Alcohol intake and risk of renal cell carcinoma: a meta-analysis of published case-control studies

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Abstract

Introduction: While some studies have indicated that alcohol intake is associated with a decreased risk of renal cell carcinoma, others have not. We conducted a meta-analysis of case-control studies to provide a quantitative assessment of the association between alcohol intake and the risk of renal cell carcinoma.
Material and methods: We identified studies by a literature search of PubMed and review of references of relevant articles. Both the fixed and random-effects models were used to obtain the summary risk estimates associated with the highest versus the lowest consumption categories depending on the heterogeneity of effects among studies. Dose-response meta-analysis was performed for studies reporting categorical risk estimates for a series of exposure levels.
Results: Fifteen studies were included in this meta-analysis. An inverse association between alcohol consumption and renal cell carcinoma was observed in both the overall alcohol intake group (OR 0.67, 95% CI 0.62-0.73) and subgroups stratified by sex, study design, geographical region, specific beverages and alcohol assessment. The dose-response meta-analysis showed that an increase in alcohol consumption of 12 g of ethanol per day was associated with a 5% statistically significant decreased risk of renal cell cancer.
Conclusions: High alcohol consumption exhibits a preventive effect for renal cell carcinoma in a dose-response manner. Further efforts should be made to clarify the underlying biological mechanisms.

Key words: alcohol drinking, alcoholic beverages, ethanol, kidney neoplasms, meta-analysis.

Introduction

Alcohol consumption is increasing in many countries and is an important cause of cancer worldwide [1]. A causal link has been established between alcohol consumption and cancers of the upper alimentary tract, liver, colorectum, and female breast [2]. Modifying alcohol consumption could be part of a prevention strategy of cancer through lifestyle changes.

Increasing incidence rates of renal cell carcinoma (RCC) have been reported worldwide [3]. Reasons for this phenomenon could be explained by both improvement in diagnostic workup and environmental factors. Smoking, obesity and hypertension are consistently associated with an increased risk of RCC [4-6], and the rising prevalences of obesity and hypertension likely have contributed to the upward cancer trends. The

association between alcohol consumption and the risk of RCC has also been widely investigated, yielding inconclusive results. Most of the earlier case-control [7-13] and cohort studies [14-18] have shown no association, while recent prospective cohort studies [19-23] found a reduced incidence of RCC in alcohol drinkers.

Recently, a pooled analysis of 12 cohort studies showed that moderate alcohol consumption was associated with a decreased risk of RCC [24]. The purpose of the present study was to re-examine the epidemiological evidence regarding the association between alcohol consumption and the risk of RCC by summarizing the results of published case-control studies, including dose-response meta-analyses, to quantify the strength of this association.

Material and methods

Selection of studies

We identified publications in PubMed using alcohol, renal cell carcinoma, renal cell cancer, kidney cancer and case-control as keywords. Hand searches were also performed via cited references from the identified articles and reviews. The criteria for inclusion were (i) case-control studies evaluating the relationship between alcohol consumption and RCC; (ii) published in English between 1980 and March 2010; (iii) providing odds ratio (OR) estimates and corresponding 95% confidence intervals (95% CI), or information allowing us to compute them. In studies with overlapping patients or controls, the latest study with the largest sample size was included.

Data extraction

For each study, data were extracted for the first author, year of publication, the country in which the study was conducted, study design, number of cases, number and range of categories of exposure, adjusted effects estimates, types of alcohol exposure, adjusted covariates and exposure assessment. We extracted the maximally adjusted ORs and CIs. When sex-stratified ORs were provided in a study, the ORs were independently involved in the overall meta-analysis.

Statistical analysis

We first quantified the associations of alcohol with RCC risk using meta-analysis of OR estimates associated with the highest versus the lowest category of alcohol intake using fixed- and random-effects models that included a term for heterogeneity. Second, subgroup analyses were performed according to study design (hospital-based or population-based case-control studies),

sex (men or women), geographical region (US/Canada or Europe), alcohol assessment (interview or questionnaire) and type of alcohol beverages (beer, wine or spirits).

