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Alcohol intake and renal cell cancer risk: a meta-analysis

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BACKGROUND: An inverse association between alcoholic beverage intake and risk of renal cell cancer has been suggested in recent studies.

METHODS: We examined the association between alcoholic beverages and renal cell cancer risk in a meta-analysis. We identified relevant studies by searching the database of PubMed, EMBASE, and MEDLINE published through August 2011. We combined the study-specific relative risks (RRs) using a random-effects model.

RESULTS: A total of 20 case–control studies, 3 cohort studies, and 1 pooled analysis of cohort studies were included in the meta-analysis. We observed that alcoholic beverage intake was associated with a lower risk of renal cell cancer in combined analysis of case–control and cohort studies; for total alcoholic beverage intake, combined RRs (95% confidence intervals) comparing top with bottom categories were 0.76 (0.68–0.85) in case–control studies, and 0.71 (0.63–0.78) in cohort studies (*P* for difference by study design = 0.02). The inverse associations were observed for both men and women and for each specific type alcoholic beverage (beer, wine, and liquor). Also, we found that one drink per day of alcoholic beverage conferred the reduction in renal cell cancer risk, but further drinking above that level did not add benefit.

CONCLUSION: The findings from our meta-analysis support the hypothesis that alcoholic beverage intake is inversely associated with a lower risk of renal cell cancer, with moderate consumption conferring the protection and higher consumption conferring no additional benefits.

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Incidence of renal cell cancer, the major type of kidney cancer, has increased worldwide (Mathew *et al*, 2002; Chow *et al*, 2010). Although smoking, obesity, and hypertension are known to be well-established risk factors for renal cell cancer (Chow *et al*, 2010), dietary modifiable risk factors for renal cell cancer have not been well defined. Alcoholic beverage has been widely consumed and its global consumption has been increasing in the last decades (World Health Organization, 2002). Merits and demerits of alcoholic beverage intake have been long explored because of its benefit for cardiovascular disease (Corrao *et al*, 2000; Fillmore *et al*, 2007; Ronksley *et al*, 2011) or carcinogenic effect (Kan *et al*, 2011). An International Review panel, sponsored by the World Cancer Research Fund (WCRF) and American Institute for Cancer Research, reported that alcoholic beverage intake increased the risk of cancers of the oral cavity, larynx, pharynx, oesophagus, liver, female breast, and colorectum (World Cancer Research Fund & American Institute for Cancer Research, 2007), but there was a limited evidence about the association between alcoholic beverage intake and kidney cancer.

As the WCRF reported the summary, further studies have examined the association between alcoholic beverage intake and kidney cancer (Greving *et al*, 2007; Hsu *et al*, 2007; Lee *et al*, 2007; Ozasa, 2007; Setiawan *et al*, 2007; Hu *et al*, 2008; Pelucchi *et al*, 2008; Kim *et al*, 2010; Lew *et al*, 2011; Allen *et al*, 2011). A few prospective studies and a pooled analysis of 12 prospective studies found an inverse association for alcoholic beverage intake. However, the associations for men and women were not consistent across studies, partly because of small sample size. Also, there was little evidence whether different types of specific alcoholic beverage including beer, wine, and liquor, confer similar effects.

To elucidate the role of alcoholic beverage intake in renal cell cancer, we investigated the association of total alcoholic beverage and specific alcoholic beverage intake in relation to risk of renal cell cancer in a comprehensive meta-analysis of cohort and case–control studies.

MATERIALS AND METHODS

Search strategy

We identified studies examining the association between alcoholic beverage intake and renal cell cancer by searching the database of PubMed, EMBASE, and MEDLINE published through August 2011. We used the following terms for the PubMed search: ((‘alcohol’ or ‘wine’ or ‘beer’ or ‘liquor’ or ‘ethanol’ or ‘spirit’) and (‘renal cell carcinoma’ or ‘kidney cancer’ or ‘renal cell cancer’ or ‘renal adenocarcinoma’ or ‘kidney adenocarcinoma’)). For the EMBASE and MEDLINE, we used the terms of (alcohol OR wine OR beer OR liquor OR ethanol) AND (carcinoma OR kidney cancer OR

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cancer OR kidney adenocarcinoma). We included human studies published in English language articles. In addition, we examined the references from the retrieved articles. We confirmed this meta-analysis according to the Meta-analysis of Observational Studies in Epidemiology guidelines (Stroup *et al*, 2000).

Selection criteria

Two authors (DY Song and S Song) independently assessed the eligibility criteria as follows; (1) case–control or cohort design, published as full-text manuscripts; (2) the exposure of interest was total alcoholic beverage or specific alcoholic beverage intake; (3) the endpoint of interest was renal cell, kidney cancer, renal, or kidney adenocarcinoma; and (4) relative risk (RR) estimates with 95% confidence intervals (CIs) for every category of alcoholic beverage intake or per unit increase in alcoholic beverage intake were reported. For one study (Wynder *et al*, 1974) that had not examined RRs and 95% CI, we calculated RRs and 95% CI based on the number of cases and controls. When there were multiple publications from the same study population, we only included the study that combined independent studies, examined alcoholic beverage intake as the main interest of exposure, or the study with the largest number of cases or more follow-up years. We did not include two studies (Ozasa, 2007; Kim *et al*, 2010) in which kidney cancer mortality was endpoint because mortality reflects both incidence and survival.

