

Total Fluid Intake and Use of Individual Beverages and Risk of Renal Cell Cancer in Two Large Cohorts

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Abstract

Moderate alcohol consumption has been inversely associated with risk of renal cell cancer in recent prospective studies, and increased total fluid intake has been hypothesized to be a possible mechanism. We prospectively examined the associations between total fluid and beverage intakes and risk of renal cell cancer. Among 88,759 women followed for 20 years in the Nurses' Health Study, and 47,828 men followed for 14 years in the Health Professionals Follow-up Study, we documented 248 incident cases of renal cell cancer. We assessed consumption of beverages every 2 to 4 years using a validated semiquantitative food frequency questionnaire, and total fluid intake was derived from the frequency of consumption of 18 to 22 beverage items. Cox proportional hazards regression was used to estimate study-specific multivariate relative risks (RR), which were pooled

using a random-effects model. We found no association between total fluid intake and risk of renal cell cancer; the pooled multivariate RR for the highest quartile versus the lowest was 0.99 (95% confidence interval, 0.63-1.55; *P*, test for trend = 0.78). Alcohol intake was marginally inversely associated with renal cell cancer risk; compared with nondrinkers, the pooled multivariate RR for ≥ 15 g/d was 0.66 (95% confidence interval, 0.43-1.00; *P*, test for trend = 0.07). We did not find clear associations between intakes of coffee, tea, milk, juice, soda, punch, and water and risk of renal cell cancer. Our data suggest an inverse association between alcohol intake and risk of renal cell cancer, but do not support the hypothesis that greater total fluid intake reduces the risk of renal cell cancer. (Cancer Epidemiol Biomarkers Prev 2006;15(6):1204-11)

Introduction

Renal cell cancer accounts for >80% of all kidney cancers, and its incidence rate has increased steadily by >2% per year among White and Black men and women in the United States (1). This rapid increase is not fully explained by the increasing detection of tumors (1), and suggests that other environmental factors, including diet, may have contributed to the upward trend. Obesity, smoking, and hypertension are associated with a greater risk of renal cell cancer (2-5) and various aspects of diet have been linked to renal cell cancer in epidemiologic studies.

The role of alcohol intake in the risk of renal cell cancer has been prospectively evaluated among postmenopausal U.S. women (124 kidney cancer cases, including 116 renal cell cancer cases; ref. 6), Swedish middle-aged and elderly women (132 renal cell cancer cases; ref. 7), and male Finnish smokers (195 renal cell cancer cases; ref. 8). To our knowledge, these three studies are the only prospective cohort studies with >100 cases that examined alcohol intake in relation to renal cell cancer risk and all found reduction in risk ranging from 38% to 48%. One hypothesized mechanism is that a diluting effect caused by high fluid intake may reduce the risk of renal cell cancer by decreasing the concentration of carcinogenic solutes in the glomerular filtrate and the time that these solutes are in contact with renal epithelial cells. Two case-control studies examined the association between total beverage intake and renal cell cancer risk and they did not find clear associations

(9, 10). Although environmental risks of contaminated water in specific regions have been investigated (11), information on the relation of the quantity of water intake, including bottled water, with risk of renal cell cancer is scant. Another possible biological mechanism for alcohol in reducing renal cell cancer risk is by reducing insulin resistance. Insulin resistance has been suggested to increase the risk of renal cell cancer. This hypothesis is supported indirectly by the increase in risk of renal cell cancer seen among obese (2, 4, 5) and diabetic individuals (12, 13).

Specific individual beverages may act differently on renal epithelial cells because types and the amount of compounds, such as alcohol, caffeine, and antioxidants, in each beverage differ. Alcohol, coffee, and tea may lead to hormonal changes in kidney (14), and antioxidants alleviate the oxidative damage to DNA, proteins, and other molecules (15). Case-control studies examining coffee and tea (9, 10, 16-25), and soda (9, 16-18, 20, 24), have shown inconsistent findings. For milk, an increased risk has been observed for whole milk (18), high-fat milk (26), and total milk (19, 20) in several case-control studies, but no association for total milk has been observed in other studies (25, 27, 28). Information on specific individual beverages from prospective studies remains sparse due to the small number of cases.

We prospectively examined total fluid intake and intakes of specific beverages in relation to risk of renal cell cancer in two large cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

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Materials and Methods

Study Population. The NHS was established in 1976, when 121,700 female registered nurses who were aged 30 to 55 years returned a mailed questionnaire. The HPFS was initiated in 1986 when 51,529 male health professionals, consisting of dentists, pharmacists, optometrists, osteopath physicians,

podiatrists, and veterinarians, aged 40 to 75 years, returned a mailed questionnaire. Participants in these two cohorts provided detailed information about medical history, lifestyle, and various risk factors for chronic diseases on biennial follow-up questionnaires. The follow-up rates for the populations were >90% of potential person-time. This study and the NHS were approved by the institutional review board of the Brigham and Women's Hospital (Boston, MA); the HPFS was approved by the institutional review board of the Harvard School of Public Health (Boston, MA).

