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Systematic Review with Meta-Analysis: Low-Level Alcohol Consumption and the Risk of Liver Cancer

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Background/Aims: Multiple meta-analyses and observational studies have reported that alcohol is a risk factor for liver cancer. However, whether there is a safe level of alcohol consumption remains unclear. We performed a systematic review and meta-analysis of the correlation between low-level alcohol consumption and the risk of liver cancer. **Methods:** Nested case-control studies and cohort studies involving the general population published prior to July 2019 were searched. In total, 28 publications (31 cohorts) with 4,899 incident cases and 10,859 liver cancer-related deaths were included. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. **Results:** Compared with those with low levels of alcohol consumption, moderate and heavy drinkers (≥1 drink/day for females and ≥2 drinks/day for males) had pooled ORs of 1.418 (95% CI, 1.192 to 1.687; p<0.001) for liver cancer incidence and 1.167 (95% CI, 1.056 to 1.290; p=0.003) for liver cancer mortality. The pooled OR for liver disease-related mortality for those with more than low levels of alcohol consumption was 3.220 (95% CI, 2.116 to 4.898; p<0.001) and that for all-cause mortality was 1.166 (95% CI, 1.065 to 1.278; p=0.001). The sensitivity analysis showed that none of the studies had a strong effect on the pooled OR. The Egger test, Begg rank correlation test, and the funnel plot showed no overt indication of publication bias. **Conclusions:** Continuous consumption of more than a low-level of alcohol (≥1 drink/day for females and ≥2 drinks/day for males) is related to a higher risk of liver cancer. **(Gut Liver 2020;14:792-807)**

Key Words: Alcohol; Liver neoplasms; Meta-analysis; Risk factors; Systematic review

INTRODUCTION

According to the World Health Organization, binge drinking is the leading cause of more than 200 diseases and injuries and is associated with premature death and disability; indeed, it is estimated that 3.3 million people worldwide die annually from drinking alcohol. In 1988, the International Agency for Research on Cancer categorized alcohol as a Group 1 human carcinogen.[1] Additionally, the International Agency for Research on Cancer regards alcohol consumption as a cause of female breast, colorectal, laryngeal, hepatic, esophageal, oral, and pharyngeal cancers.[2,3] Alcohol consumption is estimated to be responsible for 3.5% to 4.4% of cancer deaths annually worldwide.[4-6]

Animal studies have suggested that consumption of small amounts of alcohol, particularly red wine, can prevent cancer and ameliorate cardiovascular disease.[7] However, clinical trials in humans have not provided corroborative evidence regarding the benefits of red wine.[8] Few epidemiologic studies have addressed the association between alcohol consumption and cancer risk in humans. A Korean study reported that continuous alcohol consumption, even in small amounts, increases the incidence of esophageal and stomach cancer.[9]

The causes of chronic liver disease, including liver cancer, vary from region to region, but the most frequent are typically chronic viral hepatitis and alcohol. However, the recent development of effective therapeutics for chronic viral hepatitis has

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increased the importance of alcohol as a cause of liver disease. Alcohol can initiate the development of liver cancer and is related to tumor progression.[10-12] Regular consumption of 40–60 g of alcohol is related to a higher risk of liver cancer; this level has been suggested to be lower for women.[12,13] A recent meta-analysis on the incidence of alcohol-related liver cancer found a significant association between the risk of liver cancer and high-level alcohol consumption, with an excess risk of 66% for alcohol consumption of 100 g/day.[14] Nevertheless, the effect of low-level alcohol consumption (<40 g/day) on the risk of liver cancer was not evaluated and the safe level of alcohol consumption for women was not proposed.

Therefore, we carried out a meta-analysis to determine whether there is a safe level of alcohol consumption in terms of liver cancer risk in men and women. In expressing the amount of alcohol consumption, existing studies used varying units of measurement (number of drinks, ounces, milliliters, or grams consumed every day, week, month, or year); in this study, grams per day (g/day) was used as the standard measure of alcohol intake using the following equivalences: one drink=0.8 g/mL=28 g/ounce=12.5 g/drink. According to the definitions in the U.S. Government Dietary Guidelines for Americans (2015 to 2020), light alcohol drinking was defined as less than two drinks/day in males and one drink/day in females.[15] Using these criteria, we systematically reviewed the existing literature and performed a meta-analysis of the effect of alcohol consumption on the risk of liver cancer.

MATERIALS AND METHODS

1. Literature search

The search for relevant literature was independently performed by two authors (H.P. and S.K.S.), who searched for articles published prior to July 31, 2019 in Embase and PubMed, by using the following search terms: (alcohol OR ethanol) AND (neoplasm OR carcinoma OR cancer) AND (hepatocellular OR liver) AND (prospective OR cohort OR cohort studies [Medical Subject Headings; MeSH Terms]). The titles and abstracts of all retrieved studies were scanned to exclude all irrelevant studies, and inconsistencies were resolved by review of the full text and discussion. The full texts of the remaining papers were examined to assess their eligibility. We also examined the reference lists of all retrieved articles. This meta-analysis was performed according to the Preferred Reporting Items of the Systematic Reviews and Meta-Analyses statement.[16]

2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) original research articles of nested case-control or cohort studies (letters, reviews, and abstracts were excluded); (2) articles reporting the incidence and mortality of primary liver cancer or hepatocellular carcinoma as odds ratios (ORs), hazard ratios, or relative risks (RRs) (at least two levels of alcohol consumption vs nondrinkers and/or occasional drinkers); and (3) articles using standard errors or confidence intervals (CIs) of the risk estimates or those that provided sufficient data to calculate them. The exclusion criteria