For the dose-response meta-analysis, we estimated study-specific dose-response slopes from the correlated natural log of the ORs across categories of alcohol consumption using the method proposed by Greenland and Longnecker [25]. We converted all measures into grams of alcohol per day on the widely used estimation that a standard drink contains 12 g of alcohol regardless of alcohol type unless it was defined in the study population or the geographical area. The level of alcohol consumption was assigned from each study to these categories based on the calculated midpoint of alcohol consumption. When the highest category was open-ended, we assumed the width of the interval to be the same as in the preceding category.

We quantified the extent of heterogeneity using Q-test [26] and I^2 score [27] and statistical significance was considered when $p < 0.05$. Meta-regression analysis was used to explore the influence of study design, geographical region, alcohol assessment, and publication years in the heterogeneity. Publication bias was assessed using the tests of Egger [28] and Begg [29]. All statistical analyses were done with Stata Statistical Software, version 10.0.

Results

Characteristics of studies

We identified 24 articles [7-12, 30-47] that evaluated the association of RCC incidence and alcohol intake published between 1980 and March 2010. Four articles [10, 11, 42, 43] did not provide sufficient information to estimate a summary odds ratio and its 95% confidence intervals. One case-control study published results in two different articles [38, 44], while two studies published results in three different articles each [31, 37, 40, 46-48], and we extracted the latest and largest data sets from them [31, 37, 38, 40]. Of the fifteen selected studies, six were hospital-based case-control [7, 12, 30, 33, 36, 38], and nine were population-based case-control studies [8, 9, 31, 32, 34, 35, 37-40] (Table I), including a total of 9284 cases. Nine of these studies were conducted in the United States/Canada [7-9, 30, 32, 34, 37, 39-41], while 5 were in Europe [12, 33, 35, 36, 38] and 1 in multiple countries [31]. Nine articles reported the associations between consumption of specific alcoholic beverages (beer, wine or spirits) and the risk of RCC [9, 30, 31, 34-40]. Information on alcohol consumption was obtained by interview, self-administered questionnaire or both techniques.

Table I. Study characteristics of published cohort and case-control studies on alcohol intake and renal cell carcinoma

Authors, year	Study design	Country	Sex	Number of cases	Number of categories of exposure	Range of exposure	Specific alcohol beverages	Variables of adjustment	Alcohol assessment
Goodman et al., 1986	Hospital-based case-control study	US	M/W	267	2	Non-drinker vs. drinkers	Beer, wine, spirits	Sex, race, age, and time of admission	Interview
Brownson et al., 1988	Hospital-based case-control study	US	M/W	326	2	Non-drinker vs. drinkers	No	Age and smoking	Questionnaire
Maclure et al., 1990	Population-based case-control study	US	M/W	203	2	≤ 1 cup/week vs. ≥ 2 cups/week	Beer, wine, spirits	Age, sex, smoking	Interview
Benhamou et al., 1993	Hospital-based case-control study	France	M/W	196	2	Non-drinker vs. drinkers	No	Sex	Interview
Kreige et al., 1993	Population-based case-control study	Canada	M/W	518	3	The first quartile vs. the fourth quartile	No	Age, active cigarette smoking status, and combined Quetelet ndex	Questionnaire
Wolk et al., 1996	Population-based case-control study	Multiple countries	M/W	1185	5	< 1 vs. ≥ 15 drinks/week	Beer, wine, spirits	Age, sex, study centre, body mass index, smoking and total calories	Interview
Yuan et al., 1998	Population-based case-control study	US	M/W	1204	7	Non-drinker vs. ≥ 43 drinks/week	No	Level of education, body mass index, history of hypertension, number of cigarettes per day, current smoking status, total grams of analgesics consumed over lifetime and regular use of amphetamines	Interview
Parker et al., 2002	Population-based case-control study	US	M/W	406	3	Non-drinkers vs. > 35 g/week	Beer, wine, spirits	Age, pack-years of smoking, history of hypertension, history of bladder infection, family history of kidney cancer, exercise, consumption of red meat, and consumption of fruit	Interview and questionnaire
Mattioli et al., 2002	Hospital-based case-control study	Italy	M/W	324	6 (men) 3 (women)	Non-drinkers vs. > 48 g/day	No	Sex, age, place of birth, residence environment	Questionnaire

Table I. cont.