Assessment of Beverage Intakes and Other Factors. Dietary information was collected from the NHS participants using validated semiquantitative food frequency questionnaires (SFFQ) in 1980, 1984, 1986, and every 4 years since 1986, and from the HPFS participants every 4 years since 1986. In the NHS, the 1980 questionnaire included 12 beverage items, and it was expanded to include 21 items in 1984. In the HPFS, SFFQs with 22 beverage items were administered in 1986 and every 4 years thereafter.

Participants were asked how frequently, on average, during the past year they drank one standard serving of each specific beverage item in nine categories (<1/mo, 1-3/mo, 1/wk, 2-4/wk, 5-6/wk, 1/d, 2-3/d, 4-5/d, or $\geq 6/d$). If more than one item was assessed for specific beverage groups, we summed the average daily intakes of related beverages. Total fluid intake was calculated as milliliters per day by summing intakes of all beverages. We determined alcohol intake by multiplying the specific alcoholic beverage by its ethanol content; 12.8 g 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 a standard drink of liquor (29).

In comparisons with diet records, our SFFQs have shown good validity. The correlation coefficients between the SFFQs and multiple 1-week weighted diet records were 0.86 to 0.90 for alcohol (30). After correction for attenuation due to random error in diet records, the correlation coefficients were 0.78 to 0.93 for coffee, 0.62 to 0.88 for milk, 0.40 to 0.84 for soda, 0.56 for punch (noncarbonated fruit flavored drinks, Hawaiian punch, or lemonade), 0.75 to 0.89 for juice, and 0.52 for water (31, 32). Total fluid intake was reasonably measured by the SFFQs (deattenuated $r = 0.50$ with two 1-week diet records, $r = 0.59$ with 24-hour urine; ref. 33).

Information on body mass index [BMI, weight (kg)/height (m^2)], history of physician-diagnosed hypertension, history of diabetes, multivitamin use, and dose and duration of smoking were obtained using each biennial questionnaire. In the NHS, parity among women was updated until 1984.

Assessment of Outcome. Self-reported information on kidney cancer on each questionnaire was obtained, and participants, or next of kin for descendents, who reported a diagnosis of kidney cancer were asked for permission to access medical records related to the diagnosis. The deaths in the cohort were ascertained by reports from family members in response to the follow-up questionnaires; in addition, the National Death Index (34) was used to identify fatalities. Physicians blinded to participants' risk factor status reviewed medical records. We included only renal cell cancer as cases because transitional cell cancer, which arises mainly from the renal pelvis, may have a different etiology. We had information on histology for all the confirmed cases. After a review of medical records, we included clear cell carcinoma ($n = 148$), papillary carcinoma ($n = 25$), chromophobe carcinoma ($n = 3$), and renal cell carcinoma not otherwise classified ($n = 72$), based on the classification developed by the workshop held by the WHO (35). A total of 132 cases (including four cases identified from the National Death Index) in the NHS and 116 cases (including five cases identified from the National Death Index) in the HPFS were included after applying exclusion criteria.

Statistical Analyses. We excluded participants who did not return the baseline SFFQ, had been previously diagnosed with cancer (except nonmelanoma skin cancer), left extensive items blank on the baseline SFFQs for each analysis (>10 in 1980, >11 in 1984, and ≥ 70 in 1986), or reported implausible energy intake at baseline (<500 or >3,500 kcal/d for women and <800 or >4,200 kcal/d for men). As a result, 88,759 women in the NHS and 47,828 men in the HPFS were included in the analyses, for which follow-up started in 1980 and 1986, respectively. For the juice analyses for women, follow-up began in 1984 because only one question about juice was asked in 1980 (77,226 women). We used 1986 as the starting year for total fluid intake and water because water consumption was first asked in 1986 in the NHS (68,738 women). Person-years of follow-up were calculated from the date that the baseline questionnaire was returned to the date of renal cell cancer diagnosis, date of death, or end of follow-up (May 31, 2000, for women; January 31, 2000, for men), whichever came first.

