Figure 5).

The analysis of heavy alcohol drinking with gastric cancer: drinkers versus non-drinkers

To further look at the associated strength between heavy drinking and risk of gastric cancer, we performed a meta-analysis of the heavy drinkers in the 10 studies. Based on the level of alcohol consumption, we determined the risk of gastric cancer by comparing heavy drinkers with non-drinkers and observe whether heavy drinking could increase the risk of gastric cancer. We used the M-H method of analysis. The combined effect quantity OR value was 1.58 with 95% CI (1.21, 2.05), indicating that the risk of gastric cancer in heavy drinkers was higher than non-drinkers. The data suggest that heavy drinking have an increased risk of gastric cancer. The heterogeneity test showed chi-square = 35.13 and $I^2 = 74\%$. Because the heterogeneity was high, we also performed a sensitive analysis (Figure 5).

Heterogeneity test and subgroup analysis

We used RevMan software 5.0 to perform the heterogeneity inspection for study type, sample group, and region; we estimated whether the study populations had homogeneity. We applied hypothesis testing to examine whether the heterogeneity of multiple independent studies have statistically significant differences.

To further explain the heterogeneity, we performed subgroup analysis: the three study types were classified as: hospital-based...
Table 2. The subgroup analysis of meta-analysis between alcohol drinking with the risk of gastric cancer.

| Group | Number | OR     | 95% CI   | Heterogeneity test |
|-------|--------|--------|----------|--------------------|
| Study type |        |        |          |                    |
| HCC   | 4      | 1.66   | (1.40–1.97) | \(P=0.57\), \(I^2=0\)% |
| PCC   | 5      | 1.33   | (1.09–1.62) | \(P=0.07\), \(I^2=54\)% |
| NCC   | 1      | 1.08   | (0.91–1.30) |                    |
| Sample sex |      |        |          |                    |
| Men   | 1      | 1.31   | (1.07–1.61) |                    |
| Men + Women | 9    | 1.40   | (1.17–1.67) | \(P=0.004\), \(I^2=64\)% |
| Region |        |        |          |                    |
| China | 3      | 1.60   | (1.24–2.08) | \(P=0.08\), \(I^2=60\)% |
| Sweden | 3     | 1.12   | (0.98–1.29) | \(P=0.74\), \(I^2=0\)% |
| Others | 4      | 1.47   | (1.15–1.89) | \(P=0.1\), \(I^2=41\)% |

Table 3. Sensitive analysis.

| Literature rejection | Chi² | \(P\) | OR (95% CI)       |
|----------------------|------|-------|-------------------|
| Lindblad 2005       | 14.62| 45%   | 1.45 (1.26–1.68)  |
| Bao 2001            | 16.3 | 51%   | 1.33 (1.15–1.54)  |

case-control study, population-based case-control study, and nested case-control study. We divided the study participants into two groups based on the study population sex ratio: one group consisted of only men, and one group consisted of both men and women. We divided the case-control studies into three regional background groups: Chinese origin, Swedish origin, and other origin (see Table 2).

Subgroup analysis for the nested case-control studies and the Swedish studies showed no correlation between alcohol drinking and gastric cancer development. The other group analysis showed similar results. This may be because the alcohol categories and alcohol capacity were different in different countries. The researchers from Sweden found non-significant differences between the case group and the control group.

The heterogeneity test showed that the heterogeneity of the case-control studies in crowd source, groups with men and women, and different regions of China were 54%, 64%, 60%, and 41%, respectively (Table 2).

Sensitive analysis

Sensitivity analysis found two studies, Lindblad et al. 2005 and Bao et al. 2001, that had high heterogeneity. When the Lindblad study was excluded, the heterogeneity \(I^2\) value was 45%. When the Bao study was excluded, the heterogeneity \(I^2\) value was 51%. The high heterogeneity in the Lindblad study may have been due to differences in region or drinking features. The high heterogeneity in the Bao study may have been due to the nested case-control study type (Table 3).

Bias analysis

We used STATA software to analyze the publication bias for the 10 articles, Begg’s test shows that \(p\) value was higher than 0.05, indicating that there was no significant publication bias observed in the selected studies (the Begg’s funnel plot was symmetrical (Figure 6).

Dose-response relationship between alcohol consumption and gastric cancer risk

We used STATA software to analyze the dose-response relationship between alcohol consumption and gastric cancer risk. We found a significantly increased risk at any level of alcohol intake, with a minimum at 0 grams per day; the curve was <1 gram per day to 85 grams per day (Figure 7).
In order to explain the heterogeneity, we performed subgroup analysis and bias analysis. The subgroup analysis showed that only the nested case-control study and research from Sweden did not support alcohol drinking as a risk of gastric cancer. The remaining research found that alcohol consumption can increase the risk of gastric cancer. Begg’s test showed a p value >0.05, which indicated that there was no publication bias in the 10 studies. This dose effect relationship of drinking and gastric cancer risk showed significantly increased risk at any level of alcohol intake.

Conclusions

This meta-analysis includes 10 case control studies on alcohol consumption and gastric cancer risk. This met-analysis confirmed that alcohol consumption can increase the risk of gastric cancer even at lower levels of alcohol consumption. As this meta-analysis had one study type, it had high homogeneity. Hence, the meta-analysis was not affected by a variety of research study types. However, the meta-analysis results may support one-sidedness with exclusion of cohort studies and only the retention of case-control studies. Our results were different from Tramacere et al. [23,24]. This may be due to differences in the study populations, regions, alcohol usage, alcohol type, or research methods. Therefore, a more rigorous scientific study is needed to continue to explore the relationship between alcohol drinking and gastric cancer risk.

Compliance with ethical standards

Conflict of interest: All the authors declare that they have no conflict of interest.

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.
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