Data extraction

We extracted from each article the following information: the first author's last name, publication year, country in which the study was performed, study design, study period, participants' age and sex, endpoint, exposure assessment, when available, and the number of cases and controls or person–years for each category of alcoholic beverage intake and covariates for adjustment in the analysis. When several estimates were reported, we used the estimates adjusted for the most number of covariates. The authors were contacted for additional information, when necessary. If studies reported the estimate of only specific type of alcoholic beverage (McLaughlin *et al*, 1984; Asal *et al*, 1988), we still included those estimates into our meta-analysis of total alcoholic beverage. For one study that reported different types of beer and wine (Greving *et al*, 2007), we used the estimate of strong beer and strong wine when we analysed the specific type of alcoholic beverages. The quality of each study was assessed by two independent authors (DY Song and S Song) using the Newcastle–Ottawa Scale (Wells *et al*, 2011) and then averaged. Discrepancies in >1 score between two authors were resolved by consensus.

Statistical analysis

We summarised the estimates across the studies using a random-effects model (DerSimonian and Laird, 1986). We compute the combined RRs and 95% CIs from the estimates reported in each study. We also examined the non-linearity of the relationship using restricted cubic splines (Durrleman and Simon, 1989; Greenland and Longnecker, 1992; Orsini *et al*, 2012) for studies that provided the number of participants or person–years and two or greater categories of alcoholic beverage intake or ethanol intake. As a result, we included 10 case–control (Wynder *et al*, 1974; McLaughlin *et al*, 1984; Asal *et al*, 1988; Yuan *et al*, 1998; Mattioli *et al*, 2002; Parker *et al*, 2002; Greving *et al*, 2007; Hsu *et al*, 2007; Hu *et al*, 2008; Pelucchi *et al*, 2008), 3 cohort (Setiawan *et al*, 2007; Allen *et al*, 2011; Lew *et al*, 2011), and 1 pooled analysis studies (Lee *et al*, 2007) in the spline analysis. To test for non-linearity, we compared the model fit including only the linear term with the model fit including the linear and cubic spline terms using the likelihood ratio test. We used the midpoint between the upper and lower levels in the categories. If the upper level for the highest category was open-ended, we assumed that the level had the same amplitude as the neighbourhood categories.

For the meta-analysis of specific beverages, we rescaled alcoholic beverage into gram (g) of ethanol per day using the conversion factors: 1 drink = 15 g, 11.3 g of ethanol for a 4-oz (118 ml) glass of wine, 12.8 g for 12-oz (354 ml) one glass, bottle, or can for beer, and 14.0 g for one measure (45 ml) for liquor. We converted servings per day of alcoholic beverage to 15 g per day of ethanol.

A meta-regression analysis was used to investigate whether the association between alcoholic beverage and risk of renal cell cancer differed by study design (case–control and cohort studies), sex, smoking adjustment (yes, no), or hypertension adjustment (yes, no). Heterogeneity among studies was evaluated by using Q and I^2 (Higgins and Thompson, 2002) statistics. The Egger's regression asymmetry test was used to assess the publication bias (Egger *et al*, 1997). All analyses were conducted using Stata, version 10.1 (Stata Corp., College Station, TX, USA) and SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA). $P<0.05$ (two-sided) was considered statistically significant.

RESULTS

A total of 252 articles were extracted by querying PubMed, EMBASE, and MEDLINE through August 2011 (Figure 1). In all, 174 articles did not examine the association between alcoholic beverage intake and renal cell cancer, 40 were reviews, and 3 were letter, comment, or editorial. Out of 35 articles that examined the association between alcoholic beverage intake and renal cell cancer, 18 were excluded because of data overlap ($n=15$), the absence of RRs ($n=1$), assessment of alcoholism as exposure ($n=1$), and kidney cancer death ($n=1$). Seven additional studies were identified from the references of the retrieved articles. As a result, 20 case–control studies, 3 cohort studies, and 1 pooled analysis of cohort studies were included in this meta-analysis.

Study characteristics such as country, study design, dates, age, alcohol assessment, unit of alcohol, amount of intake in the beverage for top and bottom categories, outcome/endpoint, number of cases or controls or cohort size, and potential confounders controlled are presented (Tables 1 and 2). A total of 13 819 incident renal cell cancer cases and 1537 incident kidney cancer cases were included in this meta-analysis. Three of twenty-four studies examined incidence of kidney cancer (Wynder *et al*, 1974; Hsu *et al*, 2007; Benedetti *et al*, 2009) and the others examined incidence of renal cell cancer (McLaughlin *et al*, 1984; Goodman *et al*, 1986; Asal *et al*, 1988; Brownson, 1988; Maclure and Willett, 1990; Benhamou *et al*, 1993; Kreiger *et al*, 1993; Hiatt *et al*, 1994; Muscat *et al*, 1995; Wolk *et al*, 1996; Boeing *et al*, 1997; Yuan *et al*, 1998; Mattioli *et al*, 2002; Parker *et al*, 2002; Greving *et al*, 2007; Lee *et al*, 2007; Setiawan *et al*, 2007; Hu *et al*, 2008; Pelucchi *et al*, 2008; Allen *et al*, 2011; Lew *et al*, 2011). All studies were conducted in the North America and Europe. The alcoholic beverage intake of participations in each study was assessed by using food frequency questionnaire (FFQ), interview, or self-administered questionnaire. The estimates for both men and women were reported in 17 studies. Specific alcoholic beverages were examined in 15 studies. A pooled analysis combined the original data from 12 prospective studies (Lee *et al*, 2007) conducted in the USA, Finland, Canada, the Netherlands, and Sweden and a multi-centre case–control study (Wolk *et al*, 1996) combined 4 case–control studies conducted in the Australia, Denmark, Sweden, and USA. Out of 24 studies, all studies adjusted for age, and 14 studies further adjusted for obesity. Smoking status was adjusted for 19 studies. Hypertension status was adjusted for seven studies. Nineteen of twenty-two studies that reported the amount of alcoholic beverage or ethanol as an exposure considered