Authors, year	Study design	Country	Sex	Number of cases	Number of categories of exposure	Range of exposure	Specific alcohol beverages	Variables of adjustment	Alcohol assessment
Greving et al., 2007	Population-based case-control study	Sweden	M/W	855	6	Non-drinkers vs. ≥ 620 g/month	Light beer, medium-strong beer, strong beer, white wine, red wine, strong wine, hard liquor	Age, sex, BMI, and cigarette smoking	Questionnaire
Hsu et al., 2007	Hospital-based case-control study	Russia, Romania, Poland, and the Czech Republic	M/W	1065	4	Non-drinkers vs. ≥ 137.5 g/week	Beer, wine, spirits	Age, country, gender, tobacco pack-years of smoking, education, body mass index, hypertension medication use, and tertiles of total vegetable, total white meat, and total red meat consumption	Interview
Pelucchi et al., 2008	Hospital-based case-control study	Italy	M/W	1115	4	Non-drinkers vs. > 8 drinks/day	Beer, wine, spirits	Age, sex, study, study centre, education, smoking habits, body mass index and family history	Interview
Benedetti et al., 2009	Population-based case-control study	Canada	M/W	156	3	Non-drinkers vs. ≥ 7 drinks/week	Beer, wine, spirits	Age, log of the SES index, years of schooling, ethnicity, respondent status, fruit and vegetable consumption, and smoking	Interview
Brock et al., 2009	Population-based case-control study	US	M/W	323	4	Non-drinkers vs. > 2 drinks/day	No	Age, sex, proxy status, smoking, BMI at age 40, blood pressure and vegetable consumption	Questionnaire
Fu et al., 2008 and 2009	Population-based case-control study	Canada	M/W	1141	4	Non-drinkers vs. > 13.6 g/day	Beer, wine, spirits	10-year age group, province, education, body mass index, sex, pack-years of smoking, total consumption of vegetables and fruit, and total energy intake of meat, total consumption of vegetables and fruit, and total energy intake	Questionnaire

Among 15 case-control studies, seven reported significantly decreased risks of RCC in drinkers as compared with non-drinkers [30, 31, 34, 35, 37, 38, 40, 41], whereas seven studies found no association [7, 8, 12, 32, 33, 36, 41]. A study conducted by Maclure *et al.* [9] provided odds ratios for three alcoholic beverages but no data on overall alcohol intake.

Highest versus lowest

In Figure 1 we present the overall ORs of RCC comparing the highest versus the lowest alcohol consumption categories. When all these case-control studies were analysed together, we observed a statistically significant 30% reduced risk of RCC. In analysis by study design, population-based case-control studies (OR 0.65, 95% CI 0.52-0.79) reported a lower risk of RCC in drinkers compared to hospital-based case-control studies (OR 0.78, 95% CI 0.65-0.91). The results were heterogeneous across case-control studies (P_{Het} = 0.02, I^2 = 48.2%). There was no evidence of heterogeneity among hospital-based case-control studies, but some evidence in population-based studies.

In Table II, we assessed associations separately for sex (men or women), geographical region

(US/Canada or Europe) and alcohol assessment (interview or questionnaire). The OR estimates from subgroup analyses varied little, showing that alcohol consumption was consistently associated with a decreased risk of RCC. In analysis by specific beverages (Figure 2), we also found a significantly decreased risk of renal cancer for intake of beer, wine and spirits. There was no evidence of significant publication bias either with Egger's or Begg's test in any subgroup.