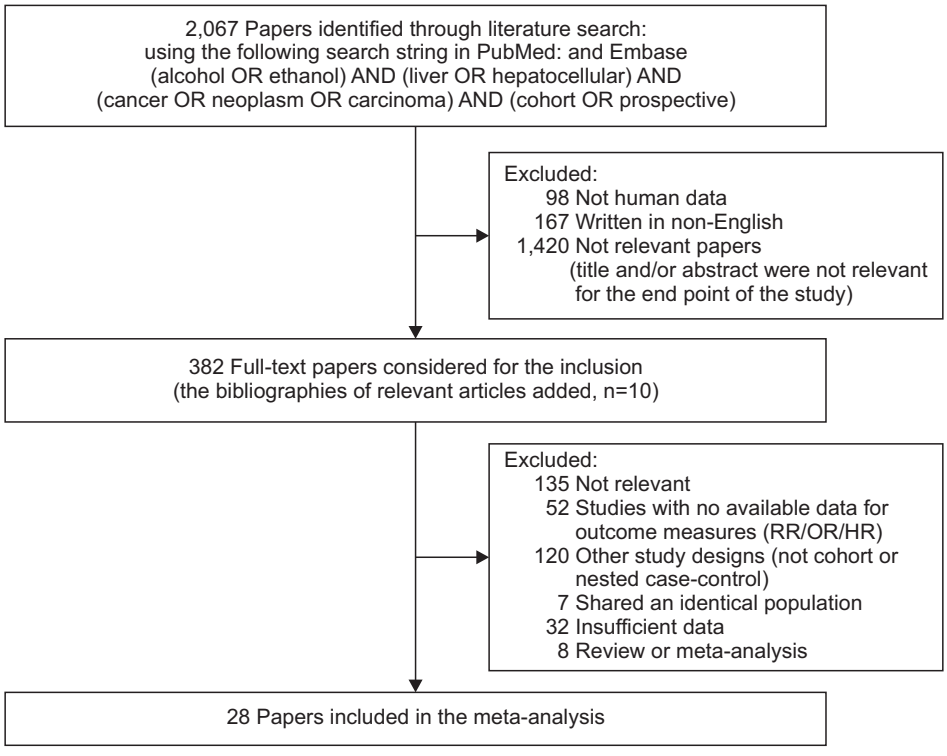


Fig. 1. Flowchart of the literature search and inclusion criteria of the meta-analysis.
RR/OR/HR, relative risk/odds ratio/hazard ratio.

Table 1. Characteristics of the Studies Included in the Meta-Analysis

First author (year)	Country	Study design	Mean follow-up, yr	Sex	Age, yr*	Participants (total)	Case (HCC incidence)	Case (HCC induced death)	Case (liver disease-related death)	Case (all-cause death)	Classification of alcohol consumption	Adjusted covariates
Allen (2009)[23]	UK	Cohort	7.2	F	55	12,980,296	337				≤2 vs none, 3–6, 7–14, ≥15 drinks/wk	Age, region of residence, socioeconomic status, BMI, smoking, physical activity, use of oral contraceptives, and hormone replacement therapy
Persson (2013)[22]	USA	Cohort	10.5	M/F	50–71	404,743	435		785		<1 vs none, 1–3, >3 drinks/day	Sex, age, race, education, smoking, BMI, and diabetes
Kawamura (2016)[25]	Japan	Cohort	5.4	M/F	19–96	9,959	49				<20 vs 20–39, 40–69, ≥70 g/day	Sex, age, BMI, alcohol intake, albumin, bilirubin, AST, ALT, LDH, G-GTP, PLT, DM, uric acid, total cholesterol, TG, LDL, HDL
Schwartz (2013)[24]	Finland	Cohort	7	M	50–69	29,133	194		213		<5.33 vs 5.33–20.44, >20.44 g/day	Age, education, smoking, BMI, DM, study arm
Setiawan (2016)[26]	USA	Cohort	19.6	M/F	45–75	38,684	189				None vs <2, ≥2 drinks/day	Cohort entry, education, BMI, alcohol intake, smoking status, diabetes, vigorous activity, and sex
		Cohort (USA born)	19.6	M/F	45–75	18,485			194			
		Cohort (foreign born)	19.6	M/F	45–75	18,379			104			
Michikawa (2012)[27]	Japan	Cohort	7	M/F	40–69	17,654	104				<150 vs 150–450 ≥450 g/wk	Age, sex, area, alcohol consumption, BMI, diabetes, coffee consumption, HBsAg, and anti-hepatitis C virus antibody
Chen (1996)[28]	Taiwan	Nested case-control	2	M/F	30–65	156	33				None vs <20, ≥20 L/yr	Age, sex
Ohishi (2008)[29]	Japan	Nested case-control	32	M/F	67.6	868	224				None vs 0–20, 20–40, ≥40 g/day	Hepatitis virus infection, continuous alcohol consumption, smoking habit, coffee drinking, BMI, DM, and radiation dose to the liver