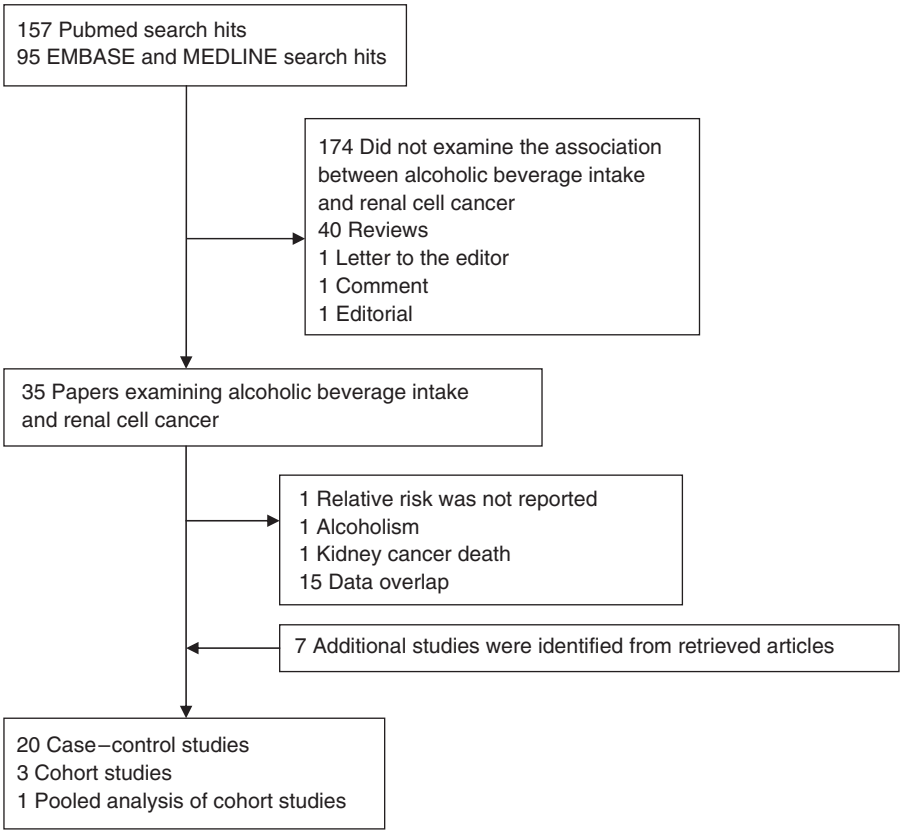

Figure 1 Flowchart of publication selection for the meta-analysis of the association between alcoholic beverage intake and renal cell cancer.

never or non-drinker as the reference and the other 3 studies selected the reference group of 0 or 1 drinks per day (Allen *et al*, 2011), low to 1 cup per week (Maclure and Willett, 1990), or <1 drink per week (Wolk *et al*, 1996). The ranges in the top category across studies were from 5 to 120 g per day.

We found a decreased risk of renal cell cancer with alcoholic beverage intake; combined RR (95% CI) comparing top with bottom category was 0.73 (0.67–0.79) for total alcoholic beverage intake (Figure 2). There was no significant heterogeneity across the studies (P for heterogeneity $= 0.34$). A stronger inverse association was observed in cohort studies compared with case–control studies (P for difference $= 0.02$); combined RRs (95% CIs) were 0.76 (0.68–0.85) for case–control studies and 0.71 (0.63–0.78) for cohort studies. When we examined the association by study period (before or after 2000), we found a stronger inverse association for recent studies; comparing top with bottom category, RRs were 0.85 (95% CI, 0.72–0.98; P for heterogeneity $= 0.32$) for earlier studies and 0.70 (95% CI, 0.64–0.76; P for heterogeneity $= 0.63$) for recent studies.

When we examined specific alcoholic beverages (Table 3), we found that intakes of all three beverage types significantly lowered risk of renal cell cancer. Notably, these inverse associations for each type of alcoholic beverage were observed in both case–control and cohort studies, and the magnitude of the association was similar across three types of alcoholic beverages. There was no evidence of publication bias based on the Egger's test for beer, wine, or liquor ($P > 0.19$).

When we examined whether the associations differed by gender, adjustment for smoking status, or adjustment for hypertension status, the associations did not vary by these factors (Table 4).

When we examined for non-linearity of the association using the regression cubic spline, we observed a significant non-linearity for overall association between ethanol intake and renal cell cancer. The degree of decline in the risk of renal cell cancer appeared to be attenuated above ~ 15 g per day (P for non-linearity < 0.001) (Figure 3A). We also found a significant or suggestive non-linearity for case–control and cohort studies (P-values for non-linearity $= 0.03$ for case–control studies and 0.10 for cohort studies; Figures 3B and C).