Dose-response analysis

Nine studies [32-41] were included in the dose-response analysis of the association between alcohol intake and risk of RCC. We excluded 4 studies with only 2 categories of alcohol consumption [7, 9, 12, 30] and one publication that did not provide the number of cases and controls, and one without exact dosage limits of alcohol for each stratum. Figure 3 shows the dose-response relationship between risk of RCC and alcohol consumption. There was a 5% (95% CI 3%-7%) decrease of risk of RCC for an increase of 12 g alcohol intake (approximately 1 drink) per day. The result was heterogeneous (p < 0.01).
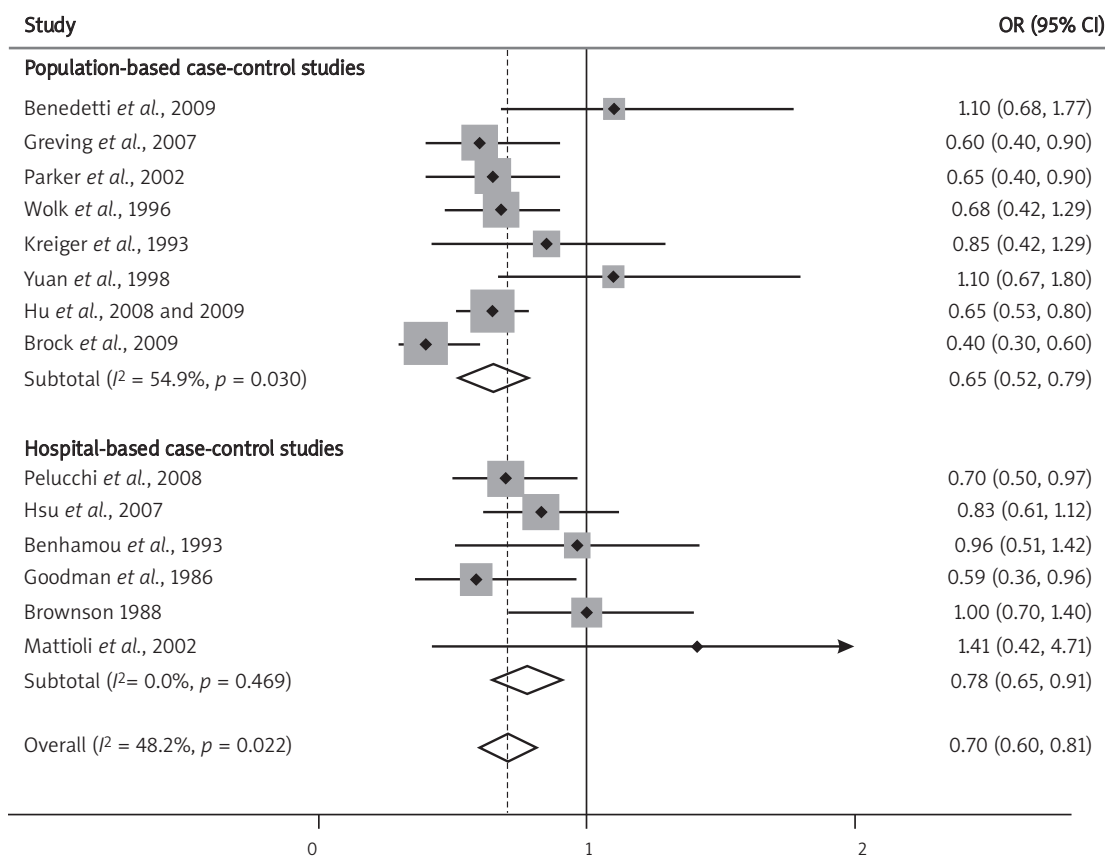
Study		OR (95% CI)
Population-based case-control studies		
Benedetti *et al.*, 2009		1.10 (0.68, 1.77)
Greving *et al.*, 2007		0.60 (0.40, 0.90)
Parker *et al.*, 2002		0.65 (0.40, 0.90)
Wolk *et al.*, 1996		0.68 (0.42, 1.29)
Kreiger *et al.*, 1993		0.85 (0.42, 1.29)
Yuan *et al.*, 1998		1.10 (0.67, 1.80)
Hu *et al.*, 2008 and 2009		0.65 (0.53, 0.80)
Brock *et al.*, 2009		0.40 (0.30, 0.60)
Subtotal (*I*² = 54.9%, *p* = 0.030)		0.65 (0.52, 0.79)
Hospital-based case-control studies		
Pelucchi *et al.*, 2008		0.70 (0.50, 0.97)
Hsu *et al.*, 2007		0.83 (0.61, 1.12)
Benhamou *et al.*, 1993		0.96 (0.51, 1.42)
Goodman *et al.*, 1986		0.59 (0.36, 0.96)
Brownson 1988		1.00 (0.70, 1.40)
Mattioli *et al.*, 2002		1.41 (0.42, 4.71)
Subtotal (*I*² = 0.0%, *p* = 0.469)		0.78 (0.65, 0.91)
Overall (*I*² = 48.2%, *p* = 0.022)		0.70 (0.60, 0.81)