Table 1. Continued

First author (year)	Country	Study design	Mean follow-up, yr	Sex	Age, yr*	Participants (total)	Case (HCC incidence)	Case (HCC induced death)	Case (liver disease-related death)	Case (all-cause death)	Classification of alcohol consumption	Adjusted covariates
Koh (2011)[30]	Singapore	Nested case-control	11.5	M/F	45–74	366	92				None vs less than daily <2, ≥2 drinks/day	Gender, age at recruitment (yr), year of recruitment, dialect group (Hokkien, Cantonese), and the level of education, BMI (<20, 20–24, >24 kg/m^2), DM (yes, no), and cups of coffee per day
Trichopoulos (2011)[31]	Europe	Nested case-control	8.9	M/F	25–70	344	115				M <10, F <5 vs M 10–40, F 5–20, M ≥40, F ≥20 g/day	All indicated possible risk factors
Yuan (2004)[32]	USA	Nested case-control	15	M	18–74	465	245				None vs 0–2, 2–4, >4 drinks/day	Age, gender, race, and level of education, smoking status, number of alcoholic drinks per day, and history of diabetes
Loftfield (2016)[33]	Finland	Nested case-control	22	M	50–69	391	138				≤11.3 vs >11.3 g/day	Age-adjusted
Yi (2018)[34]	Korea	Cohort	10.5	M/F	53.0	504,646	2,744				None vs <10, 10–39, ≥40 g/day	Age, sex, smoking status, alcohol use, physical activity, income status, BMI, diabetes status, cirrhosis and hepatitis B virus and C virus infection
Kim (2010)[35]	Korea	Cohort	5	M	48.3	919,199		1,506		16,108	None vs 1–14.9, 15–29.9, 30–89.9, ≥90 g/day	Age, residential (urban, rural), smoking status (current, former, never), ≥3 times/wk regular exercise (yes, no), BMI (kg/m^2, continuous), systolic and diastolic blood pressure (mm Hg, continuous), and fasting blood sugar (mg/dL, continuous)

Table 1. Continued

First author (year)	Country	Study design	Mean follow-up, yr	Sex	Age, yr*	Participants (total)	Case (HCC incidence)	Case (HCC induced death)	Case (liver disease-related death)	Case (all-cause death)	Classification of alcohol consumption	Adjusted covariates
Kim (2010)[35]	Korea	Cohort	5	F	49	422,194		174		3,267	None vs 1–14.9, ≥15 g/day	Age, residential (urban, rural), smoking status (current, former, never), ≥3 times/wk regular exercise (yes, no), BMI (kg/m^2, continuous), systolic and diastolic blood pressure (mm Hg, continuous), and fasting blood sugar (mg/dL, continuous)
Yi (2010)[36]	Korea	Cohort	20.8	M	66.3	2,696		36			None vs <138, <540, ≥540 g/wk	Age (year of recruitment), history of chronic disease, smoking habit, ginseng intake, pesticide use, BMI, and education status
	Korea	Cohort	20.8	F	66.9	3,595		52			None vs <12, ≥12 g/wk	Age (year of recruitment), history of chronic disease, smoking habit, ginseng intake, pesticide use, BMI, and education status
Yang (2012)[37]	China	Cohort	15	M	40–79	220,000		1,115		20,977	None vs <140, 140–279, 280–419, 420–699, ≥700 g/wk	Age, area, smoking and education
Jee (2004)[38]	Korea	Cohort	10	M/F	30–95	1,329,525		3,341			None vs 1–24.9, 25–49.9, 50–99.9, ≥100 g/day	Age, age squared, smoking, alcohol use, and diabetes
Joshi (2008)[39]	Korea	Cohort	6	M	30–59	548,530		998			None vs 1–24, 25–49, 50–99, ≥100 g/day	Age, fasting serum glucose, BMI, alcohol intake and tobacco smoking, HBsAg
Jung (2012)[40]	Korea	Cohort	9.3	M/F	>20	15,683		85			≤90 vs none, 90.01–252, 252.01–504, >504 g/wk	Age, sex, BMI, smoking habit, geographic area, and educational attainment

Table 1. Continued

First author (year)	Country	Study design	Mean follow-up, yr	Sex	Age, yr*	Participants (total)	Case (HCC incidence)	Case (HCC induced death)	Case (liver disease-related death)	Case (all-cause death)	Classification of alcohol consumption	Adjusted covariates
Kono (1986)[41]	Japan	Cohort	19	M		5,135		51		1,283	None/past vs occasional, <2, ≥2 go of sake/day	Age, smoking
Park (2006)[42]	Korea	Cohort	7	M	50.8	14,578		2,013			None vs 1–124.1 ≥124.2 g/wk	Age, alcohol consumption, BMI, fasting serum glucose level, cholesterol level, physical activity, food preference, blood pressure, and other comorbidities (heart disease, liver disease, and cerebrovascular disease)
Shih (2012)[43]	Taiwan	Cohort	10	M/F	20–75	2,273		1,488			None vs ex-drinker, <19.4, 19.5–46.1, 46.2–106.9, ≥107 g/day	Adjusted for age at recruitment, sex, maximum tumor size (<3, 3 to <5 or 5 cm), number of lesions (1, 2–3 or 4), serum a-fetoprotein levels (<20, 20–151, 152–1,519 or 1,520 ng/mL), cigarette smoking (yes or no), history of liver cirrhosis and status of HBsAg and anti-HCV
Yi (2016)[44]	Korea	Cohort	6	M	58.8	187,897			338		<1 vs 1–6, 7–13, 14-27, ≥28 drinks/wk	Adjusted for age at entry, smoking status, physical activity, household income, and BMI
Younoszai (2014)[45]	USA	Cohort	14.6	M/F	20–74	8,966			26	1,130	<20 (M) (10 [F]) vs >20 g/day	Statin use, age, male, race, alcohol consumption, obesity, diabetes, HTN, cancer, elevated liver enzyme

