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Alcohol Intake and Renal Cell Cancer in a Pooled Analysis of 12 Prospective Studies

Jung Eun Lee, David J. Hunter, Donna Spiegelman, Hans-Olov Adami, Demetrius Albanes, Leslie Bernstein, Piet A. van den Brandt, Julie E. Buring, Eunyoung Cho, Aaron R. Folsom, Jo L. Freudenheim, Edward Giovannucci, Saxon Graham, Pamela L. Horn-Ross, Michael F. Leitzmann, Marjorie L. McCullough, Anthony B. Miller, Alexander S. Parker, Carmen Rodriguez, Thomas E. Rohan, Arthur Schatzkin, Leo J. Schouten, Mikko Virtanen, Walter C. Willett, Alicja Wolk, Shumin M. Zhang, Stephanie A. Smith-Warner

- Background** The association between alcohol intake and risk of renal cell cancer has been inconsistent in case-control studies. An inverse association between alcohol intake and risk of renal cell cancer has been suggested in a few prospective studies, but each of these studies included a small number of cases.
- Methods** We performed a pooled analysis of 12 prospective studies that included 530 469 women and 229 575 men with maximum follow-up times of 7–20 years. All participants had completed a validated food-frequency questionnaire at baseline. Using the primary data from each study, the study-specific relative risks (RRs) for renal cell cancer were calculated using Cox proportional hazards models and then pooled using a random-effects model. All statistical tests were two-sided.
- Results** A total of 1430 (711 women and 719 men) cases of incident renal cell cancer were identified. The study-standardized incidence rates of renal cell cancer were 23 per 100 000 person-years among nondrinkers and 15 per 100 000 person-years among those who drank 15 g/day or more of alcohol. Compared with non-drinking, alcohol consumption (≥ 15 g/day, equivalent to slightly more than one alcoholic drink per day) was associated with a decreased risk of renal cell cancer (pooled multivariable RR = 0.72, 95% confidence interval = 0.60 to 0.86; $P_{\text{trend}} < .001$); statistically significant inverse trends with increasing intake were seen in both women and men. No difference by sex was observed ($P_{\text{heterogeneity}} = .89$). Associations between alcohol intake and renal cell cancer were not statistically different across alcoholic beverage type (beer versus wine versus liquor) ($P = .40$).
- Conclusion** Moderate alcohol consumption was associated with a lower risk of renal cell cancer among both women and men in this pooled analysis.

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The incidence of renal cell cancer has increased during the past 30 years in the United States (1), Canada (2), and Northern Europe (3). This rapid increase is not fully explained by the increase in tumor detection (1); environmental factors, including diet, may have contributed to the upward trend. Although obesity (4,5), hypertension (5), and smoking (6) are all associated with an increased risk of renal cell cancer, the independent roles of obesity and hypertension in renal cell tumorigenesis remain

AS); Department of Preventive Medicine and USC/Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA (LB); Department of Epidemiology, Nutrition and Toxicology Research Institute Maastricht, Maastricht University, Maastricht, The Netherlands (PAVDB, LJS); Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN (ARF); Department of Social and Preventive Medicine, University at Buffalo, State University of New York, Buffalo, NY (JLF, SG); Northern California Cancer Center, Fremont, CA (PLHR); Epidemiology and Surveillance Research, American Cancer Society, Atlanta, GA (MLM, CR); Department of Public Health Sciences, University of Toronto, Toronto, ON, Canada (ABM); Department of Urology, Mayo Clinic College of Medicine, Jacksonville, FL (ASP); Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY (TER); Department of Health Promotion and Chronic Disease Prevention, National Public Health Institute, Helsinki, Finland (MV).

Correspondence to: Jung Eun Lee, ScD, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115 (e-mail: jung.lee@channing.harvard.edu).

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Affiliations of authors: Channing Laboratory (JEL, DJH, EC, EG, WCW) and Division of Preventive Medicine (JEB, SMZ), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; Departments of Nutrition (DJH, EG, WCW, SASW), Epidemiology (DJH, DS, HOA, JEB, EG, WCW, SMZ, SASW), and Biostatistics (DS), Harvard School of Public Health, Boston, MA; Department of Medical Epidemiology and Biostatistics (HOA) and Division of Nutritional Epidemiology, National Institute of Environmental Medicine (AW), Karolinska Institutet, Stockholm, Sweden; Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Health Services, Bethesda, MD (DA, MFL,

CONTEXT AND CAVEATS

Prior knowledge

Results from studies of the relationship between alcohol consumption and renal cell cancer risk have been inconsistent.

Study design

Pooled analysis of 12 prospective studies to estimate relative risks of renal cell cancer by alcohol intake.

Contribution

Intake of approximately one drink per day was associated with a reduced risk of renal cell cancer, compared with no alcohol intake. The association was observed among both men and women.

Implications

Moderate intake of alcohol may be associated with reduced risk of renal cell cancer.

Study limitations

The study was survey based, and there may have been inaccuracies in reporting intake. Although the study was large, the majority of the population was white; thus, it is unknown whether the associations apply to other ethnic groups or other populations.

controversial. Furthermore, the relationships between dietary factors and renal cell cancer risk remain unclear. In 1997, a working group of the World Cancer Research Fund and the American Institute for Cancer Research (7) concluded that associations between fat, cholesterol, and fish intakes and renal cell cancer risk remain unclear due to inconsistent and limited evidence but that a positive link between meat intake and risk of renal cell cancer may exist. However, a more recent review (8) found no clear support for the hypothesis that increased intakes of meat, milk, fat, and protein may increase the risk of renal cell cancer. In addition, in 2003, an international review panel sponsored by the International Agency for Research on Cancer (9) concluded that there was only limited evidence that consuming increased quantities of fruit and vegetables is associated with reduced risk for renal cell cancer.