Participants were categorized by using absolute cut points or quartiles on the basis of the distribution of each beverage. In the main analyses, cumulative average intakes were calculated from the year that specific beverage intake was first assessed. For example, in the NHS, coffee intake in 1980 was used for analyses of renal cell cancer diagnosed from 1980 through 1984, and the average coffee intake through 1980 to 1984 was used for analyses of renal cell cancer diagnosed from 1984 through 1986. We also did analyses using just baseline exposure information and then additionally did simple updated analyses. Simple update intakes were calculated using the most recent SFFQs before the diagnosis. For example, alcohol intake in 1980 was used for analyses of renal cell cancer diagnosed from 1980 through 1984, and alcohol intake in 1984 was used for analyses of renal cell cancer diagnosed from 1984 through 1986. In the baseline analyses, we used only the baseline SFFQs. The relative risks (RR) were calculated using the Cox proportional hazards model (36) with SAS PROC PHREG (37). We tested whether the assumption of the proportional hazards was satisfied by adding interaction terms between time and beverage intake and found that the assumption was satisfied. By stratifying by age in months at start of follow-up and calendar year of the current questionnaire cycle, we finely controlled for confounding by age, calendar time, and possible two-way interactions between these two time scales. In the multivariate models, we also adjusted for possible risk factors, including BMI (<25, 25-26.9, 27-29.9, and ≥ 30 kg/ m^2), smoking (never, 1-19, 20-39, and ≥ 40 pack-years of smoking), history of hypertension (yes, no), and total energy intake (continuous) for both men and women, multivitamin use (ever, never) for men, and parity (continuous) and history of diabetes (yes, no) for women. Because multivitamin use in women and history of diabetes in men were not associated with risk of renal cell cancer, we did not include these factors in the study-specific multivariate models. Pack-years of smoking were calculated using duration and dose of smoking; one pack-year is equivalent to having smoked one pack per day for 1 year. Two-sided 95% confidence intervals (95% CI) were obtained for the RRs. To calculate the P value for the test for trend, participants were assigned the median value of their intake category, and this variable was treated as a continuous term in the model.

After obtaining RRs from each cohort, we combined \log_e RRs using a random-effects model (38, 39). Heterogeneity between the two studies was assessed by the Q statistic (40, 41).

We examined if the risk estimates for alcohol from beer, wine, and liquor varied using a contrast test (42); the null hypothesis was that there was no difference in the pooled estimates across the three alcoholic beverages. This test statistic has an approximate χ^2 distribution with 2 degrees of freedom.

We also did several subgroup analyses and examined whether the association varied by BMI, history of hypertension, smoking habits, or age. Tests for heterogeneity were conducted using a Wald test based on the pooled estimates of the cross-product term of a continuous beverage variable with a binary modifier variable. For the polychotomous exposure variables, we used a two-sample Wald test to compare the pooled multivariate RRs for the exposure level of interest (e.g., the RR for the top to bottom category contrast) across the two levels of the potential modifier.

Results

We documented 132 incident cases of renal cell cancer during 1,708,260 person-years of follow-up in the NHS and 116 cases during 608,265 person-years of follow-up in the HPFS. For analyses of total fluid intake (including water intake) in the NHS, for which follow-up started in 1986, we documented 86 incident cases of renal cell cancer during 925,663 person-years of follow-up. Women and men who had greater fluid intake were more likely to be physically active, to consume more alcohol, to take multivitamins, to smoke, and to have a history of hypertension and a history of diabetes (Table 1).

Total fluid intake was not associated with risk of renal cell cancer (Table 2). The results were similar for women and men. Compared with the lowest quartile, the multivariate RRs for the highest quartile were 0.95 (95% CI, 0.48-1.88) in women and 1.02 (95% CI, 0.56-1.86) in men. When we used more extreme absolute cut points, there was still no significant association (data not shown). When we combined the two studies into a single data set and adjusted for study in the aggregated analysis, the results were similar to the results in the pooled analysis (data not shown). When total fluid intake was modeled continuously, the pooled multivariate RR for an

increment of 240 mL/d (equivalent to one 8 oz glass of water per day) was 0.98 (95% CI, 0.93-1.04). Further adjustment for physical activity (tertiles) did not change the results (data not shown). We also alternatively adjusted for smoking habits using time since quitting among former smokers, and the number of cigarettes per day among current smokers, and found that the results did not differ from the results when we adjusted for pack-years of smoking (data not shown).

We conducted additional analyses to examine the association between total fluid intake and risk of renal cell cancer using only the baseline intake (intakes in 1986) and did not find an association (pooled multivariate RR, 0.98 for an increment of 240 mL/d; 95% CI, 0.92-1.05). When we used simple updating, which reflects recent fluid intake because intake was updated every 4 years, the pooled multivariate RR for an increment of 240 mL/d was 0.99 (95% CI, 0.95-1.04). When we excluded the first 2 years of follow-up (1986-1988 in the NHS and the HPFS; 76 renal cell cancer cases in women and 103 cases in men were included) to ensure that this finding was not due to changes in total fluid intake because preclinical symptoms, the results did not change (pooled multivariate RR for an increment of 240 mL/d, 0.98; 95% CI, 0.91-1.06). Because some covariates could be affected by renal cell cancer that had not yet been diagnosed, we did additional analyses using a 4-year lag between the assessment of covariate and diagnosis of renal cell cancer. For example, for fluid intake in the NHS, 1982 covariate information (e.g., BMI) was used to adjust the RR of renal cell cancer diagnosed from 1986 to 1988, 1984 information was used for renal cell cancer diagnosed from 1988 to 1990, and so forth. Because HPFS started in 1986, we examined the renal cell cancer cases diagnosed from 1990 onward. In this analysis that included 166 renal cell cancer cases, compared with the lowest quartile of total fluid intake, the pooled multivariate RR was 1.09 (95% CI, 0.66-1.79; *P*, test for trend = 0.90) for the highest quartile.