DISCUSSION

We observed that alcoholic beverage intake was inversely associated with risk of renal cell cancer in this comprehensive meta-analysis. The inverse association was stronger for cohort studies compared with case–control studies. The inverse associations were consistent across specific alcoholic beverages, suggesting that ethanol per se is most likely the responsible factor. We also found that alcoholic beverage intake lowered risk of renal cell cancer for both men and women. Notably, our spline analysis showed that ~ 15 g per day of ethanol intake could pose a decrease in renal cell cancer risk, but additional drinking did not confer further benefit in the prevention of renal cell cancer.

The magnitude of the association was stronger for cohort studies than case–control studies. Recall bias or selection bias in case–control studies may attenuate the association between alcoholic beverage intake and renal cell cancer risk because alcoholic beverage could be overestimated among cases or underestimated among controls. A stronger inverse association for recent studies compared with earlier studies that we observed also could be partly explained by recall or selection bias because all the studies published before 2000 were case–control studies. Also, our meta-analysis of specific type of alcoholic beverage supports the evidence that the benefits associated with alcoholic beverage intake were similar for beer, wine, and liquor.

Table 1 Characteristics of case–control studies include in meta-analysis of renal cell cancer

First author, country (reference)	Study period	Age (years)	Alcohol assess-ment	Unit of alcohol	Top *vs* bottom	Outcome/ endpoint	No. of cases	No. of controls or cohort size	Study quality[a]	Potential confounders
Wynder, USA (Wynder *et al*, 1974)	1965–1973	MF: 20–79, range	Interview	Unit per day	Total alcohol M: ⩾7 unit per day *vs* none-occasional F: ⩾3 unit per day *vs* none-occasional	Incidence of kidney adenocarci-noma	M: 129 F: 73	M: 256 F: 138	6	Age, sex, race, hospital, time of interview
McLaughlin, USA (McLaughlin *et al*, 1984)	1974–1979	M: 62, mean F: 66, mean	Interview	Bottles per week	Beer M: ⩾20 bottles per week *vs* never F: ⩾20 bottles per week *vs* never	Incidence of renal cell carcinoma	M: 307 F: 180	M: 428 F: 268	6	Age, cigarette smoking, BMI, phenacetin use, ethnicity, kidney infection, kidney stones, coffee, tea, beer and meat consumption, exposure to petroleum, tar, and pitch products
Goodman, USA (Goodman *et al*, 1986)	1977–1983	MF: 20–80, range	Interview	N/A	Total alcohol M: ever *vs* never F: ever *vs* never	Incidence of renal cell carcinoma	M: 182 F: 76	M: 182 F: 76	6.5	Age, sex, race, hospital, time of admission
Brownson, USA (Brownson, 1988)	1984–1986	N/A	N/A	N/A	Total alcohol M: ever drank *vs* never drank F: ever drank *vs* never drank	Incidence of renal cell carcinoma	M: 205 F: 121	M: 615 F: 363	4.5	Age, smoking, sex
Asal, USA (Asal *et al*, 1988)	1981–1984	MF: ⩾50 was >70% in controls	Interview	Wine: glasses per week Liquor: N/A	Wine M: >4 glasses per week *vs* never F: >3 glasses per week *vs* never Liquor M: use *vs* non-use	Incidence of renal cell carcinoma	M: 209 F: 106	Hospital M: 208 Hospital F: 105 Population M: 195 Population F: 141	6	Age, sex, race, hospital time of interview, weight
Maclure, USA (Maclure and Willett, 1990)	1976–1983	MF: ⩾30	Interview	Cups per day	Beer, wine, and liquor MF: high intake (⩾2 cups per day) *vs* low intake (⩽1cup per week)	Incidence of renal adenocarci-noma	M: 135 F: 68	M: 401 F: 204	4.5	Age, sex, precinct of residence, smoking, energy
Benhamou, France (Benhamou *et al*, 1993)	1987–1991	Case M: 61.7, mean Case F: 61.3, mean Control M: 62.8, mean Control F: 62.5, mean	Question-naire	g per day	Total alcohol M: high *vs* low F: high *vs* low	Incidence of renal cell carcinoma	M: 138 F: 58	M: 235 F: 112	5	Age, sex, hospital and interviewer
Kreiger, Canada (Kreiger *et al*, 1993)	1986–1987	MF: 25–69, range	Question-naire	N/A	Total alcohol M: high *vs* low F: high *vs* low	Incidence of renal cell carcinoma	M: 252 F: 167	M: 543 F: 592	5.5	Age, sex, geographic region of residence, active cigarette smoking status, BMI
Hiatt, USA (Hiatt *et al*, 1994)	1964–1989	Case: 50.7, mean	N/A	N/A	Total alcohol M: ever *vs* never F: ever *vs* never	Incidence of renal cell carcinoma	M: 165 F: 87	M: 166 F: 88	5	Gender, year of multiphasic health check-up (MHC), age at MHC ± 1 year
Muscat, USA (Muscat *et al*, 1995)	1977–1993	Case M: 58.7, mean Case F: 59.3, mean Control M: 58.2, mean Control F: 59.4, mean	Question-naire	Oz per day	Beer M: >7 oz per day *vs* never/occasionally F: ⩾1 oz per day *vs* never/occasionally Wine M: >4 oz per day *vs* never/occasionally F: >4 oz per day *vs* never/occasionally Liquor M: ⩾7 oz per day *vs* never/occasionally F: ⩾1 oz per day *vs* never/occasionally	Incidence of renal cell carcinoma	M: 543 F: 245	M: 476 F: 244	7	Age, education, and years of smoking, race, year of diagnosis
Wolk, Australia, Denmark, Sweden, and USA (Wolk *et al*, 1996)[b]	1989–1991	Case M: 62, mean Case F: 63, mean Control M: 62, mean Control F: 63, mean	Interviews	Total alcohol: drinks per week Beer, wine, and liquor: glasses per week	Total alcohol M: ⩾15 drinks per week *vs* <1 drinks per week F: ⩾10 drinks per week *vs* <1 drinks per week Beer M: ⩾6.3 glasses per week *vs* none F: ⩾1.3 glasses per week *vs* none Wine	Incidence of renal cell cancer	M: 698 F: 487	M: 915 F: 611	6	Age, sex, study centre, BMI, smoking, total calories