The association between alcohol intake and renal cell cancer risk has been evaluated in at least 16 studies (10–25). Some case-control studies (10–14) have found that alcohol consumption is associated with a lower risk of renal cell cancer, although others (15–21) have not. Inverse associations between alcohol intake and risk of renal cell cancer have also been observed in recent prospective studies (22–25). However, evaluation of high intake of alcohol, intake of different types of alcoholic beverages, and whether the association varied by other potential risk factors was restricted due to the small number of patients (less than 250) in each of these prospective studies.

We evaluated the association between alcohol intake and risk of renal cell cancer by reanalyzing the primary data from 12 prospective studies (22–32) using standardized criteria. This pooled analysis included the five prospective studies that had previously examined the association between alcohol intake and risk of renal cell cancer (22–25) as well as seven studies that had not previously reported on this association.

Subjects and Methods

Study Population

The Pooling Project of Prospective Studies of Diet and Cancer (herein referred to as the Pooling Project) has been described elsewhere (33). For the renal cell cancer analyses, each study that we included (22–32) (Table 1) met the following prespecified criteria: identification of at least 25 incident renal cell cancers, assessment of long-term intake of a variety of foods and beverages, and validation of the dietary assessment method used in the study or a closely related questionnaire. Studies that included both women and men were treated as two separate cohorts (one of women and one of men), and the inclusion criteria were applied to each cohort. Overall, the renal cell cancer analyses included 530 469 women and 229 575 men from 12 prospective studies. In the Pooling Project, the Nurses' Health Study was analyzed in two parts corresponding to the 1980–1986 follow-up and the 1986–2000 follow-up periods to take advantage of the increased comprehensiveness of the 1986 food-frequency questionnaire. In the renal cell cancer analyses, we only used data from the Nurses' Health Study starting in 1986 because fewer than 25 renal cell cancer cases were identified between 1980 and 1986. Each of the studies included here were reviewed and approved by the institutional review board of the institution at which the study was conducted.

Ascertainment of Renal Cell Cancer Patients

Renal cell cancer patients were ascertained by follow-up questionnaires and subsequent review of medical records (25,27), linkage to cancer registries (22,23,26,28–30), or both (24,31,32). Some studies also used linkage to mortality registries to identify incident and/or fatal outcomes (22–27,30–32). The follow-up rate of each cohort generally exceeded 90% (33). We defined renal cell cancer patients as those with histologically confirmed renal cell cancer (ICD-O-2 code = C64.9), using histologic codes based on the International Classification of Diseases for Oncology (34) or the morphologic classification provided by the study investigators. The most frequently described (61%) type of renal cell cancer in our data was renal cell carcinoma (not otherwise specified) (morphology code = 8312); the second most frequent (18%) was clear cell carcinoma. The higher proportion of renal cell carcinoma, not otherwise specified, in our database compared with surgical series that have reported clear cell carcinoma as the most common type of renal cell cancer (35) may be partially due to the large number of renal cell cancer patients in our analyses who were ascertained before 1997, when a workshop on the diagnosis and prognosis of renal cell cancer was held by the World Health Organization (35). This workshop prompted more emphasis on obtaining information on histologic types and hence more widespread use of the current classification system. Due to the insufficient number of patients with specific histologic types of renal cell cancer, we have combined all histologically confirmed renal cell cancers for our analyses.

Assessment of Alcohol and Other Dietary Factors

Each study assessed baseline dietary intake of a variety of foods and beverages with a validated food-frequency questionnaire. For each food or beverage, each study assessed the frequency of intake of specified portions (22,25,27), the frequency of intake of unspecified

portions (23,26), or both the frequency of intake and the portion consumed (24,28,30–32,36). The consumption of beer, wine, and liquor was assessed separately in all studies except the New York State Cohort, in which only total alcohol consumption was queried; the New York State Cohort was not included in the beverage-specific analyses.

Each study provided alcohol intake data as either the number of servings of alcoholic beverages consumed per day or the grams of alcohol consumed per day. For studies that quantified intake in servings per day, the intake of alcohol from each beverage was converted to grams per day using the reported frequency of intake of each beverage, study-specific serving sizes of each beverage, and study-specific conversion factors for the amount of alcohol in beer, wine, and liquor. For example, information on conversion factors appropriate for the US populations was obtained from the US Department of Agriculture (37) (12.8 g of alcohol for a 12-oz can or bottle of beer, 11.0 g for a 4-oz glass of wine, and 14.0 g for one standard drink of liquor). Total alcohol intake was calculated by summing the alcohol intake from each alcoholic beverage.

Each study investigator provided data on the intakes of other nutrients, which were calculated in their study. For those nutrients, units were standardized across studies and intakes were energy adjusted within each study using the residuals from the regression of nutrient intake on total energy intake (38).

To determine how accurately the questionnaires estimated alcohol intake, alcohol intake from the food-frequency questionnaires used in the studies or a closely related questionnaire was compared with intake estimated by either multiple diet records or 24-hour recalls. The correlation coefficients comparing the two methods generally exceeded 0.8 (39–43) (Wolk A, Horn-Ross PL: personal communication).

Assessment of Nondietary Factors

Information on nondietary factors was collected in each study using self-administered questionnaires at baseline. Information on age, height, and weight was provided in all studies; we used height and weight information to calculate body mass index (BMI [weight in kilograms/height in square meters]). All the cohort studies among women assessed parity, age at first birth, oral contraceptive use, and hormone replacement therapy use. Most studies assessed smoking history and history of hypertension.

