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*Original Article*

# A pooled analysis of alcohol intake and colorectal cancer

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**Abstract:** Object: In order to provide an updated quantification of the association between alcohol intake and colorectal cancer, we conducted a meta-analysis of published observational studies. Method: Two cohort and 22 case-control studies presenting results for at least three categories of alcohol intake were identified from a PubMed search of articles published before July 2014. Data were extracted independently by two reviewers. Random effects meta-analyses, subgroup analyses, and meta regression were performed for modeling the dose-response relation. Result: The pooled relative risk (RR) for any alcohol intake compared with non/occasional drinking was 1.13 [95% confidence interval (CI), 1.09-1.17]. The RRs were 1.07 (95% CI, 1.02-1.13), 1.23 (95% CI, 1.15-1.32) and 1.37 (95% CI, 1.26-1.49) for light (≤12.5 g/day), moderate (12.6 to 49.9 g/day) and heavy drinking (≥50 g/day), respectively. The risks were consistent in the subgroup analyses of sex and tumor site. Conclusion: This meta-analysis provides strong evidence for an association between alcohol intake and colorectal cancer risk.

**Keywords:** Alcohol intake, colorectal neoplasms, meta-analysis

## Introduction

Alcohol is widely consumed throughout the world and is thought to be related to more than 60 different medical conditions [1], and alcohol intake is a potentially modifiable behavior that may be related to risk for colorectal cancer [2]. The evidence that alcohol is a cause of bowel cancer is convincing in men and probable in women [3]. The National Institutes of Health [4], the National Cancer Institute [5], Cancer Research [6], the American Cancer Society [7], the Mayo Clinic [8], and the Colorectal Cancer Coalition [9], American Society of Clinical Oncology and the Memorial Sloan-Kettering Cancer Center list alcohol as a risk factor.

Moreover, epidemiologic studies suggest that increased alcohol is a risk factor for colorectal cancer. Previous reviews [10-13] and meta-analyses [14-16] of case-control and cohort studies suggested that high alcohol intake might be associated with an increased risk of colorectal cancer [17]. The epidemiological evidence has been complemented by recent molecular evidence on mechanisms that could explain the association [17]. However, several issues remained unresolved. First, the dose-response of alcohol intake with colorectal cancer risk has not yet been investigated in detail. Second, it is still uncertain whether the effect of alcohol varies across tumor site.

With the aim of investigating the risk of colorectal cancer at different levels of alcohol consumption, we conducted a meta-analysis of studies published before July 2014.

## Methods for meta-analysis

### *Search strategy*

A thorough search of the MEDLINE, EMBASE, and Cochrane Controlled Trials Register databases was performed using MESH terms “colorectal carcinoma”, “alcohol drinking”, “alcoholic beverages”, “colorectal neoplasms”. When necessary, manual searches of references from relevant articles were performed. Also, reference lists of the identified articles and pre-

vious literature reviews and meta-analyses were carefully examined for additional studies. The search was limited to studies published in English. Two researchers independently screened the list of references and excluded inappropriate papers. Disagreements were discussed with another reviewer and resolved by consensus.

*Inclusion criteria*

Two authors (Yue Wang and Helen Yang) independently evaluated the titles and abstracts of potentially eligible studies with the inclusion criteria as follows: (i) observational epidemiological studies (case-control, case-cohort, or cohort) on total alcohol intake and colorectal cancer incidence or mortality in general population, (ii) reporting the odds ratio (OR) or relative risk (RR) estimates with the corresponding 95% confidence intervals (CI) or sufficient information to calculate them for each alcohol exposure level, and (iii) reporting an association for at least three categories of alcohol consumption. When several reports were published on the same study, only the most recent and informative one was included.

*Data extraction*

Two reviewers (Hong Duan and Boshi Duan) independently assessed articles for inclusion, extracted data, and assessed quality. Quality assessment included assessment of randomization, allocation concealment, blinding, and description of withdrawals and dropouts and was used to give an overall rating of the risk of bias. The following information was sought form each paper: trial's name, first author, year of publication, journal, number of patients in both groups, sex, tumor site, geographic region, country and follow-up duration (**Tables 1** and **2**).

*Categories of alcohol consumption*

Different studies used different units to express alcohol intake. Therefore, alcohol consumption was converted into grams of ethanol per day using the following conversion factors: 1 drink =12.5 g; 1 ounce =28.35 g; and 1 ml=0.8 g. The dose associated with each RR estimate was computed as the midpoint of the corresponding exposure category. When the highest category was open ended, the midpoint was calculated as 1.2 times its lower bound [18]. Nondrinkers or occasional drinkers were the reference category. We defined light alcohol drinking consumption as ≤1 drink/day (≤12.5 g/day of ethanol), moderate as 2-3 drinks/day (12.6-49.9 g/day of ethanol), and heavy as consumption of ≥4 drinks/day (≥50 g/day of ethanol). When more than one study category fell in the range considered for light, moderate or heavy alcohol drinking, or when the same set of controls was used for CRA site (colon and rectum), we combined the corresponding risk estimates by using the method according to Hamling et al [19].