Epidemiology

Table 1 (*Continued*)

First author, country (reference)	Study period	Age (years)	Alcohol assess-ment	Unit of alcohol	Top *vs* bottom	Outcome/ endpoint	No. of cases	No. of controls or cohort size	Study quality[a]	Potential confounders
					M: ⩾1.3 glasses per week *vs* none F: ⩾3.0 glasses per week *vs* none Liquor M: ⩾5.5 glasses per week *vs* none F: ⩾3.0 glasses per week *vs* none					
Boeing, Germany (Boeing *et al*, 1997)	1989–1991	N/A	Interview	N/A	Total alcohol, beer, wine, and liquor MF: highest *vs* none	Incidence of renal cell carcinoma	M: 185 F: 92	M: 192 F: 94	7	Age, gender, educational status, tobacco smoking
Yuan, USA (Yuan *et al*, 1998)	1986–1994	MF: 25–74, range	Question-naire	Drinks per week	Total alcohol MF: ⩾43 drinks per week *vs* none	Incidence of renal cell carcinoma	MF: 1203	MF: 1201	6	Sex, date of birth (within 5 years), ethnicity, neighbourhood of residence, education and BMI, history of hypertension, number of cigarettes per day, current smoking status, total grams of analgesics consumed over lifetime, regular use of amphetamines
Parker, USA (Parker *et al*, 2002)	1986–1989	Case: 68, mean Control: 64, mean	FFQ	Total alcohol: g per week Beer: 12-ounce can per week Wine: 8-ounce glass per week Liquor: 1-ounce shot per week	Total alcohol M: >35 g per week *vs* none F: >35 g per week *vs* none Beer M: >1 *vs* non-drinker of beer F: >1 *vs* non-drinker of beer Wine M: >0.5 *vs* non-drinker of wine F: >0.5 *vs* non-drinker of wine Liquor M: >1 *vs* non-drinker of liquor F: >1 *vs* non-drinker of liquor	Incidence of renal cell carcinoma	M: 261 F: 145	M: 1598 F: 831	6	Age, pack-years of smoking, history of hypertension, history of bladder infection, family history of kidney cancer, exercise, consumption of red meat, consumption of fruit (men) Age, pack-years of smoking, history of hypertension, BMI, family history of kidney cancer, consumption of red meat, fruit and vegetables (women)
Mattioli, Italy (Mattioli *et al*, 2002)	1987–1994	All	Question-naire	g per day	Total alcohol M: >48 g per day *vs* 0 g per day F: >12 g per day *vs* 0 g per day	Incidence of renal cell cancer	M: 165 F: 52	M: 165 F: 52	7	Age, gender, birthplace, residence, BMI, smoking, consumption of coffee, phenacetin and/or of diuretics, and meat
Hsu, Russia, Romania, Poland, and Czech Republic (Hsu *et al*, 2007)	1999–2003	MF: 20–79, range	FFQ	g per week	Total alcohol MF: ⩾137.5 g per week *vs* none Beer MF: ⩾49.0 g per week *vs* none Wine MF: ⩾23.0 g per week *vs* none Liquor MF: ⩾157.0 g per week *vs* none	Incidence of kidney cancer	M: 622 F: 443	M: 973 F: 536	7	Age, country, gender, tobacco pack–years of smoking, education, BMI, hypertension medication use, and tertiles of total vegetable, total white meat, and red meat consumption
Greving, Sweden (Greving *et al*, 2007)	1996–1998	MF: 20–79, range Case: 64.3, mean Control: 64.4, mean	Question-naire	Total alcohol: g per month Beer, wine, and liquor: glasses per month	Total alcohol MF: >620 g per month *vs* non-users alcohol Strong beer MF: >8 glasses per month *vs* non-user strong beer Strong wine MF: >2 glasses per month *vs* non-user strong wine Liquor MF: >9 glasses per month *vs* non-user liquor	Incidence of renal cell cancer	MF: 855	MF: 1204	6	Age, sex, BMI, cigarette smoking, the other six beverages

Table 1 (*Continued*)