Statistical Analysis

After applying the study-specific exclusion criteria, we further excluded participants if they consumed an unreasonable energy intake (± 3 standard deviations from the study-specific \log_e -transformed mean energy intake), had a history of cancer at baseline (except for nonmelanoma skin cancer), or had missing data on alcohol consumption. Each study was analyzed using the Cox proportional hazards model (44). Age at baseline (in days) and the year the baseline questionnaire was returned were used as stratification variables, thereby creating a time metric that simultaneously accounted for age, calendar time, and time since entry into the study. Person-years of follow-up time were calculated from the date of the baseline questionnaire until the date of renal cell cancer diagnosis, death, loss to follow-up (if applicable), or end of follow-up, whichever came first. We tested whether the assumption of the

proportional hazards was satisfied by adding interaction terms between age and alcohol intake and found that terms were not statistically significant; thus, the assumption was satisfied. The studies were analyzed using SAS PROC PHREG (45).

We categorized alcohol intake using uniform cut points (none, 0.1–4.9 g/day, 5.0–14.9 g/day, and ≥ 15 g/day) across studies based on multiples of one drink per day (≈ 15 g/day) and based on the distribution of alcohol intake in each study. If no participants diagnosed with renal cell cancer were in the highest intake category in a study, the participants in the highest category in that study were included in the second highest intake category. To test for trend across alcohol intake, participants were assigned the median value of their intake category. This variable was entered as a continuous term in the model, the coefficient for which was evaluated by the Wald test. In multivariable analyses, we further adjusted for history of hypertension (yes, no), pack-years of smoking (continuous), energy intake (kcal/day, continuous), BMI (kg/m^2 , continuous), and, among women, parity and age at first birth (age at first birth < 25 years and parity of 1 or 2, age at first birth ≥ 25 years and parity of 1 or 2 or nulliparous, age at first birth < 25 years and parity of ≥ 3 , and age at first birth ≥ 25 years and parity of ≥ 3). Cut points for parity and age at first birth were based on their overall distribution across studies and on the magnitude of the associations with renal cell cancer that we observed in each cohort. An indicator variable was used for missing responses for each measured covariate within a study, if needed.

After calculating study- and sex-specific relative risks for each category, we combined the \log_e relative risks using a random-effects model (46–48). The individual study estimates were weighted by the inverse of their variance. We tested for heterogeneity across studies using the Q statistic, which follows an approximate chi-square distribution ($df = \text{number of studies in that analysis} - 1$) (48,49). Two-sided 95% confidence intervals (CIs) were calculated.

In additional analyses, we adjusted for smoking history using categories of never smoking, past smoking duration (< 30 , ≥ 30 years), and current smoking dose (< 15 , 15 to < 25 , ≥ 25 cigarettes/day) instead of pack-years of smoking to evaluate the effect of different parameterizations of smoking variables on the risk estimates observed for alcohol intake. Because patients who were diagnosed near the time when they complete their food-frequency questionnaire may have altered their diet due to prediagnostic disease symptoms, we also conducted analyses in which patients who were diagnosed during the first 2 years of follow-up were excluded. To address whether detection bias could have affected our results, we also conducted analyses in which we included only patients who died less than 2 years after diagnosis. We examined whether the risk estimates for alcohol from beer, wine, and liquor varied using a contrast test (50); the null hypothesis was that there was no difference in the pooled estimates across the three alcoholic beverages. This test statistic has an approximate chi-square distribution with 2 *df*.

To assess the linearity of the association between alcohol intake and risk of renal cell, we examined nonparametric regression curves using restricted cubic splines (51,52). To test for nonlinearity, the likelihood ratio test was used to compare the model fit including the linear and cubic spline terms selected by a stepwise regression procedure with the model fit including only the linear term; visual

inspection of the restricted cubic spline graphs was also used. For these analyses, all studies were combined into a single dataset and then stratified by age, the year that the questionnaire was returned, and study and then adjusted for other covariates in the model. Participants with alcohol intake of 60 g/day or more (1% of overall study population) were excluded in the cubic spline analysis to avoid excessive influence of extreme intakes.

The study-specific relative risks for alcohol intake were corrected for measurement error by regressing intake from the reference dietary assessment methods (multiple 24-hour recalls or dietary records) (39–43) (Wolk A, Horn-Ross PL: personal communication) on intake from the food-frequency questionnaires (53,54). We then computed the corrected estimates of the log_e relative risks by dividing the uncorrected estimates by the obtained regression coefficients. The corrected estimates were then pooled using a random-effects model (46–48). Under moderate measurement error as found in the validation studies for the studies included in this article, normality of residuals of the measurement error is not required (55). Although heteroscedasticity of the measurement error model can be a problem, in the case of mismeasurement of alcohol intake in cancer incidence models, the linear regression calibration method has been found to provide an accurate estimate of effect (56) (Spiegelman D, Logan R, Grove D: unpublished technical report; the manuscript is available at http://www.hsph.harvard.edu/faculty/spiegelman/manuscripts/beta_RCH.pdf).

We also assessed whether the associations for alcohol intake varied by sex, BMI (<25, ≥25 kg/m²), history of hypertension (no, yes), smoking status (never, ever), age at diagnosis (<68, ≥68; the median age at diagnosis), multivitamin use (user, non-user), total folate intake (tertile), hormone replacement therapy use among postmenopausal women (ever, never), and, among women, parity (<3 children, ≥3 children) and oral contraceptive use (yes, no) using a mixed effects meta-regression model (57). A two-sided Wald test statistic was used to test the null hypothesis that there was no modification of the alcohol–renal cell cancer association by levels of the potential effect modifiers. In these analyses, we divided alcohol intake into three categories (none, 0.1–4.9 g/day, and ≥5 g/day), instead of four categories, because only a low proportion of participants drank 15 g/day or more of alcohol.