Table 1. Baseline characteristics for total fluid intake in 1986

	Total fluid			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
NHS women				
No. participants	17,110	17,397	17,281	16,950
Median intake (mL/d)	1,258	1,770	2,217	2,874
Age (y)*	52.7	53.0	53.2	53.0
BMI (kg/m ²)*	24.8	25.1	25.5	25.9
Physical activity (METS/wk)*,†	12.4	13.2	14.5	16.0
Alcohol intake (g/d)*	4.5	5.4	6.4	8.3
Animal fat (g/d)*	32.8	32.7	32.7	32.6
Dietary fiber (g/d)*,‡	17.6	17.7	17.8	17.6
Current smoker (%)	16.7	18.9	22.3	26.4
History of hypertension (%)	22.6	24.4	25.2	26.3
History of diabetes (%)	2.9	3.5	4.1	4.5
Current multivitamin user (%)	38.0	41.3	43.9	46.2
HPFS men				
No. participants	11,662	12,138	12,128	11,990
Median intake (mL/d)	1,137	1,678	2,160	2,906
Age, mean (y)*	54.9	54.7	54.6	53.5
BMI (kg/m ²)*	25.1	25.3	25.6	26.1
Physical activity (METS/wk)*,†	19.2	20.4	21.8	22.3
Alcohol intake (g/d)*	7.0	9.6	11.8	16.8
Animal fat (g/d)*	40.8	41.0	41.2	41.6
Dietary fiber (g/d)*,‡	21.9	21.3	20.9	20.1
Current smoker (%)	6.2	8.0	10.6	13.5
History of hypertension (%)	21.2	21.2	22.2	23.5
History of diabetes (%)	2.6	2.8	3.1	4.3
Current multivitamin user (%)	39.3	41.4	41.7	44.4

NOTE: Values, except for the number of participants, fluid median intake, and age, are standardized according to the age distribution of cohort.

Abbreviation: MET, metabolic equivalents.

*Mean values. Animal fat and dietary fiber values represent the mean energy-adjusted intake.

†One MET is the energy expended by sitting quietly. Each activity was assigned a MET value, e.g., swimming = 7 METS and running = 12 METS. Total METS per week were calculated by summing all METS per week of each activity.

‡Dietary fiber was calculated using AOAC method.

Table 2. Pooled multivariate RRs of renal cell cancer associated with beverage intakes