*Statistical analysis*

All statistical tests were two-sided, and all statistical analyses were carried out with SPSS 16.0 and Stata Statistical Software 13.0. A random effects model was used to estimate pooled RRs in order to take into account the heterogeneity of the risk estimates and to provide more conservative estimates compared with the fixed effects model [20]. Forest plots were done for any, light, moderate, and heavy versus non-consumption and occasional alcohol consumption. Statistical heterogeneity between studies was assessed with the chi-square statistic and quantified by $I^2$, a statistic that represents the percentage of total variation contributed by between-study variation [20, 21]. A significant heterogeneity was defined as a $P$ value <0.10. To investigate potential sources of between study heterogeneity, subgroup analyses and meta-regression models were conducted. Also, sensitivity analyses were carried out to assess whether the summary estimates are robust to inclusion of studies. Publication bias was assessed using the tests by Egger [22], Begg and Mazumdar [23], and the contour enhanced funnel plots [24].

A dose-response analysis was carried out using both linear and nonlinear random effects models on the natural logarithm of the RR using the method by van Houwelingen [25], which was modified by our group [26]. This method accounts for correlation between reported risk estimate within the same study, heterogeneity between the studies, and nonlinear dose-risk relation. Thirty-six second-order fractional polynomial random effects models and linear random effect models were tested. The best-fitting model, defined as the one with the lowest

**Table 1.** Characteristics of case-control studies

| First author | Country | Sex | Site | Year | Cases | Controls | Duration | Variables adjusted |
|---|---|---|---|---|---|---|---|---|
| Cope47 | United Kingdom | Male, Female | Colon, Rectum | 1991 | 66 | 83 | unknown | Age, sex |
| Riboli48 | France | Male, Female | Colon, Rectum | 1991 | 252 | 641 | 1979-1985 | Age, calories without alcohol, intake of fiber from vegetables and fruit |
| Honjo49 | Japan | Male | Colon | 1992 | 116 | 930 | 1989-1990 | Smoking, Self-Defense Forces Rank, BMI |
| Martinez50 | United States | Male, Female | Colon, Rectum | 1995 | 157 | 480 | 1991-1993 | Age, sex, race, dietary fiber, dietary vitamin C, smoking BMI, family history, physical activity, NSAIDs |
| Todoroki51 | Japan | Male | Colon | 1995 | 228 | 1484 | 1991-1992 | Pank, BMI, physical activity, hospital, survey season, smoking |
| Ulrich52 | United States | Male, Female | Colon, Rectum | 1999 | 527 | 645 | 1991-1994 | - |
| Morimoto53 | United States | Male, Female | Colon, Rectum | 2002 | 437 | 708 | 1991-1994 | Age, sex, BMI, HRT, smoking |
| Tiemersma54 | Netherlands | Male, Female | Colon, Rectum | 2003 | 433 | 436 | 1995-2000 | Sex, age, indication for endoscopy |
| Boyapati55 | United States | Male, Female | Colon, Rectum | 2004 | 177 | 228 | 1995-1997 | Age, sex, energy |
| Toyomura56 | Japan | Male | Colon, Rectum | 2004 | 754 | 1547 | 1995-2002 | Bank, hospital, body mass index, physical activity, smoking |
| Diergaarde57 | Netherlands | Male, Female | Colon, Rectum | 2005 | 278 | 414 | 1997-2001 | Age, gender, total energy intake |
| Stern58 | United States | Male, Female | Colon, Rectum | 2006 | 753 | 799 | 1991-1995 | Age at diagnosis, sex, race, clinic, and exam date, study phase status, smoking status |
| Tabata59 | Japan | Male | Colon, Rectum | 2006 | 446 | 914 | 1997-2001 | unknown |
| Hazra60 | United States | Female | Colon, Rectum | 2007 | 556 | 557 | 1989-1998 | unknown |
| Jung61 | United States | Male, Female | Colon, Rectum | 2008 | 530 | 645 | 1991-1994 | unknown |
| Lightfoot62 | United Kingdom | Male, Female | Colon, Rectum | 2008 | 317 | 296 | 1997-2000 | unknown |
| Shrubsole19 | United States | Male, Female | Colon, Rectum | 2008 | 639 | 1773 | 2003-2005 | Age, sex, site, year, recruitment type, BMI, height, indication for colonoscopy, educational attainment, race, family history, NSAIDs, physical activity, menopausal status, daily intakes of fruits and vegetables, dairy foods, meat, smoking |
| Yamaji63 | Japan | Male, Female | Colon, Rectum | 2009 | 782 | 738 | 2004-2005 | Smoking, drinking status, BMI, family history, NSAIDs |
| Yamamoto64 | Japan | Male, Female | Colon, Rectum | 2010 | 86 | 258 | 2004-2007 | unknown |
| Shin43 | Korea | Male, Female | Colon, Rectum | 2011 | 1242 | 3019 | 2007-2009 | Sex, age, waist circumference, family history, smoking |
| Corral65 | United States | Male, Female | Colon, Rectum | 2013 | 721 | 736 | 1991-1995 | unknown |
| Hamachi66 | Japan | Male | Colon, Rectum | 2013 | 455 | 1052 | 1997-2001 | unknown |