All statistical tests were two-sided. *P* values less than .05 were considered to be statistically significant.

Results

During maximum follow-up periods of 7–20 years across studies, 1430 patients (711 women and 719 men) were diagnosed with renal cell cancer among 530469 women and 229575 men (Table 1). Alcohol was consumed more commonly and consumed in greater quantities among men than women. The proportion of women in the combined dataset of all studies (referred to as the aggregated dataset) who reported drinking a specific alcoholic beverage was 26% for beer, 49% for wine, and 30% for liquor; the corresponding proportions among men were 55%, 43%, and 52%, respectively. Among drinkers of each specific alcoholic beverage, median daily alcohol intakes were 1.8 g from beer, 3.3 g from wine, and 4.5 g

from liquor among women and 3.3 g from beer, 1.9 g from wine, and 6.0 g from liquor among men. Median intakes of each beverage among drinkers of each specific alcoholic beverage varied at least 2.4-fold across the studies for women and 1.6-fold across the studies for men.

Total alcohol intake was inversely associated with risk of renal cell cancer. In the age-adjusted model, a modest inverse association was observed compared with nondrinkers (for alcohol intake of 0.1–4.9 g/day, pooled age-adjusted RR = 0.94, 95% CI = 0.81 to 1.08; for intake of 5.0–14.9 g/day, RR = 0.78, 95% CI = 0.67 to 0.92; for intake of ≥15 g/day, RR = 0.75, 95% CI = 0.62 to 0.89; *P*_{trend}<.001). The associations became slightly stronger when we adjusted for pack-years of smoking (consumers of ≥15 g/day of alcohol versus nondrinkers, pooled age- and smoking-adjusted RR = 0.69, 95% CI = 0.58 to 0.82; *P*_{trend}<.001). When we alternatively adjusted for smoking history using categories of never smoking, past smoking duration (<30, ≥30 years), and current smoking dose (<15, 15 to <25, ≥25 cigarettes/day) instead of pack-years of smoking, the results differed little (data not shown). The results from the multivariable model (comparing consumers of ≥15 g/day versus nondrinkers, RR = 0.72, 95% CI = 0.60 to 0.86; *P*_{trend}<.001; Table 2) were similar to those from the age- and smoking-adjusted model. The study-standardized incidence rates of renal cell cancer were 23 per 100000 person-years among nondrinkers and 15 per 100000 person-years among those who drank 15 g/day or more of alcohol. A statistically nonsignificant lower risk of renal cell cancer was observed in nearly all studies for this comparison (Fig. 1). Furthermore, there was no evidence of heterogeneity across studies (*P*_{heterogeneity} = .99), indicating that the differences in results across studies were compatible with random variation. Results were similar for women and men (*P*_{heterogeneity} = .89). When we limited the analyses to alcohol drinkers, an inverse association was also observed (*P*_{trend}<.001).

When patients who were diagnosed during the first 2 years of follow-up were excluded (n = 161), the results were similar (≥15 g/day versus nondrinkers, the pooled multivariable RR = 0.71, 95% CI = 0.58 to 0.87; *P*_{trend}<.001). The multivariable relative risks obtained in the aggregated dataset were not different from the pooled multivariable relative risks (data not shown).

Because detection bias is less likely to be present among patients who died soon after diagnosis compared with those who had a longer survival, we conducted a sensitivity analysis in which we limited the analyses to patients who died less than 2 years after diagnosis (the 378 patients included represented 26% of the total). Because the smaller number of patients available for this analysis prevented calculation of study-specific results, we examined the association in the aggregated dataset only. In addition, due to the small number of patients with higher alcohol intake, we set the highest alcohol intake category at 5 g/day or more of alcohol. The relative risks in comparisons of individuals in the highest intake category with nondrinkers from analyses only including patients who died less than 2 years after diagnosis (multivariable RR = 0.77, 95% CI = 0.67 to 0.88; *P*_{trend}<.001) were similar to those observed when all patients were included (pooled multivariable RR = 0.75; 95% CI = 0.65 to 0.87; *P*_{trend}<.001).

When we assessed associations separately for specific alcoholic beverages, alcohol intakes from beer, wine, and liquor were each

Table 1. Baseline characteristics of the participants in the cohort studies included in the pooled analyses of alcohol intake and risk of renal cell cancer