Beverage	Categories				<i>P</i> , test for trend	<i>P</i> , test for between-studies heterogeneity
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		
Total fluid*						
Median (mL/d), women/men	1,334/1,191	1,816/1,689	2,235/2,136	2,832/2,823		
RR (95% CI)	1.00	1.15 (0.77-1.73)	1.09 (0.72-1.65)	0.99 (0.63-1.55)	0.78	0.88
Alcohol (g/d)	None	0.1-4.9	5.0-14.9	≥15.0		
No. cases, women/men	30/28	53/35	34/27	15/26		
RR (95% CI)	1.00	0.96 (0.68-1.34)	0.87 (0.46-1.64)	0.66 (0.43-1.00)	0.07	0.36
Beer	None	Drinkers				
No. cases, women/men	114/50	18/64				
RR (95% CI)	1.00	0.67 (0.37-1.24)				0.05
RR (95% CI)†	1.00	0.68 (0.38-1.23)				0.07
Wine (serving)	<1/mo	1/mo to <2/wk	≥2/wk			
No. cases, women/men	48/45	51/45	33/26			
RR (95% CI)	1.00	1.12 (0.84-1.50)	1.06 (0.71-1.58)		0.72	0.24
RR (95% CI)†	1.00	1.16 (0.86-1.55)	1.12 (0.70-1.79)		0.72	0.17
Liquor (serving)	<1/mo	1/mo to <2/wk	≥2/wk			
No. cases, women/men	79/50	30/28	23/37			
RR (95% CI)	1.00	0.88 (0.64-1.21)	0.84 (0.60-1.16)		0.32	0.97
RR (95% CI)†	1.00	0.90 (0.65-1.23)	0.87 (0.62-1.21)		0.44	0.91
Coffee (cups)	<1/mo	1/mo to <1/d	1 to <3/d	≥3/d		
No. cases, women/men	23/31	22/33	63/35	24/15		
RR (95% CI)	1.00	0.91 (0.62-1.34)	0.85 (0.60-1.21)	0.84 (0.54-1.30)	0.41	0.40
Decaffeinated coffee (cups)‡	<1/mo	1/mo to <1/d	1 to <2/d	≥2/d		
No. cases, women/men	40/40	30/45	16/15	19/15		
RR (95% CI)	1.00	0.94 (0.57-1.57)	0.95 (0.62-1.46)	1.20 (0.80-1.80)	0.38	0.57
Tea (cups)	<1/mo	1/mo to <1/wk	1/wk to <1/d	≥1/d		
No. cases, women/men	39/43	15/25	41/34	37/12		
RR (95% CI)	1.00	0.78 (0.46-1.32)	0.93 (0.55-1.56)	0.78 (0.54-1.13)	0.49	0.63
Milk (servings)	<2/wk	2/wk to <1/d	1/d to <2/d	≥2/d		
No. cases, women/men	39/29	46/44	33/17	14/26		
RR (95% CI)	1.00	0.91 (0.63-1.33)	0.82 (0.56-1.20)	1.09 (0.39-2.99)§	0.83	0.02
Juice (servings)†	<2/wk	2/wk to <1/d	1 to <2/d	≥2/d		
No. cases, women/men	26/29	38/43	36/35	6/9		
RR (95% CI)	1.00	0.98 (0.69-1.39)	1.11 (0.77-1.60)	1.12 (0.61-2.07)	0.51	0.98
Soda (servings)	<1/wk	1/wk to <1/d	1/d to <2/d	≥2/d		
No. cases, women/men	36/32	56/60	22/16	18/7		
RR (95% CI)	1.00	1.12 (0.82-1.52)	0.99 (0.66-1.50)	1.03 (0.64-1.68)	0.99	0.56
Water (servings)*	<1/d	1-<3/d	3-<5/d	≥5/d		
No. cases, women/men	11/17	34/56	28/33	13/10		
RR (95% CI)	1.00	1.07 (0.70-1.64)	1.12 (0.71-1.76)	0.83 (0.47-1.48)	0.80	0.98

NOTE: In the NHS, multivariate RRs were adjusted for BMI (<25, 25-26.9, 27-29.9, or ≥30 kg/m²), history of hypertension (yes, no), parity (continuous), history of diabetes (yes, no), smoking status (never, 1-19, 20-39, ≥40 pack-years), and total energy intake (continuous). In the HPFS, multivariate RRs were adjusted for BMI (<25, 25-26.9, 27-29.9, or ≥30 kg/m²), history of hypertension (yes, no), smoking status (never, 1-19, 20-39, ≥40 pack-years), multivitamin use (never, past, current), and total energy intake (continuous). Models of all beverages, except alcoholic beverages, were additionally adjusted for alcohol intake (continuous).

*In the NHS, follow-up was started in 1986 and 86 cases were included.

†Additionally adjusted for two other alcoholic beverages (continuous).

‡In the NHS, follow-up was started in 1984 and 106 cases were included.

§Multivariate RRs were 0.64 (95% CI, 0.34-1.22) in the NHS and 1.80 (95% CI, 1.02-3.16) in the HPFS.

Alcohol was associated with a decreased risk of renal cell cancer (Table 2). The inverse association was largely driven by the association in men; however, the difference by gender was not statistically significant. Compared with nondrinkers, the multivariate RRs for ≥15 g/d were 0.83 (95% CI, 0.43-1.58) in women and 0.55 (95% CI, 0.31-0.97) in men (*P*, test for

between-studies heterogeneity = 0.36). The most important confounding factor was smoking; the pooled age- and smoking-adjusted RR for ≥15 g/d versus nondrinkers was 0.69 (95% CI, 0.45-1.07; *P*, test for trend = 0.12). The results did not differ when we adjusted for smoking habits using time since quitting among former smokers and the number of

cigarettes per day among current smokers instead of pack-years of smoking (data not shown). When we combined the two studies into a single data set and adjusted for study, the results were similar to the results in the pooled analysis (data not shown). We did additional analyses to examine the temporal relation between alcohol intake and renal cell cancer risk. In the simple update analyses, which used alcohol consumption closest to and before diagnosis, the association was inverse, but not significant (compared with nondrinkers, pooled multivariate RR for ≥ 15 g/d = 0.75; 95% CI, 0.48-1.17; *P*, test for trend = 0.13). This weaker association could be explained by error due to measuring intake with a single assessment, which was reduced in the analyses using the cumulative update average, or by a weaker association with recent alcohol intake than with long-term alcohol intake. Also, it is plausible that the association for alcohol intake is compatible with a long induction period because we found that baseline alcohol intake was inversely associated with risk of renal cell cancer (compared with nondrinkers, the pooled multivariate RR for ≥ 15 g/d = 0.64; 95% CI, 0.43-0.96; *P*, test for trend = 0.06). When we used a 4-year lag for covariate information, the pooled multivariate RRs were 0.94 (95% CI, 0.65-1.35) for 0.1-4.9 g/d of alcohol, 0.85 (95% CI, 0.39-1.86) for 5.0-14.9 g/d, and 0.63 (95% CI, 0.32-1.26; *P*, test for trend = 0.25) for ≥ 15 g/d. In this analysis that included 212 renal cell cancer cases, an inverse pattern was observed although the association for alcohol intake was not significant.