**Table 2.** Characteristics of cohort studies

| First author | Country | Sex | Sites | Year | Cases | Non cases | Followed | Adjusted variable |
|---|---|---|---|---|---|---|---|---|
| Giovannucci67 | United States | Male, Female | Colon | 1993 | 895 | 25 474 | Male (1986-1990)<br>Female (1980-1990) | Age, sex, BMI, parental history of colorectal cancer, body fat and dietary fiber intake, indications of endoscopy, history of endoscopy |
| Cho31 | United states | Female | Colon, Rectum | 2007 | 2408 | 39 246 | 1984-2002 | Age, smoking, BMI, physical activity, family history of colon cancer, history of endoscopic screening, year of endoscopy, NSAIDs, HRT, energy, folate, total fiber and calcium |

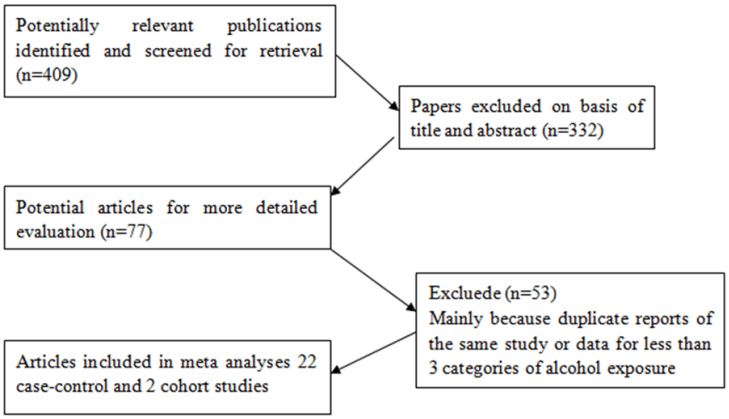


**Figure 1.** Flow diagram of assessment of studies identified in the systematic review.

Akaike's information criterion, a model fit statistic, was selected as the final dose-risk relation model.

## Results

*Study detail*

**Figure 1** shows the number of studies assessed and excluded through the stages of the meta-analysis. A total of 24 studies on colorectal cancer incidence and alcohol intake published between 1991 and 2013 were identified, among which 8 studies were from Asia (Japan and Korea), 5 from Europe (United Kingdom, France and Netherlands), and 11 from United States.

As a whole, **Figure 2** shows the study-specific and pooled RRs of colorectal cancer, along with 95% CIs, for any alcohol drinking versus none/occasional drinking. The overall pooled RR was 1.13 (95% CI, 1.09-1.17) and there was no significant between studies heterogeneity ($I^2$= 21.7%, p for heterogeneity =0.17). The corresponding estimates were 1.13 (95% CI, 1.09-1.17) for case–control studies ($I^2$=26.6%, p for heterogeneity =0.12) and 1.15 (95% CI, 0.98-1.31) for cohort studies ($I^2$=0.0%, p for heterogeneity =0.39). Data were available for light intake from 23 studies, for moderate intake from 20 studies and for heavy intake from 9 studies. The pooled RRs for light (≤1 drink/day), moderate (>1 to b3 drinks) and heavy drinking (≥3 drinks/day) were equal to 1.07 (95% CI, 1.02-1.13), 1.23 (95% CI, 1.15-1.32) and 1.37 (95% CI, 1.26-1.49) respectively (**Table 3**).

As for sex, **Figure 3** showed RRs estimated for CRA incidence in male (1.11, 95% CI 1.00-1.23) and female (1.03, 95% CI 0.95-1.10) and individually, in the comparison between all drinkers and non-/occasional drinkers ($I^2$=18.60%, P=0.27). And there was no significant difference in CRA risk between male and female among light ($I^2$=0.00%, P=0.711), moderate ($I^2$=30.90%, P=0.15) and heavy ($I^2$=0.00%, P=0.474) drinkers, compared with non-/occasional drinkers (**Table 3**).

As for geographical region, we proposed RRs for CRA risk stratified by Asia, Europe and US. The result is (1.19, 95% CI 1.11-1.27), (1.22, 95% CI 1.10-1.34) and (1.10, 95% CI 1.05-1.15) respectively. Moreover, the risk in European studies was higher than them in the US and Asia. And there was difference in the pooled analysis of all drinkers ($I^2$=21.70%, P=0.17), light drinkers ($I^2$=33.00%, P=0.06) and moderate drinkers ($I^2$=52.10%, P=0.00), compared with non-/occasional drinkers (**Figure 4**; **Table 3**).