Study (sex*)	Country	Follow-up period	Baseline cohort size	Age range, y	No. of patients	% Drinkers of alcohol	Median intake among drinkers, g/day (10th–90th percentiles)			
							Total alcohol†	Alcohol from beer†	Alcohol from wine†	Alcohol from liquor†
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (M)	Finland	1985–1999	26 987	50–69	187	89	13 (1.6–47)	4.6 (0.8–23)	2.1 (0.4–9.6)	8.0 (0.6–23)
Breast Cancer Detection Demonstration Project Follow-up Study (W)	United States	1987–1999	42 007	40–93	49	51	3.1 (0.2–19)	0.9 (0.1–7.5)	1.4 (0.1–11)	2.2 (0.2–15)
California Teachers Study (W)	United States	1995–2001	100 036	22–104	35	67	7.8 (3.3–22)	4.0 (4.0–13)	3.3 (3.3–11)	4.5 (4.5–15)
Canadian National Breast Screening Study (W)	Canada	1980–2000	49 613	40–59	81	77	6.2 (1.0–27)	1.7 (0.4–8.5)	3.1 (0.5–16)	2.3 (0.5–16)
Cancer Prevention Study II Nutrition Cohort (W)	United States	1992–2001	74 138	50–74	86	52	4.3 (0.7–24)	0.9 (0.5–7.3)	1.4 (0.5–11)	2.1 (0.9–23)
Cancer Prevention Study II Nutrition Cohort (M)		1992–2001	66 166	50–74	220	65	9.6 (0.9–45)	1.9 (0.9–17)	1.9 (0.9–14)	7.0 (0.9–41)
Health Professionals Follow-up Study (M)	United States	1986–2000	47 780	40–75	116	76	9.6 (1.8–37)	1.8 (1.0–13)	1.8 (0.9–10)	6.0 (1.1–35)
Iowa Women’s Health Study (W)	United States	1986–2000	34 588	55–69	117	45	3.4 (0.9–21)	1.8 (1.1–13)	1.7 (0.9–6.2)	2.1 (1.2–15)
Netherlands Cohort Study (W)	The Netherlands	1986–1993	62 573	55–69	68	67	4.1 (0.5–23)	1.1 (0.3–7.4)	3.2 (0.5–19)	4.6 (0.4–24)
Netherlands Cohort Study (M)		1986–1993	58 279	55–69	134	85	12 (2.0–38)	2.3 (0.5–15)	3.8 (0.7–19)	9.3 (1.1–28)
New York State Cohort (M)	United States	1980–1987	30 363	15–107	62	89	4.8‡ (0.2–34)	–‡	–‡	–‡
Nurses’ Health Study (W)	United States	1986–2000	68 523	40–65	86	64	4.7 (0.9–28)	1.8 (1.0–13)	1.8 (0.9–11)	2.0 (1.1–14)
Swedish Mammography Cohort (W)	Sweden	1987–2004	60 604	40–76	140	68	2.8 (0.4–7.4)	0.9 (0.3–3.7)	1.8 (1.6–3.6)	1.0 (0.9–1.8)
Women’s Health Study (W)	United States	1993–2004	38 387	45–89	49	59	3.7 (0.9–17)	1.9 (0.9–9.0)	1.7 (0.9–10)	2.1 (1.2–15)
Total			760 044		1430					

* W = women; M = men.

† Ethanol.

‡ The New York State Cohort did not measure the consumption of individual alcoholic beverages separately.

associated with a lower risk of renal cell cancer among women and men combined (Table 2). When these associations were examined separately by sex, the statistically significant inverse association was limited to alcohol from wine among women and to alcohol from beer and from liquor among men, although the differences in the risk estimates between women and men for each beverage were not statistically significant. In addition, the risk estimates for the three types of alcoholic beverages were not significantly different from each other for the category of 5 g/day or more of alcohol ($P = .40$).

The nonparametric regression curve and a formal test showed statistically significant nonlinearity in the association between alcohol consumption and renal cell cancer risk in the age- and calorie-adjusted ($P_{\text{curvature}} = .02$) and multivariable ($P_{\text{curvature}} = .03$) analyses. A linear inverse association was observed primarily in those with alcohol intakes of less than 30 g/day, and the relationship appeared flat above approximately 30 g/day (Fig. 2).

We corrected the study-specific relative risks for bias due to measurement error in alcohol intake in the nine cohort studies that assessed alcohol intake in their respective food-frequency ques-

tionnaires’ validation studies (39–43) (Wolk A, Horn-Ross PL: personal communication). For these analyses, we excluded participants who drank more than 30 g/day of alcohol (6% of the participants), so we could model alcohol consumption as a continuous variable over the intake range for which the association appeared linear on the log scale. The pooled corrected age- and calorie-adjusted relative risk for a 10 g/day increment (RR = 0.79, 95% CI = 0.70 to 0.89) was similar to the pooled uncorrected age- and calorie-adjusted relative risk (RR = 0.81, 95% CI = 0.74 to 0.90).

Because alcohol consumption was higher among men than women, we performed additional analyses in which we divided the 15 g/day or more alcohol intake category into three categories. As observed in the nonparametric regression curve analyses for the entire study population, the association was similar for these additional categories (all compared with nondrinkers) (for 0.1–4.9 g/day, pooled multivariable RR = 1.08, 95% CI = 0.87 to 1.35; $n = 203$; for 5.0–14.9 g/day, RR = 0.82, 95% CI = 0.61 to 1.10; $n = 162$; for 15.0–29.9 g/day, RR = 0.68, 95% CI = 0.51 to 0.90; $n = 93$; for 30.0–44.9 g/day, RR = 0.75, 95% CI = 0.54 to 1.06; $n = 49$; and for

Table 2. Pooled multivariable* relative risks (RRs) and 95% confidence intervals (CIs) of renal cell cancer associated with alcohol intake