Figure 1. A forest plot showing risk estimates from case-control studies estimating the association between overall alcohol consumption and risk of renal cell carcinoma

Table II. Summary of pooled risk ratios of renal cell carcinoma by sex, geographical region, type of alcoholic beverages, body mass index, and smoking status

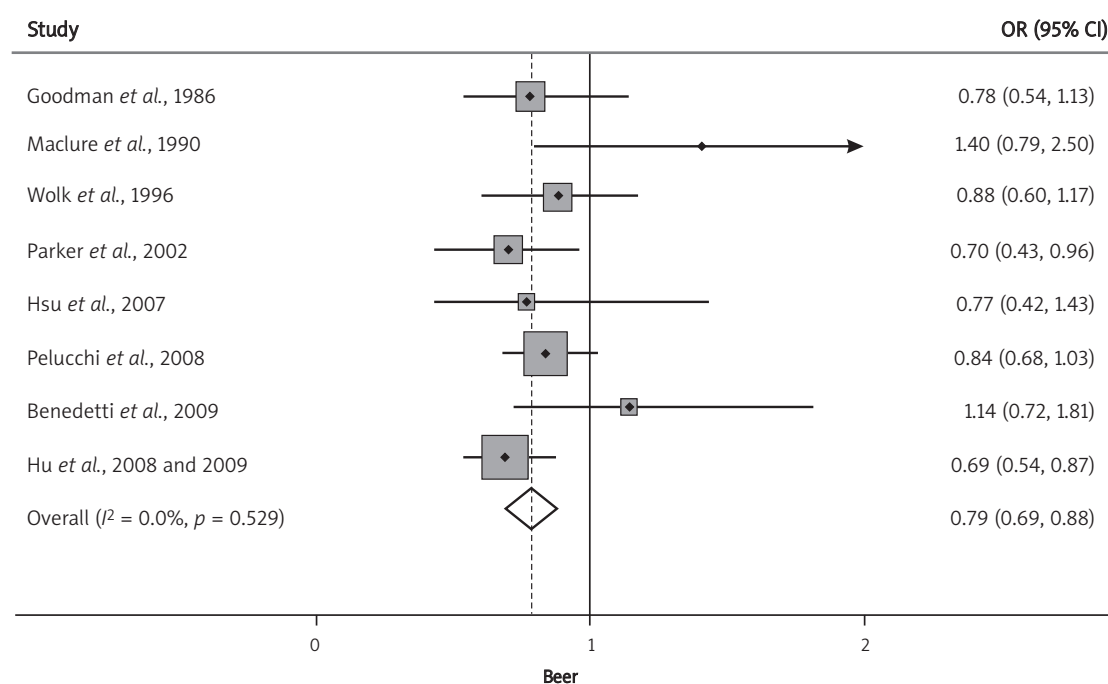| Subgroup	Number of studies	Pooled OR (95% CI)	P_heterogeneity (I^2 score)	Egger's test Value of p	Begg's test Value of p
All studies	14[7, 8, 12, 13, 30-37, 39-41]	0.70 (0.60, 0.81)	0.02 (48.2%)	0.17	0.32
Sex					
Men	9[7, 8, 12, 30, 31, 33, 34, 37, 38]	0.80 (0.69, 0.91)	0.47 (0)	0.66	0.60
Women	9[7, 8, 12, 30, 31, 33, 34, 37, 38]	0.61 (0.47, 0.76)	0.56 (0)	0.49	1
Geographical region					
Europe	5[12, 33, 35, 36, 38]	0.73 (0.60, 0.87)	0.55 (0)	0.38	0.46
US/Canada	8[7, 8, 30, 32, 34, 37, 39-41]	0.71 (0.54, 0.87)	0.01 (64.8%)	0.40	0.62
Alcohol assessment					
Interview	7[12, 30-32, 36, 38, 39]	0.75 (0.64, 0.87)	0.43 (0)	0.30	0.76
Questionnaire	6[7, 8, 33, 35, 40, 41]	0.62 (0.44, 0.79)	0.02 (64.6%)	0.57	0.57

Meta-regression analysis

We also performed meta-regression analysis to explore the influence of publication year, geographical region, study design, and method of alcohol assessment on the heterogeneity. However, none of the above was identified as a possible source of heterogeneity among all the included studies.