As for tumor site, we evaluated for CRA risk in colon and rectum were 1.17 (95% CI 1.06-1.29) and 1.32 (95% CI 0.87-1.77) respectively with no significant heterogeneity ($I^2$=0.00%, P= 0.911). In addition, there was no significant difference in CRA risk between colon and rectum among light ($I^2$=0.00%, P=0.945), moderate ($I^2$=0.00%, P=0.873) and heavy ($I^2$=0.00%, P=0.535) drinkers, compared with non-/occasional drinkers (**Figure 5**; **Table 3**).

*Publication bias*

Begg's test was carried out to access the publication bias in our studies. In the analysis of all drinkers vs. non-/occasional drinkers, Begg's test revealed a significant publication bias (Begg's Test, P=0.03). However, the studies on light alcohol category and CRA risk showed no statistical evidence of publication bias (Begg's Test, P=0.09). Moreover, the studies on moderate alcohol category and CRA risk also presented no statistical evidence of publication bias (Begg's Test, P=0.167).

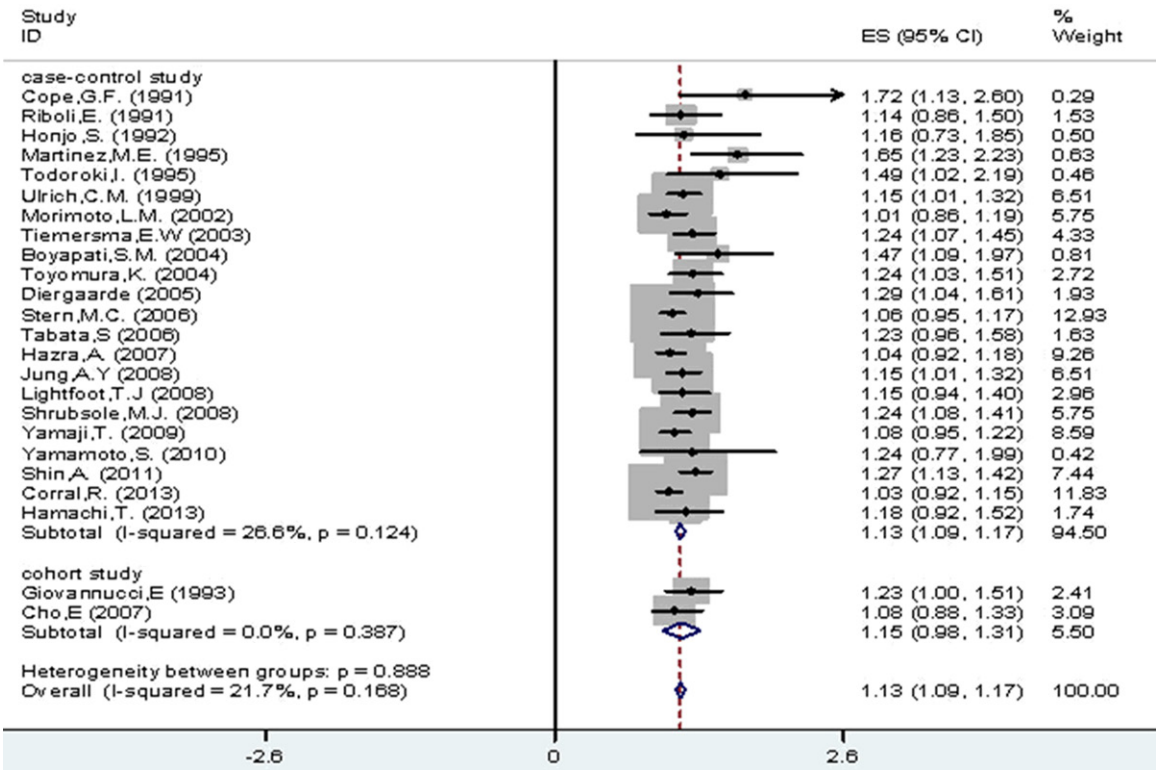


**Figure 2.** All drinkers vs. non-/occasional drinkers according to type of studies.

*Sensitivity analyses*

In the sensitivity analysis, when one study was removed and the rest were analyzed sequentially by meta-analysis. Any study in overweight or obesity group was omitted, the pooled RRs were not materially altered with the overall pooled RRs, indicating that our results were statistically robust.

*Dose-response analysis*

Our meta-regression analysis shows a significant dose-response relation between alcohol intake and colorectal cancer risk, the more alcohol intake, the higher risk of colorectal cancer. All drinkers were associated with 13% increased risk for CRA, the rational polynomial model estimates of RR were1.03 (95% CI 0.92-1.20), 1.08 (95% CI 1.02-1.19), 1.14 (95% CI 1.07-1.21) and 1.43 (95% CI 1.25-1.64) for 10, 25, 50 and 100 g/day of alcohol intake respectively, compared with nondrinkers or occasional alcohol drinkers (**Figure 6**).

## Discussion

We have systematically reviewed published studies on the association between alcohol intake and the risk of colorectal cancer. In this meta-analysis, alcohol consumption was positively associated with risk for colorectal cancer.