Table 1. Continued

First author (year)	Country	Study design	Mean follow-up, yr	Sex	Age, yr*	Participants (total)	Case (HCC incidence)	Case (HCC induced death)	Case (liver disease-related death)	Case (all-cause death)	Classification of alcohol consumption	Adjusted covariates
Fuchs (1995)[46]	USA	Cohort	12	F	30–55	85,709				836	0 vs 0.1–1.4, 1.5–4.9, 5.0–14.9, 15.0–29.9, ≥30 g/day	Adjusted for age (in 5-yr categories), smoking status, BMI (in quintiles), regular aspirin use (2 days/wk), regular vigorous exercise (1 day/wk), high plasma cholesterol level, diabetes, HTN, myocardial infarction in a parent at 60 yr of age, past or present oral-contraceptive use, menopausal status, past or present postmenopausal hormone use, and energy-adjusted intake of dietary fiber and saturated fat
Marugame (2007)[47]	Japan	Cohort	11.9	M/F	40–69	41,702 (M)/ 47,044 (F)				2,658 (M)/ 9,338 (F)	Occasional drink vs 1–149, 150–299, 300–449, 450 g/wk	Adjusted for age at baseline (continuous), study area (nine public health center areas), smoking status, BMI, green vegetable intake (3–4 times/wk and almost every day), and leisure-time physical activity
Ferrari (2014)[48]	Europe	Cohort	12.6	M	25–70	101,935 (M) /247,795 (F)				8,964 (M) /11,492 (F)	0.1–4.9 vs never, 5–14.9, 15–29.9, 30–59.9, ≥60 g/day	Age at recruitment, BMI and height, former drinking, time since alcohol quitting, smoking status, duration of smoking, age at start smoking, educational attainment and energy intake

Table 1. Continued

First author (year)	Country	Study design	Mean follow-up, yr	Sex	Age, yr*	Participants (total)	Case (HCC incidence)	Case (HCC induced death)	Case (liver disease-related death)	Case (all-cause death)	Classification of alcohol consumption	Adjusted covariates
Saito (2018)[49]	Japan	Cohort	18.2	M/F	40–69	102,849				15,203	Never vs 1–149, 150–299, 300–449, 450–599, ≥600 g/wk	Adjusted for age, smoking status (never, former, <20, ≥20 cigarettes/day), BMI (<18.5, 18.5 to <25, 25 to <30, ≥30), history of HTN, flushing response, history of diabetes, leisure-time sports or physical exercise, intake of coffee and green tea (almost never, ≥1 cup/wk, and ≥1 cup/day), energy intake, intakes of fruits, vegetables, fish, meat, dairy products, and job status

HCC, hepatocellular carcinoma; M, male; F, female; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactic dehydrogenase; G-GTP, gamma glutamyl transpeptidase; PLT, platelet count; DM, diabetes mellitus; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; HBsAg, hepatitis B surface antigen; HTN, hypertension.
*Mean or range.

Table 2. Methodological Quality of the Cohort Study Included in the Final Analysis of Hepatocellular Carcinoma Incidence Based on the Newcastle-Ottawa Scale

Cohort study	Selection				Comparability	Outcome			Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total (0–9)
Allen (2009)[23]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Persson (2013)[22]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Kawamura (2016)[25]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Schwartz (2013)[24]	-	☆	☆	☆	☆	☆	☆	☆	7
Setiawan (2016)[26]	☆	☆	☆	☆	☆	☆	☆	☆	8
Michikawa (2012)[27]	☆	☆	☆	☆	☆☆	☆	☆	☆	9

Table 3. Methodological Quality of the Case-Control Study Included in the Final Analysis of Hepatocellular Carcinoma Incidence Based on the Newcastle-Ottawa Scale

Case-control study	Selection				Comparability	Outcome		Score
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Total (0–9)
Chen (1996)[28]	☆	☆	☆	☆	☆☆	☆	☆	8
Ohishi (2008)[29]	☆	☆	☆	☆	☆☆	☆	☆	8
Koh (2011)[30]	☆	☆	☆	☆	☆☆	☆	☆	8
Trichopoulos (2011)[31]	-	☆	☆	☆	☆☆	☆	☆	7
Yuan (2004)[32]	☆	☆	☆	☆	☆☆	☆	-	7
Loftfield (2016)[33]	☆	-	☆	☆	☆☆	☆	☆	7
Yi (2018)[34]	☆	☆	☆	☆	☆☆	☆	☆	8

were: (1) non-English language articles; (2) non-human studies; and (3) no classification of alcohol consumption. When multiple studies involved the same population, the most recent article was included.

3. Data extraction and quality assessment

Two independent authors (H.P. and S.K.S.) extracted data from the included studies. The following details were retrieved from each study: (1) first author's name and the year of publication, (2) country, (3) design, (4) follow-up period, (5) subjects' gender distribution, (6) subjects' mean age, (7) number of subjects, (8) classification of alcohol consumption, (9) effect size (OR, harzard ratio, or relative risk and 95% CI), and (10) confounders adjusted for. The Newcastle-Ottawa Scale (NOS) was used to estimate the quality of the studies.[17] The NOS score ranges from 0 to 9 and is defined as the sum of the scores of the following three subscales: selection of studies, comparability, and outcome. A higher score indicates greater methodological quality. Studies with NOS scores ≥7 were noted as high quality.