Discussion

In this meta-analysis we have observed an inverse association between alcohol intake and the risk of RCC. This finding is consistent with the previous pooled analysis by Lee *et al.* [24], which used the patient-level data and provided more convincing results and deeper analysis. However, in that study the case-control studies were not included. We included all the case-control studies so far for a total of 9,284 RCC cases. Our results showed that case-control studies, which may be subject to selection and recall bias, also provided support for a negative relationship between alcohol consumption and RCC. There was no evidence of heterogeneity among studies included in this analysis. Furthermore, we performed a meta-analysis of dose-response relationship between alcohol intake and the risk of RCC. An increase in

Study		OR (95% CI)
Goodman *et al.*, 1986		0.78 (0.54, 1.13)
Maclure *et al.*, 1990		1.40 (0.79, 2.50)
Wolk *et al.*, 1996		0.88 (0.60, 1.17)
Parker *et al.*, 2002		0.70 (0.43, 0.96)
Hsu *et al.*, 2007		0.77 (0.42, 1.43)
Pelucchi *et al.*, 2008		0.84 (0.68, 1.03)
Benedetti *et al.*, 2009		1.14 (0.72, 1.81)
Hu *et al.*, 2008 and 2009		0.69 (0.54, 0.87)
Overall (I^2 = 0.0%, p = 0.529)		0.79 (0.69, 0.88)

Beer

Figure 2. Forest plots showing the odds ratio of each study and the pooled odds ratios for specific alcoholic beverages

Study		OR (95% CI)
Goodman *et al.*, 1986		0.66 (0.45, 0.96)
Maclure *et al.*, 1990		0.95 (0.30, 3.00)
Wolk *et al.*, 1996		0.33 (0.18, 0.47)
Parker *et al.*, 2002		1.06 (0.58, 1.54)
Hsu *et al.*, 2007		1.05 (0.51, 2.08)
Pelucchi *et al.*, 2008		0.50 (0.27, 0.92)
Benedetti *et al.*, 2009		0.91 (0.52, 1.59)
Hu *et al.*, 2008 and 2009		0.73 (0.55, 0.96)
Overall ($I^2 = 66.0\%$, $p = 0.004$)		0.67 (0.46, 0.88)