In general, all drinkers were associated with 13% increased risk for CRA, compared with nondrinkers or occasional alcohol drinkers. The dose-response analysis demonstrated that for drinkers of 10, 25, 50 and 100 g/day alcohol consumption, the estimated RRs of CRA were 1.03 (95% CI 0.92-1.20), 1.08 (95% CI 1.02-1.19), 1.14 (95% CI 1.07-1.21) and 1.43 (95% CI 1.25-1.64) respectively, in comparison with non-/occasional drinkers. Our meta-regression analysis shows a significant dose-response relation between alcohol intake and colorectal cancer risk-that is, the more alcohol intake, the higher risk of colorectal cancer. Furthermore, it is acknowledged that the dose-response relation from meta-regression (that is, between study investigation) should be viewed as exploratory and could be prone to confounding. Meta-analysis with individual participant data would have an advantage both statistically and clinically [27, 28] and, if available, should be used in the future to explore the dose-response relation further. Nevertheless, the dose-response

**Table 3.** Stratified RR estimates for colorectal adenoma risk

| Factors stratified | Drinkers vs. non-/occasional drinkers | | | | | | Light vs. non-/occasional drinkers | | | | | | Moderate vs. non-/occasional drinkers | | | | | | Heavy vs. non-/occasional drinkers | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | RR | LCI | UCI | *P* value | $I^2$ (%) | No. | RR | LCI | UCI | *P* value | $I^2$ (%) | No. | RR | LCI | UCI | *P* value | $I^2$ (%) | No. | RR | LCI | UCI | *P* value | $I^2$ (%) |
| All studies | 24 | 1.13 | 1.09 | 1.17 | | | 23 | 1.07 | 1.02 | 1.13 | | | 20 | 1.23 | 1.15 | 1.32 | | | 9 | 1.37 | 1.26 | 1.49 | | |
| Study type | | | | | | | | | | | | | | | | | | | | | | | | |
| Case-control | 22 | 1.13 | 1.09 | 1.17 | 0.17 | 21.70% | 21 | 1.08 | 1.02 | 1.14 | 0.06 | 33.00% | 18 | 1.24 | 1.15 | 1.33 | 0.01 | 52.10% | 9 | 1.37 | 1.26 | 1.49 | 0.69 | 0.00% |
| Cohort | 2 | 1.15 | 0.98 | 1.31 | | | 2 | 1.02 | 0.85 | 1.21 | | | 2 | 1.25 | 0.96 | 1.64 | | | 0 | unknown | unknown | unknown | | |
| Sex | | | | | | | | | | | | | | | | | | | | | | | | |
| Male | 8 | 1.19 | 1.07 | 1.32 | 0.21 | 24.00% | 7 | 0.97 | 0.86 | 1.10 | 0.71 | 0.00% | 7 | 1.28 | 1.15 | 1.44 | 0.15 | 30.90% | 7 | 1.38 | 1.22 | 1.57 | 0.47 | 0.00% |
| Female | 4 | 1.03 | 0.95 | 1.10 | | | 3 | 0.98 | 0.91 | 1.06 | | | 4 | 1.14 | 1.04 | 1.25 | | | 1 | 0.95 | 0.64 | 1.42 | | |
| Geographical region | | | | | | | | | | | | | | | | | | | | | | | | |
| Asia | 9 | 1.20 | 1.12 | 1.28 | 0.01 | 43.70% | 8 | 1.03 | 0.94 | 1.14 | 0.06 | 33.00% | 8 | 1.29 | 1.13 | 1.47 | 0.01 | 52.10% | 7 | 1.36 | 1.23 | 1.51 | 0.69 | 0.00% |
| Europe | 5 | 1.24 | 1.12 | 1.36 | | | 4 | 1.19 | 1.06 | 1.34 | | | 4 | 1.30 | 1.11 | 1.52 | | | 1 | 1.14 | 0.87 | 1.51 | | |
| USA | 11 | 1.12 | 1.05 | 1.20 | | | 11 | 1.06 | 0.99 | 1.14 | | | 8 | 1.18 | 1.08 | 1.28 | | | 1 | 1.50 | 1.28 | 1.75 | | |
| Tumor site | | | | | | | | | | | | | | | | | | | | | | | | |
| Colon | 6 | 1.18 | 1.08 | 1.30 | 0.91 | 0.00% | 5 | 1.02 | 0.91 | 1.14 | 0.59 | 0.00% | 6 | 1.35 | 1.21 | 1.50 | 0.87 | 0.00% | 4 | 1.23 | 1.03 | 1.47 | 0.54 | 0.00% |
| Rectum | 3 | 1.42 | 1.03 | 1.96 | | | 2 | 1.28 | 0.83 | 1.98 | | | 3 | 1.41 | 0.95 | 2.08 | | | 2 | 1.77 | 1.09 | 2.88 | | |