To address the possibility that participants with symptoms that could be related to renal cell cancer abstained from alcohol, we excluded participants who were nondrinkers at baseline but reported having reduced their alcohol intake in the past (2 renal cell cancer cases in women and 22 cases in men were excluded in the analysis). A similar pattern of an inverse association was observed; compared with nondrinkers in the past and at baseline, the pooled multivariate RR for ≥ 15 g/d was 0.66 (95% CI, 0.42-1.06; *P*, test for trend = 0.12). In another analysis, we excluded the first 2 years of follow-up, and the results were not changed.

We also examined the associations with specific alcoholic beverages (Table 2). Because of low intake of beer in women

(75% women were non-beer drinkers across the follow-up periods), we were only able to compare beer drinkers versus non-beer drinkers. Multivariate RRs for beer drinkers versus nondrinkers were 0.49 (95% CI, 0.30-0.81) in women and 0.90 (95% CI, 0.61-1.34) in men. The difference in the risk estimates between women and men could be due to chance. We did not observe any significant associations for each alcoholic beverage in the pooled analysis of the two cohorts, but we had limited power. When we analyzed intakes of specific alcoholic beverages as continuous variables, the pooled RRs for an increment of two servings per week were 0.87 (95% CI, 0.75-1.02) for beer, 1.00 (95% CI, 0.93-1.08) for wine, and 0.99 (95% CI, 0.91-1.07) for liquor. We did not observe significant differences in associations for the three types of alcoholic beverages (*P*, test for differences across beer, wine, and liquor = 0.19, for women and men combined).

Because alcohol was inversely associated with risk and contributed to total fluid intake, we examined total nonalcoholic fluid intake by excluding alcoholic beverages from total fluid intake; compared with the lowest quartile, the pooled multivariate RR for the highest quartile of total nonalcoholic fluid intake was 0.94 (95% CI, 0.60-1.47).

Neither caffeinated nor decaffeinated coffee was associated with risk of renal cell cancer (Table 2). Tea consumption was also not significantly associated with risk of renal cell cancer (Table 2). For total milk intake and risk of renal cell cancer, we found significant heterogeneity between the two cohorts; a significant positive association (multivariate RR, 1.80; 95% CI, 1.02-3.16) was seen in men; and a nonsignificant inverse association (multivariate RR, 0.64; 95% CI, 0.34-1.22) was observed in women (Table 2). The average proportion of participants who drank ≥ 2 servings of milk per day across the follow-up period was 17% in men and 18% in women. For whole milk, the pooled multivariate RR for an increment of one serving per day was 1.05 (95% CI, 0.76-1.46; *P*, test for between-studies heterogeneity = 0.27), and the pooled multivariate RR for an increment of one serving per day of low-fat milk was 1.05 (95% CI, 0.80-1.37; *P*, test for between-studies heterogeneity = 0.07). Juice and soda consumption were not associated with risk of renal cell cancer (Table 2). Also, there

Table 3. Pooled multivariate RRs of renal cell cancer associated with total fluid intake and alcohol intake by other variables