Category	RR (95% CI) by intake of alcohol, g/day				$P_{\text{trend}}^{\dagger}$	$P_{\text{between-study heterogeneity}}^{\ddagger}$	$P_{\text{between-study heterogeneity due to sex}}^{\S}$
	Nondrinker	0.1–4.9	5.0–14.9	≥15.0			
All alcohol 							
No. of patients (W, M)	322, 166	236, 203	97, 162	50, 186			
Women	1.00 (referent)	0.91 (0.76 to 1.08)	0.83 (0.66 to 1.05)	0.73 (0.54 to 0.98)	.03	.92	
Men	1.00 (referent)	1.08 (0.87 to 1.35)	0.82 (0.61 to 1.10)	0.71 (0.56 to 0.89)	<.001	.96	
Pooled	1.00 (referent)	0.97 (0.85 to 1.11)	0.82 (0.69 to 0.96)	0.72 (0.60 to 0.86)	<.001	.99	.89
Alcohol from beer							
No. of patients (W, M)	563, 299	121, 222	21, 134				
Women	1.00 (referent)	0.90 (0.74 to 1.10)	1.04 (0.57 to 1.88)		.97	.15	
Men	1.00 (referent)	1.05 (0.87 to 1.26)	0.79 (0.64 to 0.98)		.01	.73	
Pooled	1.00 (referent)	0.98 (0.85 to 1.12)	0.87 (0.68 to 1.11)		.09	.24	.19
Alcohol from wine¶							
No. of patients (W, M)	418, 408	238, 177	49, 70				
Women	1.00 (referent)	0.86 (0.68 to 1.08)	0.64 (0.48 to 0.86)		.002	.95	
Men	1.00 (referent)	1.01 (0.84 to 1.22)	0.79 (0.60 to 1.03)		.09	.43	
Pooled	1.00 (referent)	0.93 (0.79 to 1.08)	0.72 (0.59 to 0.87)		.001	.88	.32
Alcohol from liquor 							
No. of patients (W, M)	512, 290	131, 153	62, 212				
Women	1.00 (referent)	1.05 (0.87 to 1.27)	1.04 (0.80 to 1.36)		.86	.97	
Men	1.00 (referent)	0.97 (0.79 to 1.19)	0.81 (0.66 to 0.98)		.02	.45	
Pooled	1.00 (referent)	1.02 (0.88 to 1.17)	0.88 (0.75 to 1.03)		.05	.82	.13

* All models were adjusted for age, history of hypertension (yes/no), body mass index (kg/m², continuous), pack-years of smoking (continuous), combination of parity and age at first birth (age at first birth < 25 years and parity of 1 or 2; age at first birth ≥ 25 years and parity of 1 or 2 or nulliparous; age at first birth < 25 years and parity of ≥3; and age at first birth ≥ 25 years and parity of ≥3), and total energy intake (kcal/day, continuous). For specific alcoholic beverage, models were additionally adjusted for other alcoholic beverages (continuous). For alcohol intakes from beer, wine, and liquor, the highest category is ≥5.0 g/day.

† P_{trend} values (two-sided) were calculated using the Wald test statistic.

‡ For the highest category. $P_{\text{between-study heterogeneity}}$ values (two-sided) were calculated using the Q test statistic.

§ For the highest category. $P_{\text{between-study heterogeneity}}$ values (two-sided) due to sex were calculated using the Wald test statistic.

|| The Swedish Mammography Cohort was excluded from the highest category because no cases were included in this category. The participants who would have been in the highest category were included in the next highest category.

¶ The Breast Cancer Detection Demonstration Project Follow-up Study was excluded from the highest category because no cases were included in this category. The participants who would have been in the highest category were included in the next highest category.

≥45 g/day, RR = 0.76, 95% CI = 0.53 to 1.08; n = 44). When we additionally analyzed alcohol from beer and liquor using 15 g/day or more of alcohol intake as the highest category among men, the associations comparing 15 g/day or more of alcohol versus nondrinkers were inverse, but not statistically significant (for alcohol from beer, n = 36, pooled multivariable RR = 0.76, 95% CI = 0.53 to 1.09; $P_{\text{trend}} = .05$; and for alcohol from liquor, n = 93, RR = 0.79, 95% CI = 0.56 to 1.13; $P_{\text{trend}} = .25$).

We examined whether the association between alcohol intake and risk of renal cell cancer was modified by several risk factors for renal cell cancer (Table 3). The associations did not vary appreciably by BMI, history of hypertension, smoking status, or age at diagnosis. In addition, multivitamin use, total folate intake, hormone replacement therapy use among postmenopausal women, and parity and oral contraceptive use among women did not modify the association (data not shown).

Discussion

In this pooled analysis of 1430 renal cell cancer patients from 12 prospective studies, we found that moderate alcohol intake was associated with a statistically significantly lower risk of renal cell cancer. Inverse, but non-statistically significant, associations were observed in nearly all the individual studies, including five

(27–29,31,32) of the seven prospective studies that had not previously published their findings on alcohol intake and renal cell cancer risk. The lack of statistical significance of the study-specific associations could be due to the small number of cases in each study as only one of which included more than 200 patients. The association between alcohol intake and risk of renal cell cancer in the pooled analysis was not modified by several renal cell cancer risk factors, including age, BMI, history of hypertension, and smoking status. We found a stronger inverse association for alcohol from wine among women and for alcohol from beer and liquor among men, although the difference between the multivariable relative risks for the three beverages was not statistically significant. Non-statistically significant associations observed for alcohol from beer among women, alcohol from liquor among women, and alcohol from wine among men may be due to a lack of power because of low consumption of these alcoholic beverages. In these analyses of specific alcoholic beverages, we were restricted to using 5.0 g/day or more (2–3 drinks per week) as the highest category, especially for women, because of the limited number of patients with higher alcohol intakes for each beverage.