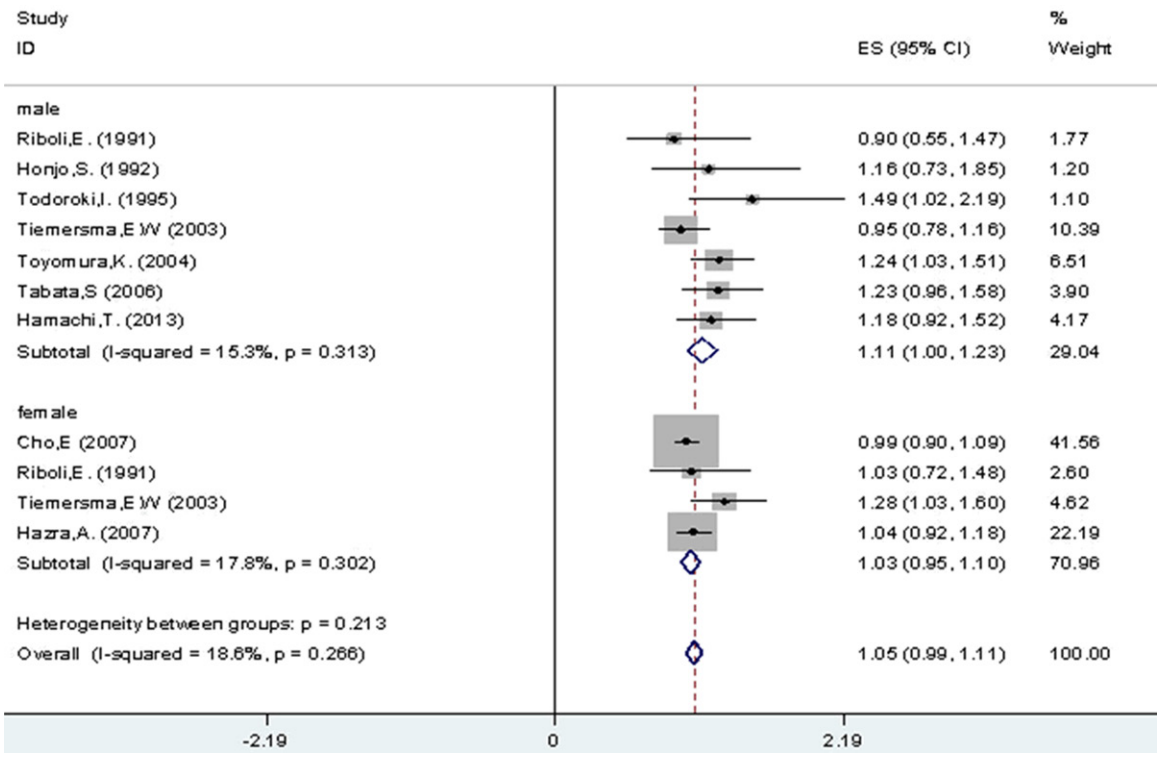


Figure 3. All drinkers vs. non-/occasional drinkers according to gender.

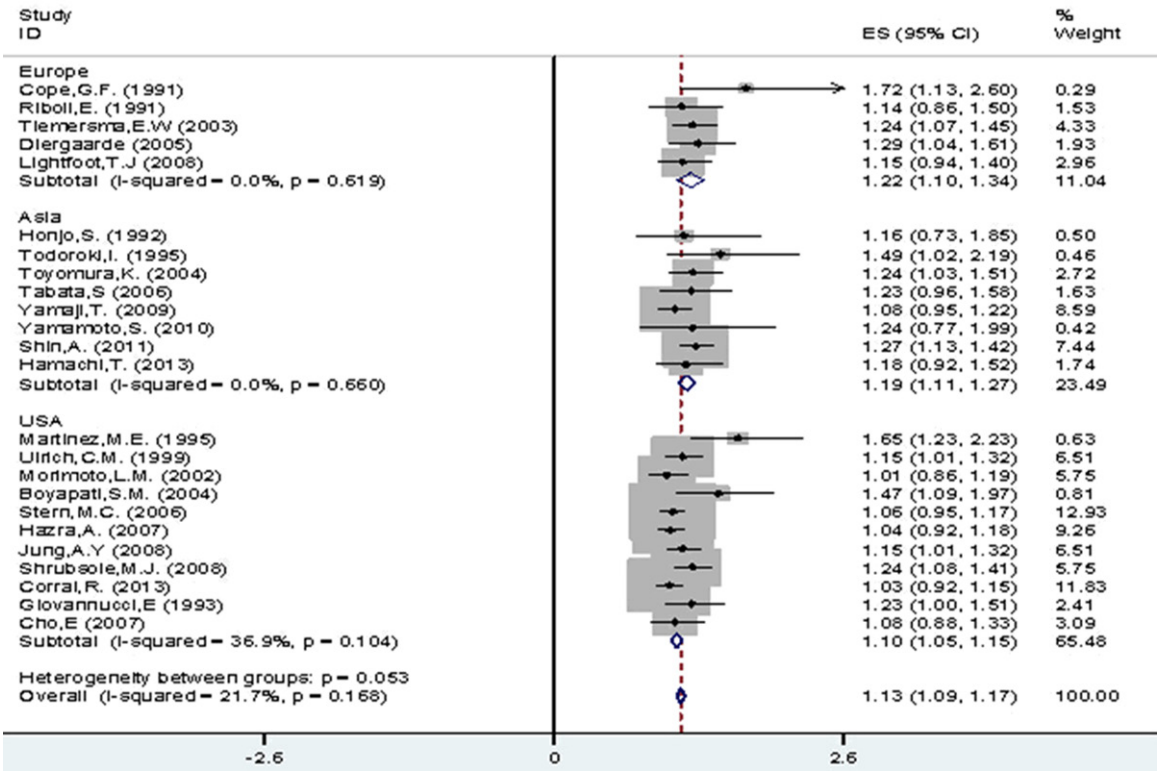


Figure 4. All drinkers vs. non-/occasional drinkers according to geographic region.