Variables (no. cases)	RR			<i>P</i> , test for trend	<i>P</i> , test for between-studies heterogeneity	<i>P</i> , test for interaction*
	RR (95% CI)	RR (95% CI)	RR (95% CI)			
	Total fluid					
	Tertile 1	Tertile 2	Tertile 3			
BMI (kg/m ²)						
<25 (<i>n</i> = 76)	1.00	0.84 (0.48-1.47)	1.01 (0.54-1.88)	0.98	0.99	0.78
≥ 25 (<i>n</i> = 126)	1.00	1.11 (0.71-1.73)	0.88 (0.54-1.43)	0.54	0.99	
History of hypertension						
Yes (<i>n</i> = 109)	1.00	1.16 (0.71-1.90)	1.06 (0.62-1.79)	0.91	0.65	0.46
No (<i>n</i> = 93)	1.00	0.80 (0.48-1.31)	0.68 (0.39-1.19)	0.17	0.54	
Smoking						
Ever (<i>n</i> = 122)	1.00	1.41 (0.87-2.30)	1.07 (0.63-1.82)	0.94	0.40	0.63
Never (<i>n</i> = 80)	1.00	0.54 (0.31-0.94)	0.79 (0.38-1.64)	0.38	0.22	
		Alcohol (g/d)				
	None	0.1-4.9	≥ 5.0			
BMI (kg/m ²)						
<25 (<i>n</i> = 102)	1.00	0.84 (0.48-1.46)	0.69 (0.26-1.80)	0.54	0.07	0.71
≥ 25 (<i>n</i> = 146)	1.00	1.10 (0.71-1.71)	0.89 (0.57-1.40)	0.32	0.61	
History of hypertension						
Yes (<i>n</i> = 127)	1.00	0.72 (0.43-1.20)	1.07 (0.66-1.74)	0.23	0.30	0.42
No (<i>n</i> = 121)	1.00	1.31 (0.82-2.09)	0.62 (0.31-1.21)	0.04	0.18	
Smoking						
Ever (<i>n</i> = 150)	1.00	0.98 (0.60-1.61)	0.88 (0.55-1.42)	0.42	0.86	0.91
Never (<i>n</i> = 98)	1.00	1.07 (0.66-1.73)	0.81 (0.26-2.51)	0.67	0.03	

NOTE: The same covariates listed in Table 2 were adjusted. For total fluid, alcohol intake (continuous) was additionally adjusted.

*For the highest category.

was no association with intake of fruit juice alone (RR for an increment of one serving per day, 1.06; 95% CI, 0.88-1.28). No significant association was observed for artificially sweetened or sugar-sweetened soda and risk of renal cell cancer; the pooled multivariate RR for an increment of one serving per day of sugar sweetened soda was 0.95 (95% CI, 0.69-1.31), and the pooled multivariate RR for an increment of one serving per day of artificially sweetened soda was 0.97 (95% CI, 0.82-1.15). We did not find any association between punch consumption and risk of renal cell cancer (data not shown), but we had limited power because of the high proportion of non-punch drinkers (the average of 64% women, and 67% men across the follow-up period). Water consumption was not associated with renal cell cancer risk in men or women. In the water analyses, adjustment for physical activity (tertiles) did not alter the results (data not shown).

The associations of total fluid intake and alcohol intake with risk of renal cell cancer did not vary by BMI, history of hypertension, and smoking status (Table 3). The associations between intakes of coffee, tea, milk, juice, soda, punch, and water and risk of renal cell cancer were also not modified by BMI, history of hypertension, and smoking status (data not shown). Similarly, age (<65, ≥65 years) did not modify the associations of total fluid intake and intakes of individual beverages with risk of renal cell cancer (data not shown).

Discussion

In a pooled analysis of two large cohorts, we found that total fluid intake was not associated with risk of renal cell cancer, but moderate alcohol intake was associated with a lower risk. Although the inverse association for alcohol was mainly driven by the association in men, the difference by gender was not statistically significant.

The results from some case-control studies have shown an inverse association between alcohol intake and risk of renal cell cancer (9, 16, 17, 43), but no clear association (18, 20, 21, 25, 27, 44, 45) or a positive association (24) was found in others. Because dietary intake among the cases in case-control studies is measured after diagnosis, differential misclassification of alcohol intake may have occurred because recall of alcohol consumption among the cases or selection of controls may have been biased by their health status or awareness of health-related behaviors. In our data, smoking was the strongest confounder of the association between alcohol intake and risk of renal cell cancer, and adjustment for smoking strengthened the association of alcohol intake with renal cell cancer risk. Although most case-control studies adjusted for smoking habits, the lack of control for potential bias, including inadequate control for smoking habits due to recall bias or selection bias, could lead to no or a positive association.

Some cohort studies examined the risk of kidney cancer among alcoholics or heavy drinkers (46-49), but these studies were limited due to the small number of cases, generalizability, and the absence of information on confounders. Our findings are consistent with results from the only three large prospective studies (6-8) with >100 renal cell cancer cases that examined the association between alcohol intake and risk of renal cell cancer. In these prospective studies, the multivariate RRs were 0.52 (95% CI, 0.29-0.92) for ≥3 g/d versus nondrinkers among postmenopausal U.S. women (6), 0.62 (95% CI, 0.41-0.94) for one or more servings per week versus less than one serving per week among middle-aged and elderly Swedish women and 0.53 (95% CI, 0.34-0.83) for the highest quartile (median 39.1 g/d) versus the lowest (median 0.4 g/d) among male Finnish smokers (8).