First author, country (reference)	Study period	Age (years)	Alcohol assess-ment	Unit of alcohol	Top *vs* bottom	Outcome/ endpoint	No. of cases	No. of controls or cohort size	Study quality[a]	Potential confounders
Pelucchi, Italia (Pelucchi *et al*, 2008)	1985–2004	MF: 22–79, range	Interview	Total alcohol, and wine: drinks per day Beer, and liquor: N/A	Total alcohol MF: >8 drinks per day *vs* non-drinkers Beer MF: drinkers *vs* non-drinkers Wine MF: >8 drinks per day *vs* non-drinkers liquor MF: drinkers *vs* non-drinkers	Incidence of renal cell cancer	M: 730 F: 385	M: 1741 F: 841	7	Age, sex, study, study centre, education, smoking habits, BMI, family history of renal cancer
Hu, Canada (Hu *et al*, 2008)	1994–1997	MF: 20–76, range	FFQ	g per day	Total alcohol M: ⩾30 g per day *vs* non-drinkers F: ⩾20 g per day *vs* non-drinkers Beer, wine, and liquor M: >10.68 g per day *vs* non-drinkers F: >6 g per day *vs* non-drinkers	Incidence of renal cell carcinoma	M: 617 F: 521	M: 2547 F: 2492	5	Age, province, education, BMI, total consumption meat, total consumption of vegetables and fruit, pack-years of smoking
Benedetti, Canada (Benedetti *et al*, 2009)	Early 1980s	Case: 58.3 mean age	Interview	Drinks per week	Total alcohol M: ⩾7 drinks per week *vs* never drinkers	Incidence of kidney cancer	M: 156	M: 507	6.5	Age, smoking status, cigarette-year, respondent status, ethnicity, census tract income, years of schooling, and time since quitting

Abbreviations: BMI = body mass index; F = women; FFQ = food frequency questionnaire; M = men; MF = men and women; N/A: not available. [a]Study quality was judged based on the Newcastle–Ottawa Scale (range, 1–9 stars). [b]Multiple studies included.

Table 2 Characteristics of cohort and pooled analysis studies include in meta-analysis of renal cell cancer

First author, country (reference)	Study period	Age (years)	Alcohol assessment	Unit of alcohol	Top *vs* bottom	Outcome/ endpoint	No. of cases	No. of controls or cohort size	Study quality[a]	Potential confounders
Lee, Finland, USA, Canada, The Netherlands, and Sweden (Lee *et al*, 2007)[b]	1980–2004	MF: 15–107, range	FFQ	g per day	Total alcohol M: ⩾15.0 g per day *vs* non-drinker F: ⩾15.0 g per day *vs* non-drinker Beer, wine, and liquor M: ⩾5.0 g per day *vs* non-drinker F: ⩾5.0 g per day *vs* non-drinker	Incidence of renal cell cancer	M: 711 F: 719	M: 229 575 F: 530 469	8	Age, history of hypertension, BMI, pack-years of smoking, combination of parity and age at first birth, total energy intake
Setiawan, USA (Setiawan *et al*, 2007)	1993–2002	M: 59.3, mean F: 58.8, mean	Questionnaire	g per day	Total alcohol M: ⩾10.9 g per day *vs* none F: ⩾3.3 g per day *vs* none	Incidence of renal cell cancer	M: 220 F: 127	M: 75 162 F: 85 964	8	Age, ethnicity, smoking, hypertension, physical activity
Lew, USA (Lew *et al*, 2011)	1995–2006	MF: 50–71, range	FFQ	g per day	Total alcohol M: ⩾30 g per day *vs* 0 g per day F: ⩾30 g per day *vs* 0 g per day Beer, wine, and liquor M: ⩾15 g per day *vs* 0 g per day F: ⩾5 g per day *vs* 0 g per day	Incidence of renal cell cancer	M: 1348 F: 466	M: 293 666 F: 198 721	8	Age, race, BMI, marital status, education, vigorous physical activity, smoking, history of hypertension, intakes of protein and total energy excluding energy from alcohol
Allen, UK (Allen *et al*, 2011)	1996–2007	F: 59, mean	FFQ	Drinks per day	Total alchol F: ⩾2 drinks per day *vs* 0 or 1drinks per day	Incidence of renal cell carcinoma	F:588	F:779 369	8	Age, socioeconomic status, BMI, smoking, use of menopausal hormone therapy, treatment for high blood pressure

Abbreviations: BMI = body mass index; F = women; FFQ = food frequency questionnaire; M = men; MF = men and women; N/A: not available. [a]Study quality was judged based on the Newcastle–Ottawa Scale (range, 1–9 stars). [b]Multiple studies included.

The possible mechanism by which alcoholic beverage intake reduces the risk of renal cell cancer could be beneficial changes in insulin sensitivity or vasculature. Light to moderate alcohol consumption has been associated with improved insulin sensitivity (Facchini *et al*, 1994; Davies *et al*, 2002; Joosten *et al*, 2008). Increased risk of renal cell cancer among diabetic (Lindblad *et al*, 1999; Joh *et al*,