Our results confirm the suggestive inverse associations observed in the five published prospective studies (22–25) (all of which were included in our analysis) and help to resolve the inconsistency of the results from case-control studies (10–21), which may be

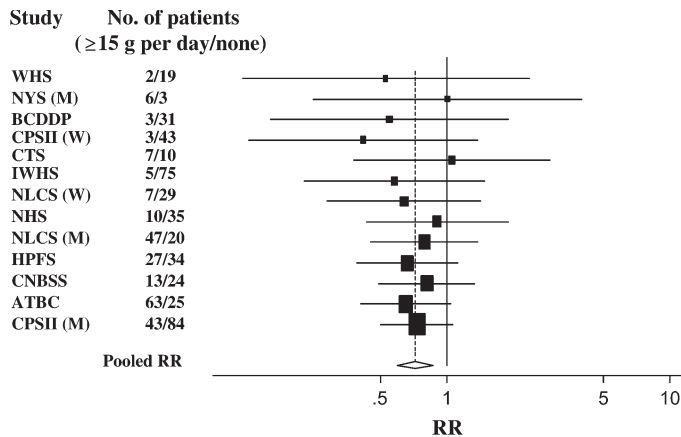


Fig. 1. Study-specific and pooled multivariable relative risks (RRs) and 95% confidence intervals of renal cell cancer for consumers of 15 g/day or more of alcohol versus nondrinkers. The relative risks were adjusted for the same covariates listed in Table 2. The **black squares** indicate the study-specific relative risks; the **horizontal lines** represent the 95% confidence intervals. The area of the black squares reflects the study-specific weights (inverse of the variance). The **dashed line** represents the pooled relative risk and the **diamond** represents the 95% confidence interval for the pooled relative risk. WHS = Women's Health Study; NYS = New York State Cohort; BCDDP = Breast Cancer Detection Demonstration Project Follow-up Study; CPSII = Cancer Prevention Study II Nutrition Cohort; CTS = California Teachers Study; IWHS = Iowa Women's Health Study; NLCS = Netherlands Cohort Study; NHS = Nurses' Health Study; HPFS = Health Professionals Follow-up Study; CNBSS = Canadian National Breast Screening Study; ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; M = men; W = women. The Swedish Mammography Cohort was excluded from this figure because this study had no patients in the top category of alcohol intake (≥ 15 g/day).

subject to recall and selection biases. Inconsistent results regarding the association between alcoholism or heavy drinking and kidney cancer have been reported in some cohort studies (58–61), but these studies were limited by the absence of information on confounding factors, the inclusion of only alcoholics or heavy drinkers, and a small number of renal cell cancer patients. Due to the small proportion (1%) of participants in the studies we analyzed who reported drinking more than 60 g of alcohol per day, we were unable to evaluate associations with heavy drinking.

A potential mechanism by which alcohol may reduce the risk of renal cell cancer is by improving insulin sensitivity. Light to moderate alcohol consumption is associated with enhanced insulin sensitivity (62–65) and inversely associated with the risk of diabetes (66), which is usually characterized by impaired insulin sensitivity (67). At least two lines of evidence suggest that improving insulin sensitivity may lower the risk of renal cell cancer. First, persons who are obese, a known risk factor for renal cell cancer, have higher insulin levels than people who are not obese (68). Second, individuals with diabetes are more likely to develop renal cell cancer than individuals without diabetes (69,70).

The diuretic effect of alcohol intake could also be, in theory, hypothesized to lower the risk of renal cell cancer by decreasing the time that carcinogenic solutes are in contact with renal epithelial cells. This possible mechanism could be investigated by examining whether the diluting effect caused by high fluid intake is associated with a reduced risk of renal cell cancer. However, a pooled analysis of the Nurses' Health Study and the Health

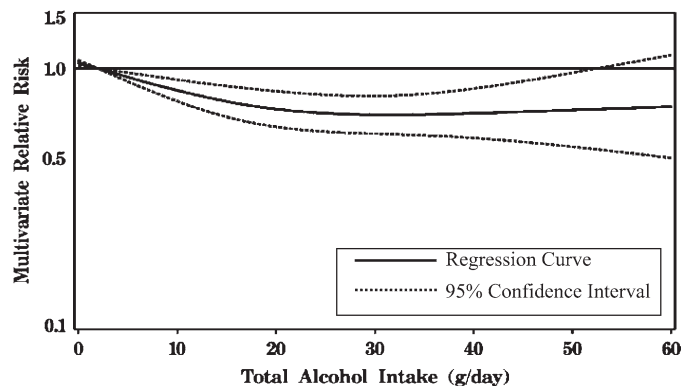


Fig. 2. Nonparametric regression curve for the association between alcohol intake and renal cell cancer (test for curvature, $P = .03$; test for overall statistical significance of the curve, $P < .001$; from the likelihood ratio test). Participants with alcohol intake of 60 g/day or more (1% of the population) were excluded. The model was adjusted for the same covariates listed in Table 2.

Professionals Follow-up Study, both of which were included in our analyses, reported that total fluid intake was not associated with a lower risk of renal cell cancer (25).

Alcoholic beverages contain antioxidant phenolic compounds, which also may help to decrease the risk of renal cell cancer by removing oxidized carcinogenic agents, reducing lipid peroxidation, reducing cell proliferation, or promoting apoptosis (71,72). Although we also cannot exclude the possibility that these compounds are responsible for the apparent favorable association between alcoholic beverage intake and renal cell cancer risk, the finding that all three types of alcoholic beverages were associated with lower risk suggests that alcohol per se is most likely the responsible factor.