Wine

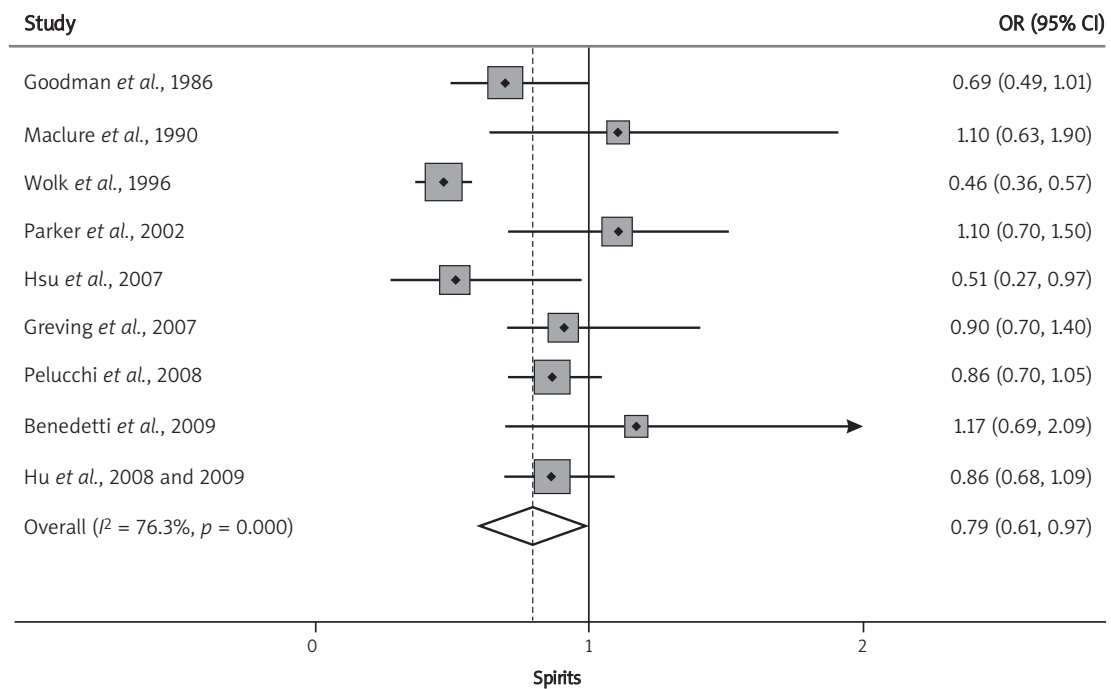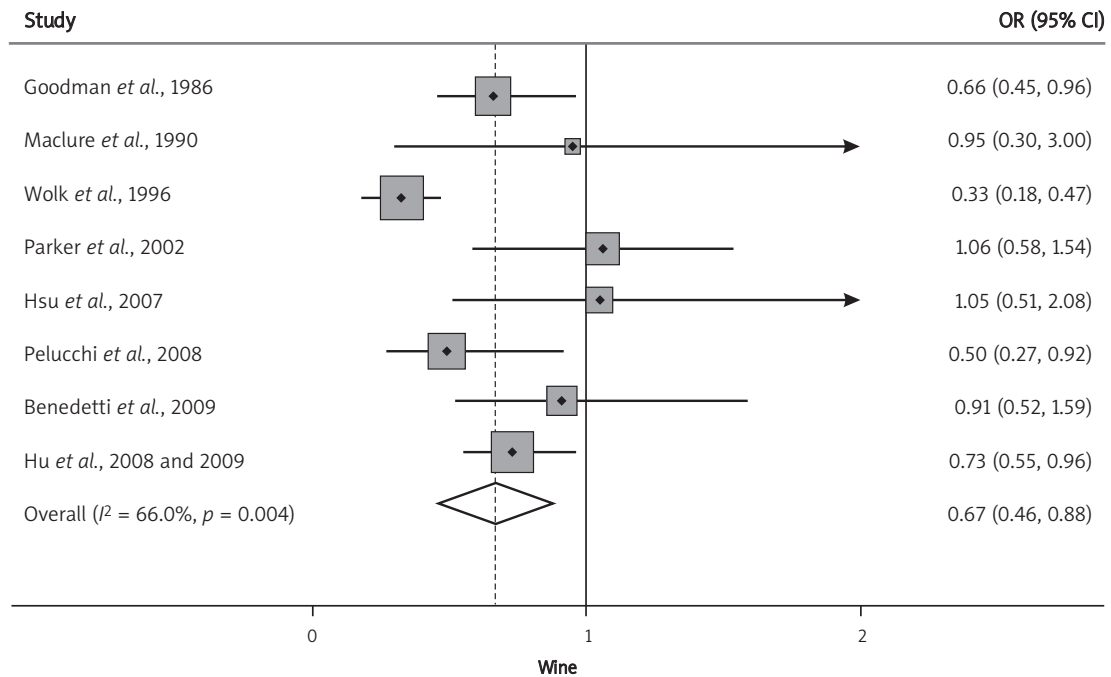| Study		OR (95% CI)
Goodman *et al.*, 1986		0.69 (0.49, 1.01)
Maclure *et al.*, 1990		1.10 (0.63, 1.90)
Wolk *et al.*, 1996		0.46 (0.36, 0.57)
Parker *et al.*, 2002		1.10 (0.70, 1.50)
Hsu *et al.*, 2007		0.51 (0.27, 0.97)
Greving *et al.*, 2007		0.90 (0.70, 1.40)
Pelucchi *et al.*, 2008		0.86 (0.70, 1.05)
Benedetti *et al.*, 2009		1.17 (0.69, 2.09)
Hu *et al.*, 2008 and 2009		0.86 (0.68, 1.09)
Overall ($I^2 = 76.3\%$, $p = 0.000$)		0.79 (0.61, 0.97)

Spirits

Figure 2. Cont.

alcohol consumption of 12 g of ethanol per day was statistically significantly associated with a 5% decrease in risk of RCC.