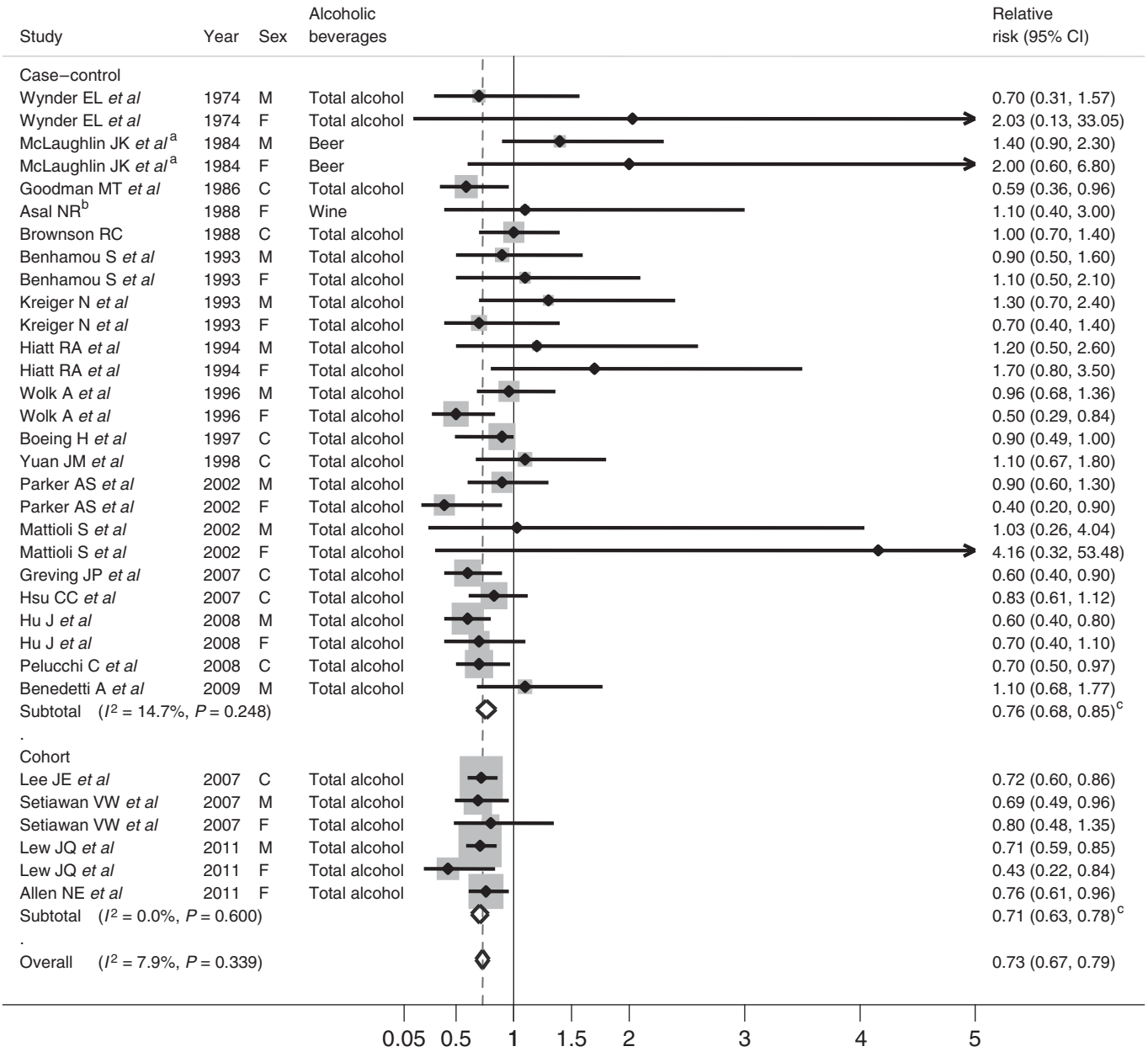

Figure 2 Combined RRs of renal cell cancer for total alcoholic beverage, comparing top with bottom category. McLaughlin *et al*[a] examined only beer consumption, Asal[b] examined only wine consumption. M, F, and C represented male, female, and combined gender, respectively. [c]*P* for difference by study design was 0.02.

Table 3 Combined RR of (95% CI) renal cell cancer for specific alcoholic beverages, comparing top with bottom category

Beverages (no. of study)	Bottom RR	Top RR (95% CI)	*P* for heterogeneity
Case–control study (n = 12)			
Beer	1.00	0.81 (0.70–0.91)	0.26
Wine	1.00	0.75 (0.59–0.91)	<0.001
Liquor	1.00	0.76 (0.66–0.87)	0.12
Cohort study (n = 2)			
Beer	1.00	0.75 (0.55–0.95)	0.16
Wine	1.00	0.81 (0.65–0.97)	0.17
Liquor	1.00	0.87 (0.77–0.97)	0.99

Abbreviations: CI = confidence interval; RR = relative risk.

2011) or obese individuals (Chow *et al*, 2000; Adams *et al*, 2008) may suggest that factors contributing to the development of insulin resistance are important determinants for renal cell cancer risk. Alcoholic beverage intake may increase high-density lipoprotein cholesterol levels or decrease blood clotting (Booyse *et al*, 2007) in blood vessels surrounding kidney, a vascular-rich organ.

Our meta-analysis had some limitations. Residual confounding by un-adjustment for confounding factors or inadequate measurement of covariates cannot be ruled out, although the significant inverse association was observed for those adjusted for smoking status and hypertension. Measurement error in assessment of alcoholic beverage intake could attenuate or de-attenuate the association, but the consistent significant inverse associations by different study design, specific types of alcoholic beverage, and gender may not support the possibility that measurement error fully explained our findings in this meta-analysis. The wider CIs

Table 4 Combined RR (95% CI) of renal cell cancer for the associations by gender, study design, and smoking status

Variable (no. of study)	Bottom RR	Top RR (95% CI)	*P* for difference	Variable (no. of study)	Bottom RR	Top RR (95% CI)	*P* for difference
Case–control study (n = 18)				*Cohort study (n = 4)*			
Gender (*n* = 12)				Gender			
Men	1.00	0.83 (0.70–0.96)	0.35	Men (*n* = 3)	1.00	0.71 (0.61–0.80)	0.78
Women	1.00	0.61 (0.46–0.76)		Women (*n* = 4)	1.00	0.70 (0.56–0.84)	
Adjustment for smoking status				*Adjustment for smoking status*			
No (*n* = 5)	1.00	0.76 (0.54–0.98)	0.52	—	—	—	
Yes (*n* = 13)	1.00	0.77 (0.67–0.87)		Yes (*n* = 4)	1.00	0.71 (0.61–0.80)	
Adjustment for hypertension status				*Adjustment for hypertension status*[a]			
No (*n* = 15)	1.00	0.75 (0.66–0.85)	0.85	—	—	—	
Yes (*n* = 3)	1.00	0.78 (0.52–1.04)		Yes (*n* = 4)	1.00	0.71 (0.61–0.80)	

Abbreviations: CI = confidence interval; RR = relative risk. [a]All cohort studies considered adjustment for smoking and hypertension status.