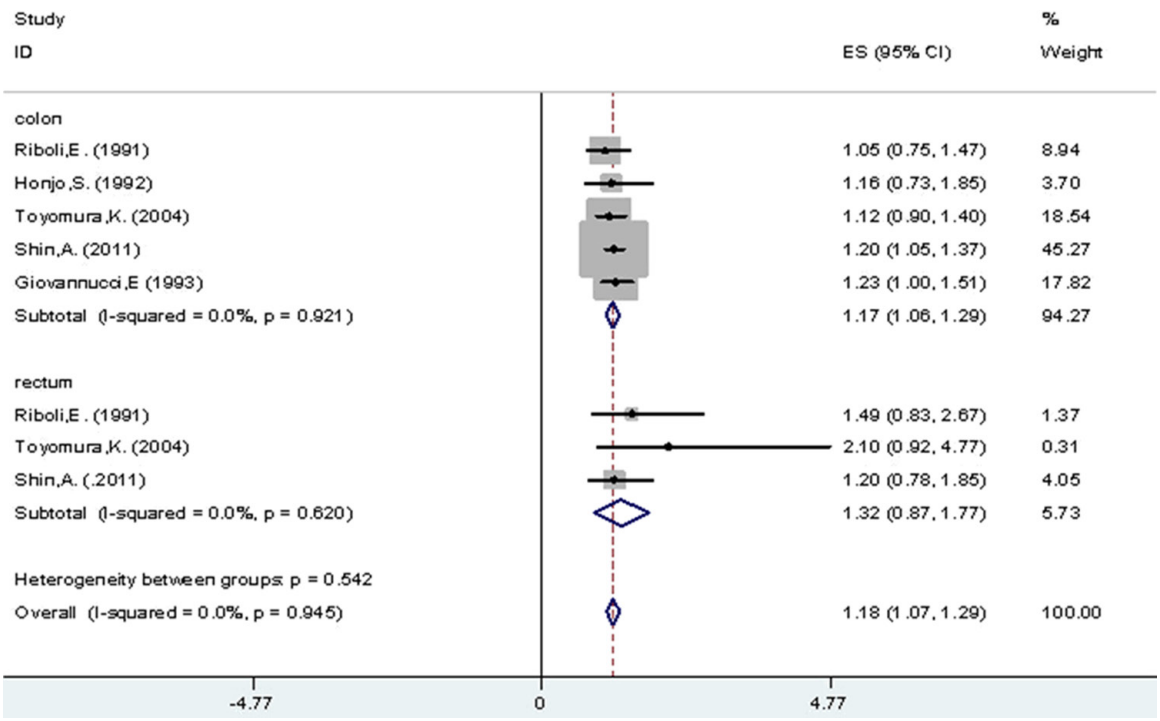


**Figure 5.** All drinkers vs. non-/occasional drinkers according to tumor site.

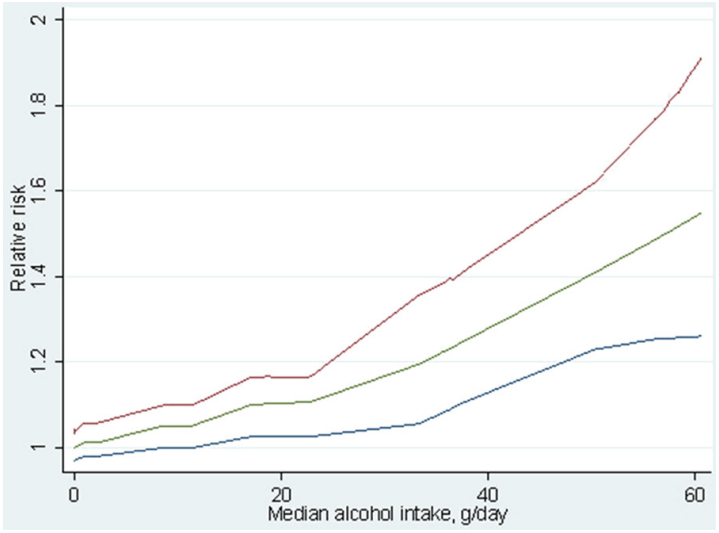


**Figure 6.** Dose-response association of alcohol intake and colorectal cancer risk.

relation found in our study is consistent with that observed from rigorously controlled trials with multiple levels of alcohol intake, which provided the most persuasive evidence.