Ecological studies have found a strong correlation between per capita consumption of coffee and mortality rate (50) and the incidence rate of renal cell cancer (51). Because an excess of

coffee drinking may be correlated with smoking, this result for coffee could be confounded by smoking. In case-control studies of renal cell cancer, findings for coffee intake have been inconsistent (9, 10, 16-22, 24, 25). Prospective studies of coffee intake and risk of renal cell cancer have been few and small (44-62 renal cell cancer cases; refs. 52-54). In a Norwegian prospective study (44 cases; ref. 53), coffee consumption was associated with a lower risk of renal cell cancer but the highest category included only two cases. Two other prospective studies did not find significant associations (52, 54). We did not observe any significant associations between either caffeinated or decaffeinated coffee and risk of renal cell cancer.

Although several polyphenolic substances in tea have been suggested to inhibit carcinogenesis (55), most case-control studies, in agreement with our data, have not found any significant associations between tea intake and renal cell cancer risk (9, 16-23).

High milk consumption (18-20, 26) or high protein consumption (mainly animal protein; refs. 18, 56, 57) has been associated with an increased risk of renal cell cancer in several case-control studies, but we saw no association for milk intake in the pooled analysis. We found a nonsignificant inverse association with milk intake among women and a significantly higher risk among men. Although this gender difference may be due to chance, we cannot rule out the possibility that the effects of nutrients in milk or other compounds in milk on renal cell cancer risk differ by gender. It is possible that a higher circulating level of insulin-like growth factor I among milk drinkers (58) is associated with an increased risk of renal cell cancer among men. Further research is needed to confirm an increased risk among men and any effect modification by sex hormones with a larger sample size.

Some case-control studies (17, 18, 24) have reported an increase in risk of renal cell cancer among users of artificial sweeteners or low-calorie soda, but no clear associations for total soft drink (9, 16, 20), low-calorie drink (16), or artificial sweeteners (16, 25) have been observed in other studies. Likewise, we did not find any significant associations for either artificially sweetened or sugar-sweetened soda. One prospective study observed a nonsignificant increase in risk of renal cell cancer among women who consumed ≥2 to 3 servings of fruit juice per week compared with nondrinkers (59). We did not find any association for either fruit juice or total juice.

Our findings suggest that a diluting effect by high overall fluid intake is unlikely to be a mechanism underlying renal cell cancer risk reduction. Because a validation study of the SFQs used in this study showed that total fluid intake has been fairly well measured ($r = 0.59$ with 24-hour urine; ref. 33) and because the use of repeated assessments of intake reduced measurement error, misclassification of total fluid intake is not likely to explain our results. Also, in these cohorts, total fluid intake has been associated with a lower risk of bladder cancer (33) and kidney stones (60, 61). Further adjustment for physical activity or time since quitting and the number of current cigarettes per day did not change our results.

A potential mechanism for the inverse association with alcohol is improvement of insulin sensitivity (62-64). Indirect evidence suggests that insulin resistance may increase the risk of renal cell cancer. Obesity, a known risk factor for renal cell cancer, increases insulin resistance, and hyperinsulinemia elevates the bioactivity of insulin-like growth factor-I (65). Experimental studies have shown that insulin-like growth factor-I has adverse effects on progression of renal cell cancer (66-68). Individuals with type 2 diabetes, which results from reduced insulin sensitivity (69), may be more likely to develop renal cell cancer (12, 13).

Improvement of vascular function by alcohol through an increase in high-density lipoprotein level, and a decrease in fibrinogen, and other hemostatic factors (70) could be considered, as higher incidence of renal cell cancer was

observed among patients who had venous thromboembolism in the year preceding the cancer diagnosis (71), and among patients with ischemic syndromes (72), and lower incidence among patients who used statins (73), although the possibility of reverse causation, uncontrolled potential confounders, and other effects of statins in these studies should not be neglected.

The strengths of this study are the relatively large number of cases in a prospective design, with a long and high rate of follow-up. To our knowledge, our study has the largest number of prospective cases examining various types of beverages in relation to the risk of renal cell cancer. Also, we were able to examine total fluid intake in relation to risk of renal cell cancer because water consumption, the primary contributor to total fluid intake (74), was measured in our study. Because nondietary and dietary measures were updated, we were able to account for changes in intake over time and examined both recent and long-term beverage consumption. Given the validity of our measurement of most beverage intakes, random misclassification is not likely to obscure the associations, although we cannot rule out the possibility of a small effect. Although we had many cases relative to other prospective studies of renal cell cancer, we could not examine drinking patterns of alcohol, high intake of alcohol, and more than a 2-year lag due to a limited number of cases.

In conclusion, we found that moderate alcohol intake was associated with a lower risk of renal cell cancer, whereas total fluid intake and consumption of other beverages were not associated with risk of renal cell cancer. The inverse association between alcohol intake and renal cell cancer risk in our data warrants further study of underlying biological mechanisms.

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Total Fluid Intake and Use of Individual Beverages and Risk of Renal Cell Cancer in Two Large Cohorts

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