4. Statistical analysis

We used the fixed- and random-effects models to estimate the pooled ORs with 95% CIs. Sufficiently homogenous groups of studies were analyzed with the fixed-effects model, and more heterogeneous groups of studies were analyzed with the random-effects model.[18] We used Forest plots to identify the heterogeneity among studies, which was quantified using the I^2 index, which represents the percentage of the total variability in a set of effect sizes rising from the true heterogeneity among studies.[19] To evaluate the stability of the meta-analysis, we carried out a sensitivity analysis. The pooled OR of the remaining studies was computed by excluding one study at a time and compared with that of the fixed-effects model or random-effects model. The funnel plot or Egger regression test was utilized to evaluate the publications.[20] When the articles provided ORs by using a different reference category, the ORs were newly calculated by dividing each OR by the OR for non-drinking; CIs were calculated by employing the standard errors of the crude OR estimates that were penalized by a factor of 1.5.[21,22]

Comprehensive Meta-Analysis version 2.0 (Biostat, Inc., Englewood, NJ, USA) was used for carrying out all statistical analyses. p-values smaller than 0.05 (two-sided) were considered statistically significant.

RESULTS

A total of 2,067 articles were initially retrieved from PubMed and Embase. After applying the exclusion criteria, the full texts of 382 potentially relevant studies were reviewed. Of these, 28 were finally included for meta-analysis (Fig. 1):[22-49] 22 were cohort studies and six nested case-control studies; 18 studies were from Asia, five were from the United States, and the other five were from Europe.

Table 1 shows the characteristics of the included studies. In total, 28 publications (31 cohorts) were included. A total of 4,899 incident cases and 10,859 deaths from liver cancer were included in the articles as a whole. A total of 1,669 deaths from liver disease and 91,256 all-cause deaths were also included.

Tables 2 and 3 shows the methodological qualities of the cohort and nested case-control studies. The average score was 7.5 for case-control studies and 8.5 for cohort studies (range, 7–9). All included studies were of high quality (NOS score ≥7). Quality assessment regarding alcohol and mortality from liver cancer, all-cause, and liver diseases was also performed (Supplement Tables 1-3).

Fig. 2A shows the Forest plot regarding the relationship between the incidence of liver cancer and more than light drinking versus never or light drinking. The pooled OR was 1.418 (95% CI, 1.192 to 1.687; p<0.001; I^2=60.5%) based on 13 studies. The sensitivity analysis showed that no single study had significantly affected the overall results (Fig. 2B). The funnel plot in the analysis of liver cancer incidence and more than light drinking versus never or light drinking showed evidence of publication bias in Egger test (p=0.010), but not Begg rank correlation test (p=0.502) (Fig. 2C). After using the trim-and-fill analysis to correct for this bias, a pooled OR of 1.141 (95% CI, 0.958 to 1.259) was calculated using the random-effects model.

The pooled OR for mortality from liver cancer for more than light drinking versus never or light drinking was 1.167 (95% CI, 1.056 to 1.290; p=0.003; I^2=61.1%) based on nine studies (11 cohorts) (Fig. 3A). The sensitivity analysis demonstrated that no single study conferred a significant impact on the pooled OR (Fig. 3B). The funnel plot, Egger (p=0.409) and Begg rank correlation test (p=0.640) indicated no overt indication of publication bias in the analysis of liver cancer mortality (Fig. 3C).

The pooled OR of liver disease-related mortality for more than light drinking versus never or light drinking was 3.220 (95% CI, 2.116 to 4.898; p<0.001; I^2=66.7%) based on five studies (six cohorts) (Fig. 4A). The pooled OR for all-cause mortality for more than light drinking versus never or light drinking was 1.166 (95% CI, 1.065 to 1.278; p=0.001; I^2=48.9%) based on eight studies (10 cohorts) (Fig. 5A). In both analyses, the sensitivity analysis demonstrated that no single study conferred a significant impact on the pooled OR (Figs. 4B, 5B), and the funnel plot, Egger (p=0.603 and p=0.466, respectively) and Begg rank correlation test (p=0.133 and p=1.000, respectively) indicated no overt indication of publication bias (Figs. 4C, 5C).

DISCUSSION

We investigated the relationship between liver cancer and alcohol consumption. Most previous studies of the incidence and mortality of liver cancer have been conducted on people who drink more than 40–69 g of alcohol per day for both genders. In