Our results from subgroup analyses suggested that an inverse relationship between alcohol intake and risk of RCC was seen in both men and women, and a stronger association was observed in women compared to men, although the difference in risk estimate was not statistically significant. This gender-specific association may suggest an underlying hormonal mechanism. There is some evidence that oestrogens increase risk of RCC [49, 50]. However, the data regarding effects of alcohol on oestrogen levels are inconsistent [51, 52], and recent studies suggest that alcohol's favourable effect does not appear to involve hormonal

mechanisms [53]. The summarized OR estimates were not statistically different across different alcoholic beverage types, indicating that the negative association is attributable to ethanol intake itself rather than to a specific beverage, though certain ingredients in beer and wine, such as xanthohumol and resveratrol, have been demonstrated to possess cancer chemopreventive properties [54, 55]. Our results also suggest that the association between alcohol consumption and RCC was not modified by different geographical regions or methods of alcohol assessment.

Several biological mechanisms for the negative relationship of alcohol consumption with the development of RCC have been proposed. One potential explanation is that the diuretic effect of alcoholic beverages may reduce the concentration of carcinogens and decrease the time that carcinogens stay in the kidney. This hypothesis could be verified by investigating the relationship of total fluid intake and RCC. However, a pooled analysis of 2 cohorts detected no association and a population-based case-control study found a positive relationship between total fluid intake and risk of RCC [22, 40]. Enhanced insulin sensitivity might be a mechanism by which alcohol intake exerts its protective effect against RCC. Obesity and diabetes are risk factors for RCC [56, 57], and light to moderate alcohol intake is associated with improved insulin sensitivity [58]; thus it is possible that insulin is a potential intermediate component in the association between alcohol consumption and RCC. It would be informative to determine whether the protective effect exists in patients with different insulin sensitivity levels, and well-designed cohort studies are needed to further clarify the consistency within diabetic and non-diabetic subjects.

Several potential limitations of our study need to be considered. First, as this meta-analysis is based on case-control studies, the possibility of bias and uncontrolled or residual confounding factors cannot be excluded, although we extracted the maximally adjusted ORs, which have been controlled for variables that might be related to RCC in most of the studies. However, different studies may have adjusted for different covariates, which could probably bias the results. Second, we did not attempt to uncover unpublished observations, which could bring a publication bias, even though no significant evidence of a publication bias was observed in Egger's and Begg's test. Third, both volume of alcohol consumption and patterns of drinking have been shown to influence the alcohol-related burden of disease, while most of the included studies did not provide data on alcohol intake over time or life drinking patterns.
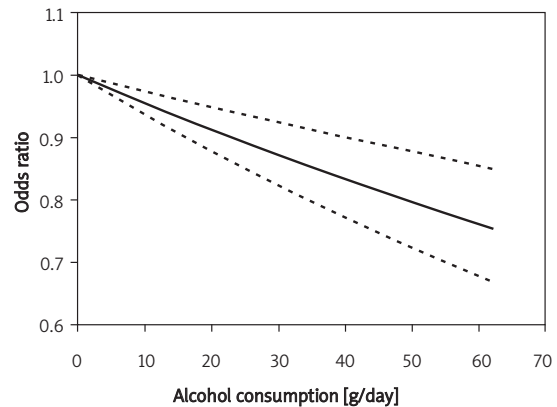

Figure 3. Odds ratio for renal cell carcinoma by doses of alcohol intake based on the results of the dose-response meta-analyses. Solid line represents the estimated odds ratios and the dotted lines represent the 95% confidence intervals

Consequently, we did not have sufficient data to evaluate the risk of RCC associated with these other dimensions of alcohol intake.

In conclusion, this study applied a detailed meta-analytic approach for combining OR estimates from case-control studies on the relationship between RCC incidence and alcohol consumption. We found that high alcohol consumption was consistently associated with a lower risk of renal cell cancer when stratified by sex, study design, geographical region and alcoholic types, and decreased risk for RCC in a dose-response manner. Future research to determine the likely biological mechanism is warranted.

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