This pooled analysis had several limitations. We had only a baseline measure of alcohol intake and could not investigate changes in intake, intakes at earlier ages, or lifetime consumption. We also could not examine patterns or timing of alcohol consumption or the effects of high alcohol intake, particularly for specific alcoholic beverages. The amount of alcohol consumed may have been underreported, particularly by heavy drinkers, even though, overall, the validation studies for the food-frequency questionnaires used in these studies or closely related questionnaires showed that alcohol intake was measured accurately compared with the referent methods (39–43) (Wolk A, Horn-Ross PL: personal communication). However, we cannot rule out the possibility that any errors in the food-frequency questionnaires and in the referent methods were correlated, which would result in incomplete removal of all the bias due to measurement error (54,73–75). We did not have information on some risk factors for renal cell cancer, including family history of renal cell cancer, environmental exposures such as asbestos, medications such as phenacetin, or advanced kidney disease and thus were unable to control for these factors in our analyses. However, the inverse associations for alcohol intake that we observed are not likely to be fully explained by confounding because these exposures would need to be both common and strongly associated with alcohol consumption. In our analyses, smoking was the strongest confounder for the association between alcohol intake and risk of renal cell cancer among the

Table 3. Pooled multivariable relative risks (RRs) and 95% confidence intervals (CIs) of renal cell cancer for alcohol intake stratified by other factors

Variable (No. of patients)	RR (95% CI) by intake of alcohol, g/day			<i>P</i> _{trend} [*]	<i>P</i> _{interaction} [†]
	Nondrinkers	0.1–4.9	≥5		
Body mass index, kg/m ² ‡					
<25 (n = 535)	1.00 (referent)	1.02 (0.82 to 1.28)	0.82 (0.65 to 1.04)	.009	.37
≥25 (n = 857)	1.00 (referent)	0.94 (0.78 to 1.14)	0.70 (0.58 to 0.85)	<.001	
History of hypertension§					
Yes (n = 418)	1.00 (referent)	0.79 (0.58 to 1.07)	0.77 (0.58 to 1.03)	.09	.47
No (n = 654)	1.00 (referent)	1.09 (0.89 to 1.33)	0.74 (0.55 to 0.99)	.004	
Smoking					
Never (n = 433)¶	1.00 (referent)	0.91 (0.67 to 1.25)	0.66 (0.51 to 0.86)	.001	.22
Ever (n = 838)	1.00 (referent)	0.95 (0.78 to 1.16)	0.78 (0.65 to 0.94)	.002	
Age at diagnosis, y‡,#					
<68 (n = 836)	1.00 (referent)	0.93 (0.73 to 1.19)	0.76 (0.63 to 0.92)	.001	.83
≥68 (n = 584)	1.00 (referent)	1.04 (0.85 to 1.29)	0.78 (0.61 to 0.98)**	.03	

* *P*_{trend} values (two-sided) were calculated using the Wald test statistic.

† For the highest category. *P*_{interaction} values (two-sided) were calculated using the Wald test statistic.

‡ Models were adjusted for age, history of hypertension (yes/no), body mass index (kg/m², continuous), pack-years of smoking (continuous), combination of parity and age at first birth (age at first birth < 25 years and parity of 1 or 2; age at first birth ≥ 25 years and parity of 1 or 2 or nulliparous; age at first birth < 25 years and parity of ≥3; and age at first birth ≥ 25 years and parity of ≥3), and total energy intake (kcal/day, continuous).

§ Models were adjusted for age, body mass index (kg/m², continuous), pack-years of smoking (continuous), combination of parity and age at first birth (age at first birth < 25 years and parity of 1 or 2; age at first birth ≥ 25 years and parity of 1 or 2 or nulliparous; age at first birth < 25 years and parity of ≥3; and age at first birth ≥ 25 years and parity of ≥3), and total energy intake (kcal/day, continuous). The Breast Cancer Detection Demonstration Project Follow-up Study, the Canadian National Breast Screening Study, the New York State Cohort, and the Swedish Mammography Cohort were excluded from these analyses because data on history of hypertension were not available at baseline in these studies.

|| Models were adjusted for age, history of hypertension (yes/no), body mass index (kg/m², continuous), pack-years of smoking (continuous; only for ever smokers), combination of parity and age at first birth (age at first birth < 25 years and parity of 1 or 2; age at first birth ≥ 25 years and parity of 1 or 2 or nulliparous; age at first birth < 25 years and parity of ≥3; and age at first birth ≥ 25 years and parity of ≥3), and total energy intake (kcal/day, continuous). The Swedish Mammography Cohort was excluded from these analyses because data on smoking history were not available at baseline in this study.

¶ The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study was excluded from these analyses because the cohort included only current smokers.

Median age at diagnosis was 68 years.

** The Swedish Mammography Cohort was excluded from the highest category because no patients were included in this category. The participants who would have been in the highest category were included in the next highest category.

potential known risk factors that we controlled for in our study, and adjustment for smoking strengthened the association. With more thorough control for smoking, the true inverse relationship may have been stronger. We were not able to examine whether the associations differed by ethnicity because more than 90% of the participants in our study were white. Finally, we did not have sufficient information or power to examine associations separately by histologic type of renal cell cancer or by tumor characteristics.

This analysis also has important strengths. Because of the prospective design and high follow-up rates of the studies, recall bias or selection bias are very unlikely to account for our findings. In addition, because our study had more patients than the single prospective studies that were included, we achieved better precision than the individual prospective studies. Because we analyzed the primary data from each study, we were able to use uniform categories of alcohol intake and covariates across studies in the analyses to remove potential sources of heterogeneity across studies.

In conclusion, we found that modest intake of alcohol was associated with a lower risk of renal cell cancer. Also, our findings did not suggest that intake of any particular alcoholic beverage was more strongly associated with a lower risk of renal cell cancer. Future investigations are needed to provide information on potential mechanisms supporting this association. However, because alcohol drinking is associated with increased risks of cancers of the oral cavity, larynx, pharynx, esophagus, liver (76),

and breast (77), and probably the colon and rectum (7,78), maintaining a healthy weight and avoiding smoking are the principal known means to reduce the risk of renal cell cancer that should be encouraged and doing so may also reduce the risk of many other cancers as well as cardiovascular disease.

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Notes

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