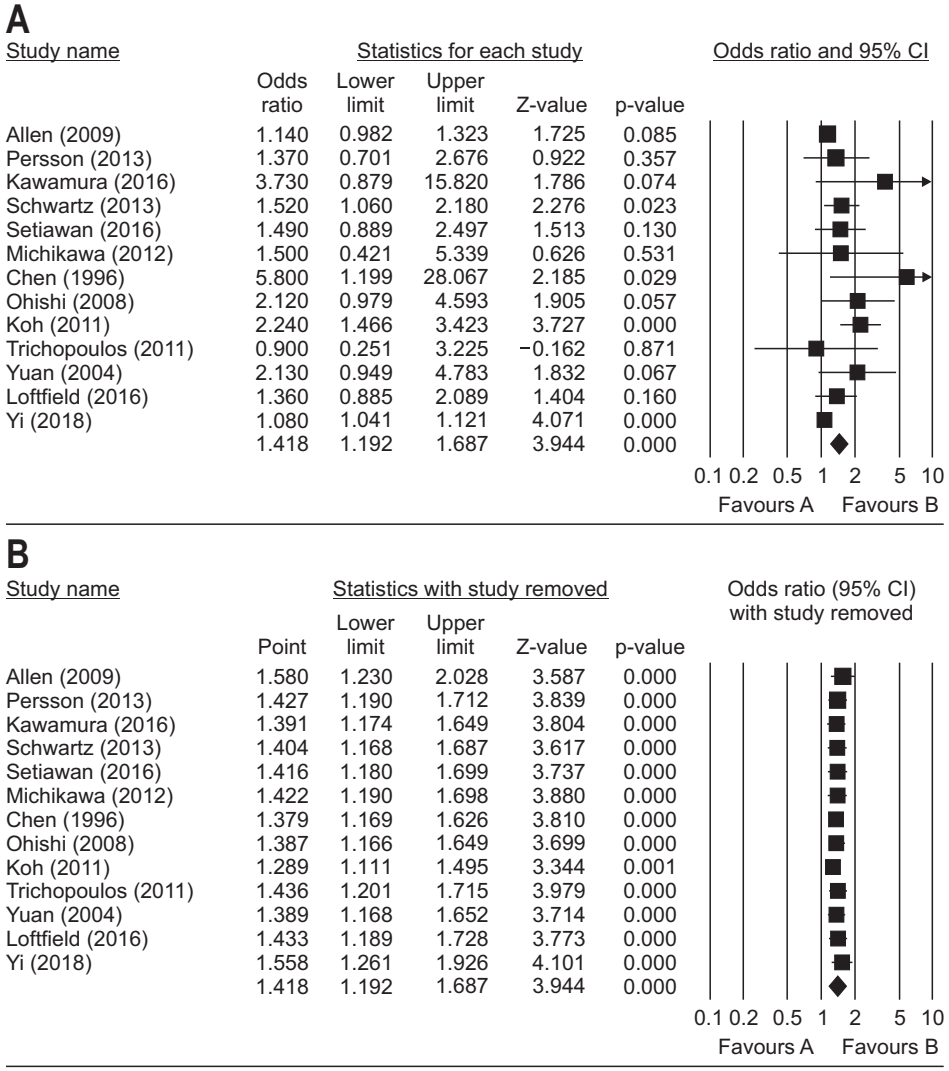


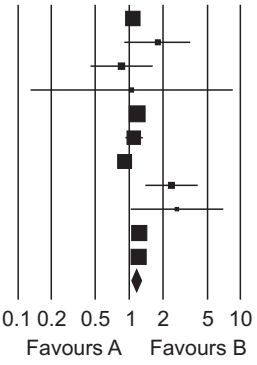
Fig. 2. Meta-analysis of studies examining the relationship between the incidence of liver cancer and moderate/heavy light alcohol consumption versus never or a low level of alcohol consumption. (A) Forest plot; (B) sensitivity test; (C) funnel plot.
CI, confidence interval.

this study, however, light alcohol consumption standards of less than two drinks/day for males and one drink/day for females were used for analysis. We also assessed the overall relationship between alcohol and liver disease based not only on the incidence of liver cancer and the associated mortality rates but also on the mortality rate of liver disease and the all-cause mortality rate.

More than light alcohol drinkers had a 42% increased risk of liver cancer incidence and 17% increased risk of liver cancer death compared to those who drink less alcohol. The liver-related mortality rate was 3.2-fold higher in more than moderate drinkers compared to those who drink less alcohol, demon-

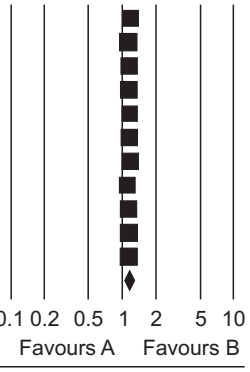
A

Study name	Odds ratio	Lower limit	Upper limit	Z-value	p-value
Kim (2010)_male	1.080	0.935	1.247	1.049	0.294
Kim (2010)_female	1.800	0.904	3.585	1.672	0.094
Yi (2010)_male	0.860	0.449	1.647	−0.455	0.649
Yi (2010)_female	1.060	0.131	8.556	0.055	0.956
Yang (2012)	1.180	1.071	1.301	3.332	0.001
Jee (2004)	1.110	0.928	1.327	1.143	0.253
Joshi (2008)	0.920	0.796	1.064	−1.124	0.261
Jung (2012)	2.410	1.398	4.154	3.166	0.002
Kono (1986)	2.700	1.035	7.041	2.031	0.042
Park (2006)	1.250	1.109	1.409	3.656	0.000
Shih (2012)	1.220	1.097	1.357	3.674	0.000
	1.167	1.056	1.290	3.022	0.003



B

Study name	Point	Lower limit	Upper limit	Z-value	p-value
Kim (2010)_male	1.186	1.058	1.331	2.914	0.004
Kim (2010)_female	1.157	1.047	1.278	2.853	0.004
Yi (2010)_male	1.175	1.061	1.301	3.104	0.002
Yi (2010)_female	1.168	1.055	1.294	2.978	0.003
Yang (2012)	1.175	1.036	1.332	2.506	0.012
Jee (2004)	1.179	1.053	1.320	2.849	0.004
Joshi (2008)	1.202	1.106	1.307	4.315	0.000
Jung (2012)	1.141	1.046	1.244	2.974	0.003
Kono (1986)	1.155	1.049	1.272	2.942	0.003
Park (2006)	1.156	1.029	1.299	2.445	0.014
Shih (2012)	1.164	1.031	1.314	2.457	0.014
	1.167	1.056	1.290	3.022	0.003



C

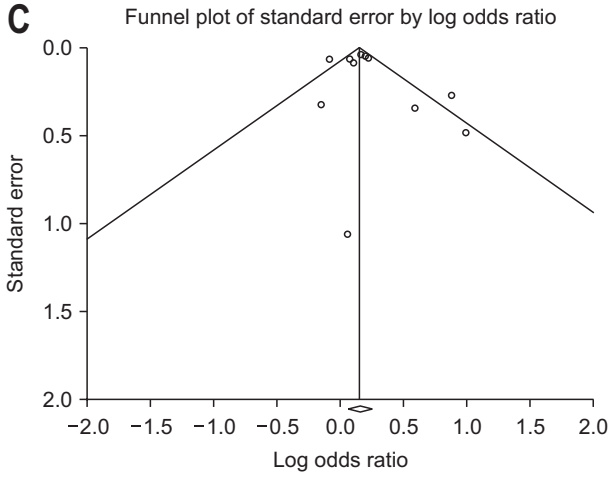


Fig. 3. Meta-analysis of studies examining the relationship between mortality from liver cancer and moderate/heavy alcohol consumption versus never or a low level of alcohol consumption. (A) Forest plot; (B) sensitivity test; (C) funnel plot.
CI, confidence interval.