In our study, the significant relationship between alcohol consumption and CRA risk was consistent for both female and male in the subgroup analyses of sex. Moreover, one research showed a stronger association in men compared to women, possibly because alcohol intake is higher and more popular in men than in women. As for tumor site, the association of alcohol drinking with colorectal cancer risk did not differ between colon and rectal anatomic subsites, which stands in line with previous meta-analysis [29-31] and pooled analysis [32, 33]. Some previous observational studies and one pooled study [34, 35-38] showed a stronger positive association of moderate and heavy alcohol drinking with cancer in the distal colon compared with cancer in the proximal colon, but the difference was not statistically significant. In terms of geographical region, a large number of researches enabled us to investigate whether there is a difference among Asian, European and USA populations. Our study has found the association was stronger in European studies, compared with the studies in the USA and Asia, except heavy and past drinkers. Potential explanations for these findings

include (i) a high prevalence (up to 30%) of the slow-metabolizing variant of aldehyde dehydrogenase enzyme, which is associated with increased blood levels of acetaldehyde after alcohol ingestion [39], and (ii) other non-genetic factors, for instance, body composition [40]. The next step, further research about colorectal cancer-alcohol intake among South American and African populations should be done.

Furthermore, evidence suggests that alcohol can act as a prooxidant in tissues, including lung tissue [41-48], and on lipids, including lung membrane lipids [41, 49]. Alcohol can induce the expression of enzymes that are related to carcinogen metabolism [50], and compounds other than ethanol that are contained in alcoholic beverages may have carcinogenic effects. Several mechanisms have been proposed for the effect of alcohol on risk for colorectal cancer. First, acetaldehyde, an oxidation product of alcohol, may be responsible for colorectal carcinogenesis [51, 52]. A recent study reported that high levels of acetaldehyde in rat colon degrade folate, a nutrient that is hypothesized to reduce the risk for colorectal cancer [53]. Second, alcohol is an antagonist of methyl-group metabolism and may contribute to abnormal DNA methylation, an early step in colonic carcinogenesis [54, 55]. Finally, greater alcohol intake may increase the risk for colorectal cancer indirectly through immune suppression, delay of DNA repair, activation of liver procarcinogens by induction of cytochrome P-450 enzymes, or changes in bile acid composition [56].

Moreover, acetaldehyde is produced by the liver as it breaks down ethanol. The liver then normally eliminates 99% of the acetaldehyde. An average liver can process 7 grams of ethanol per hour. For example, it takes 12 hours to eliminate the ethanol in a bottle of wine, giving 12 hours or more of acetaldehyde exposure. A study of 818 heavy drinkers found that those who are exposed to more acetaldehyde than normal through a defect in the gene for alcohol dehydrogenase are at greater risk of developing cancers of the upper gastrointestinal tract and liver [57]. There are many associations between alcohol drinking and different types of cancer. Data that is based from 2009, there were about 3.5 percent of cancer deaths in the U.S. alone because of alcohol drinking [58].

Our study had several strengths. First, our meta-analysis included a large number of studies published up to July 2014, and these cancer cases allowed to investigate the risk associated with three categories of alcohol consumption. Then Begg's test was carried out to access the publication bias in our studies, and did not support the presence of major publication bias, providing further indication of the robustness of our findings. Finally, linear and nonlinear random effects models on the natural logarithm of the RR were used to investigate the association between colorectal cancer risk and alcohol consumption, which allowed us to conduct traditional meta-analysis by categories of alcohol drinking and dose-response analysis.

Limitations of our study, first, we noted that the majority of the data were derived from case-control studies, which may be subject to certain types of bias, for instance, recall and selection bias. But the findings got from case-control studies were in line with prospective cohort studies. Then, for non-drinkers of a specific alcoholic beverage might drink other type of beverage, so the type of alcoholic beverage together with lifetime exposure to alcohol, and drinking patterns, were not included in our study. As a result, considering certain type of beverage might induce to an underestimation of the risk associated with the true amount of alcohol consumed. Then, the type of alcoholic beverage, as well as lifetime exposure to alcohol, and drinking patterns, were not included in the analyses because nondrinkers of a specific alcoholic beverage might drink other beverages. Thus, considering specific beverages could lead the true amount of alcohol consumed to be underestimated. The next, we had only one measure of alcohol consumption at baseline and could not investigate a whole lifetime alcohol consumption, changes in alcohol consumption or alcohol consumption at younger ages. Finally, no attempt was made to identify unpublished work and grey literature, for example university theses or conference proceedings. As a result, publication bias may have influenced the results [59, 60]. And only English literatures were included in this study, it is possible that our findings are biased for many non-English literatures are not included.

## Conclusion

Our results have shown that alcohol consumption was associated with an increase in risk for colorectal cancer. Moreover, the risk was consistent in subgroup analyses of sex and tumor site, while it was stronger in European studies than the studies in the US and Asia. Thus, public health recommendations for colorectal cancer prevention should consider limiting intake of alcoholic beverages.

## Disclosure of conflict of interest

None.

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