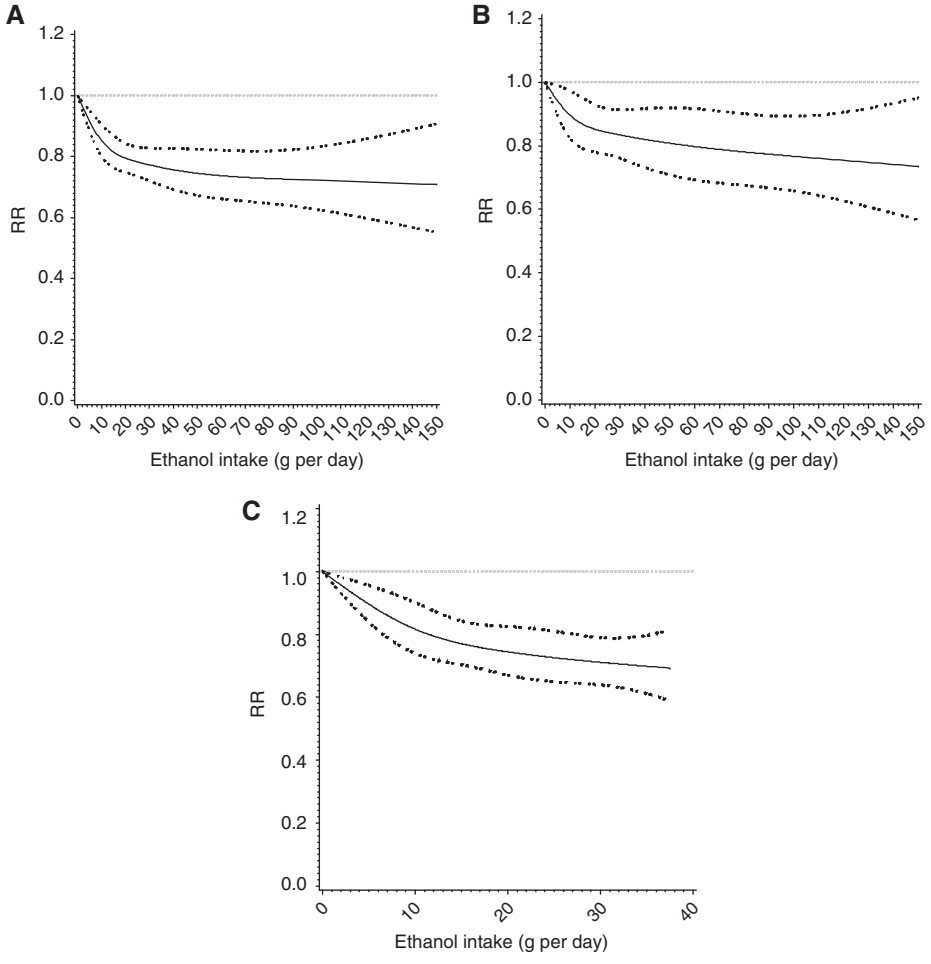

Figure 3 (**A**) Combined RR (95% CI) of renal cell cancer and test for the non-linearity of the association using the regression cubic spline. (**B**) Combined RR (95% CI) of renal cell cancer and test for the non-linearity of the association using the regression cubic spline in case–control studies. (**C**) Combined RR (95% CI) of renal cell cancer and test for the non-linearity of the association using the regression cubic spline in cohort studies.

observed at heavy alcoholic beverage intake in our spline analysis warrants further studies because of the limited number of renal cell cancer cases for heavy drinking.

In conclusion, we found that alcoholic beverage intake lowered the risk of renal cell cancer with the greatest reduction at the moderate level, but suggesting the evidence that drinking >15 g per day of ethanol does not confer additional benefit for prevention in renal cell cancer risk. Also, reduction of risk was not restricted to any specific type of alcoholic beverages. Moderate alcohol drinking may confer health benefits in the overall survival

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(Di Castelnuovo *et al*, 2006), cardiovascular disease (Rimm *et al*, 1996), and overall health status among elderly (Sun *et al*, 2011). However, drinking guidelines for men and women from various countries generally limit alcohol drinking to 1–2 standard units of drink (ICAP, 2009) because excessive drinking is associated with increased the risk of birth defects, injury, hypertension, stroke, type 2 diabetes, cancers of oral cavity and pharynx, oesophagus and larynx, stomach, colon and rectum, liver, breast, and ovary (Bagnardi *et al*, 2001; Reynolds *et al*, 2003; Baliunas *et al*, 2009; Taylor *et al*, 2009; Rehm *et al*, 2010). Along with the potential for health benefit and risks associated with alcohol consumption, our finding provides the evidence that light to moderate alcohol drinking is enough to reduce renal cell cancer risk without additional benefit above the level of one drink.

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