strating that consumption of even one or two alcoholic drinks daily can have an adverse effect on health. The risk of all-cause mortality in more than light drinkers was 16% higher compared to those who drink less alcohol. A slight decrease in the risk of all-cause mortality compared to that of liver-related mortality can be assumed that cardiovascular diseases reported to be able to protect with a small amount of drinking was included in all-cause mortality.

Studies in animals have shown that alcohol consumption in small amounts, especially red wine, can prevent cancer and ameliorate cardiovascular disease. Indeed, some components of red wine, such as resveratrol, have anticancer activity.[7] Resveratrol is also present in peanuts, grapes, raspberries, and some other plants. Resveratrol is a polyphenol antioxidant produced by various plants to defend against fungi, stress, injury, infection, and excess sunlight; moreover, its effect on cancer and

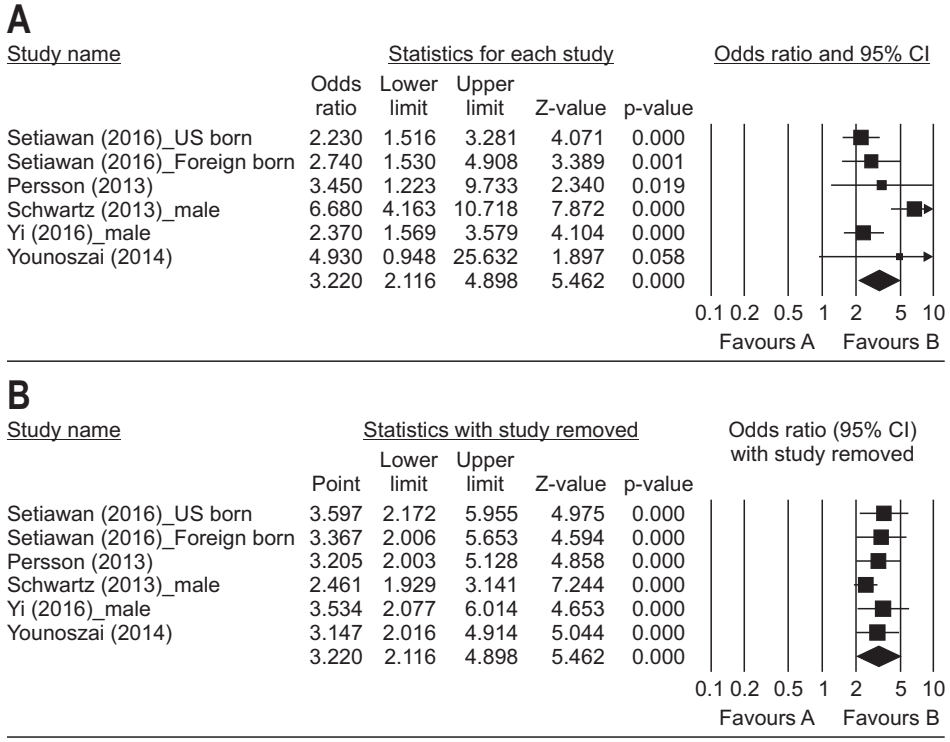


Fig. 4. Meta-analysis of studies examining the relationship between liver disease-related mortality and moderate/heavy alcohol consumption versus never or a low level of alcohol consumption. (A) Forest plot; (B) sensitivity test; (C) funnel plot.
CI, confidence interval.

heart disease is under investigation. However, clinical trials have shown that resveratrol is not effective for preventing or treating cancer.[8] Alcohol was categorized as a human liver carcinogen by the International Agency for Research on Cancer in 1988.[1] Alcohol can initiate the development of liver cancer and is significantly associated with tumor progression. The underlying mechanisms of the promotion by alcohol and its metabolite, acetaldehyde, of liver carcinogenesis include:[10-12] (1) increased oxidative stress, which damages DNA and hampers its repair; (2) induction of liver injury, promoting fibrogenesis and cirrhosis (most alcohol-related liver cancers develop from liver cirrhosis); (3) interactions with other environmental carcinogens, such as tobacco smoke; (4) interruption of one-carbon metabolism, leading to impaired DNA methylation and altered gene expression.

Previous meta-analyses have reported that regular consumption of 40–60 g of alcohol is related to a higher risk of liver cancer and proposed a lower level of safe alcohol consumption for women.[12,13] Turati *et al.*[14] systematically reviewed and meta-analyzed the relation between alcohol intake and the incidence of liver cancer and death by including 16 articles (19 cohorts) that comprised a total of 4,445 incident cases and 5,550 liver cancer-related deaths; as a results, the authors found a significant linear association between alcohol consumption and liver cancer risk (excess risk 46% for 50 g of alcohol per day and 66% for 100 g per day). Although the authors reported a dose-risk association between alcohol consumption and liver cancer risk, they did not evaluate the risk of consumption of smaller amounts of alcohol and did not analyze gender standards separately. Additionally, the risk of liver cancer comprised both the

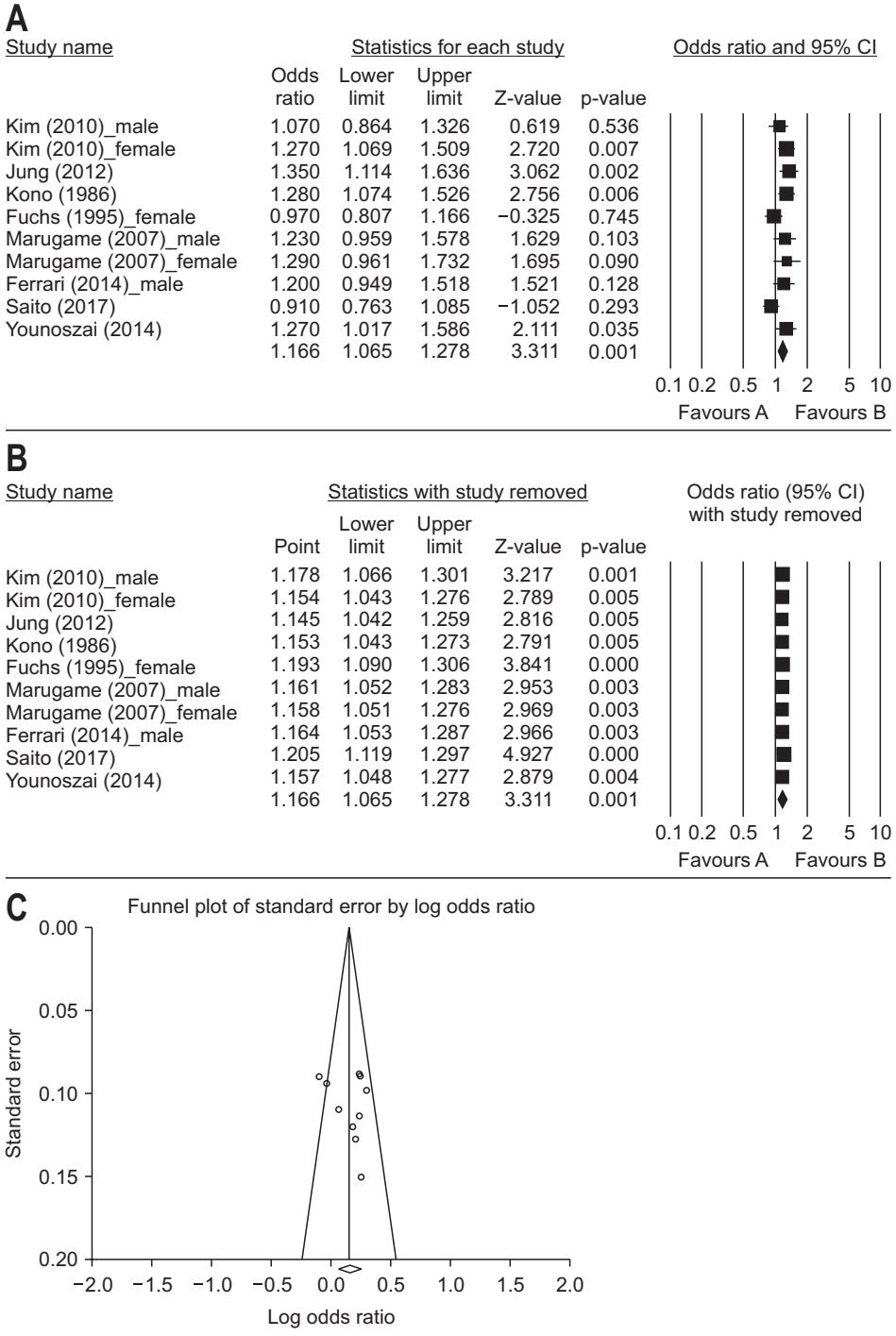


Fig. 5. Meta-analysis of studies examining the relationship between all-cause mortality and moderate/heavy alcohol consumption versus never or a low level of alcohol consumption. (A) Forest plot; (B) sensitivity test; (C) funnel plot.
CI, confidence interval.

incidence and mortality rates of liver cancer; these were not evaluated separately. Another recent meta-analysis demonstrated that alcohol consumption is associated with a higher risk of liver cancer in a dose-dependent manner (8% for 12 g alcohol per day, 54% for 50 g per day, and 3.2-fold for 100 g per day).[50] Moreover, synergistic effects with other risk factors such as hepatitis and diabetes were detected. However, the enrolled studies showed significant heterogeneity as well as publication bias.

This study had the following limitations. First, we may have omitted the liver cancer data included in the results of our study with all kinds of cancer since we found a paper exclusively for the event in livers. Secondly, there was some heterogeneity among the articles, as with most meta-analyses. However, we overcame this limitation by applying random-effects and fixed-effects models according to heterogeneity. Sensitivity analyses supported the robustness of our study results. Moreover, Egger tests for funnel plot asymmetry and the funnel plot did not indicate the presence of major publication bias.

In conclusion, this meta-analysis supports previous reports

of the association between alcohol consumption and the risk of liver cancer. Furthermore, our research shows that continuous consumption of even a small amount of alcohol is related to liver cancer risks. Based on this analysis, more than light alcohol consumption should be considered harmful as it not only increases the incidence of liver cancer but also increases liver disease and overall mortality.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: H.P., S.K.S., I.J., D.S.S., J.W.J. Data acquisition; data analysis and interpretation: H.P., S.K.S., J.W.J. Drafting of the manuscript; critical revision of the manuscript for important intellectual content: H.P., S.K.S. Statistical analysis: H.P., S.K.S. Study supervision: J.W.J., J.W.P.

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