Prospective Study of Alcohol Drinking and Renal Cell Cancer Risk in a Cohort of Finnish Male Smokers

Somdat Mahabir,[1] Michael F. Leitzmann,[2] Mikko J. Virtanen,[3] Jarmo Virtamo,[3] Pirjo Pietinen,[3] Demetrius Albanes,[2] and Philip R. Taylor[1]

[1]Cancer Prevention Studies Branch, Center for Cancer Research, and [2]Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; and [3]Department of Epidemiology and Health Promotion, National Public Health Institute, Helsinki, Finland

Abstract

Of the few studies that have examined alcohol consumption in relation to risk of renal cell cancer (RCC), most are case-control studies. The extent to which alcohol affects RRC risk is unclear. We prospectively examined the association between total alcohol intake as well as specific types of alcoholic beverage and RCC in a large cohort of Finnish male smokers. Men from the Alpha-Tocopherol, BetaCarotene (ATBC) Cancer Prevention Study were followed for 12 years and RCC cases were identified. Alcohol consumption was assessed at baseline using a questionnaire previously shown to be both reproducible and valid. Cox proportional hazards modeling was used to adjust simultaneously for known or suspected risk factors for RCC. We ascertained 195 incident cases of RCC. In multivariate analysis, the relative risks and 95% confidence intervals (CI) of RCC according to increasing quartiles of total alcohol intake were 1.0, 0.91 (0.62-1.33), 0.94 (0.64-1.38), and 0.53 (0.34-0.83), respectively (*P* value for trend = 0.005); for spirit consumption, 1.0, 0.93 (0.63-1.39), 0.84 (0.58-1.20), and 0.55 (0.36-0.85) (*P* for trend = 0.02); and for beer intake, 1.0, 1.22 (0.85-1.76), 0.83 (0.57-1.22), and 0.55 (0.36-0.85) (*P* for trend = 0.003). Too few people in this cohort drank wine to assess its association with risk of RCC. These data suggest that alcohol consumption is associated with decreased risk of RCC in male smokers. Because most of the risk reductions were seen at the highest quartile of alcohol intake and alcohol is a risk factor for a number of cancers particularly among smokers, these data should be interpreted with caution. (Cancer Epidemiol Biomarkers Prev 2005;14(1):170–5)

Introduction

The incidence of renal cell cancer (RCC), the most common form of kidney cancer, has been increasing in the United States (1), other Western countries (2,3) and worldwide (4). In the United States, incidence rates of RCC have increased by about 2% per year among the major race groups since 1970 (5). RCC also now accounts for approximately 2% of cancers in the United States (6) as well as worldwide (4). RCC is more common among men than women and the incidence rates vary more than 10-fold in the world. The highest rates are found in North America and Europe and the lowest in Asia (4).

Whereas there is good evidence that smoking (7,8) and obesity (8,9) are risk factors for RCC, it is unclear whether alcohol consumption plays a role in RCC carcinogenesis. Most previous case-control (10-15) and cohort studies (16-20) have shown no association of RCC with alcohol consumption, which may be due to small sample sizes. However, two large case-control studies (21,22) and one prospective cohort study (9) reported that alcohol consumption was associated with significant reduction of risk for RCC in women only.

We examined the relationship between alcohol consumption and risk of RCC in a large prospective cohort of middle-aged Finnish male smokers with detailed information on body mass index (BMI), diet, and lifestyle factors.

Received 6/3/04; revised 8/10/04; accepted 8/20/04.

Grant support: USPH contracts N01 CN45165 and 45035 from the National Cancer Institute, National Institutes of Health and Human Services and Cancer Prevention Fellowship Program, Office of Preventive Oncology, Division of Cancer Prevention, National Cancer Institute (S. Mahabir).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Somdat Mahabir, Cancer Prevention Studies Branch, Center for Cancer Research, National Cancer Institute, 6116 Executive Boulevard, Suite 705, MSC 8314, Bethesda, MD 20892-7058. Phone: 301-451-4987; Fax: 301-435-8645. E-mail: mahabirs@mail.nih.gov

Materials and Methods

Study Population. The Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study was a randomized, double-blind, placebo-controlled, two-by-two factorial design, primary prevention trial that tested whether α-tocopherol (50 mg/d) and/or β-carotene (20 mg/d) reduced the incidence of lung cancer in male smokers living in southwestern Finland. The ATBC cohort consisted of 29,133 white males, between 50 and 69 years of age, who smoked five or more cigarettes per day at study entry. All subjects were recruited into the trial between 1985 and 1988, and the trial ended in April 1993 after 5 to 8 years of active intervention (median, 6.1 years). Participants were randomized to one of four intervention groups: 50 mg/d α-tocopherol, 20 mg/d β-carotene, 50 mg/d α-tocopherol plus 20 mg/d β-carotene, or placebo. Post-intervention follow-up continued through the Finnish Cancer Registry. Study eligibility was as-sessed prior to randomization; subjects who were diagnosed with prior cancer or serious disease limiting long-term participation, as well as those taking supplements of vitamins E, A, or β-carotene in excess of defined amounts, were ineligible for participation. Other details of the ATBC trial have been described previously (23). The current study population consisted of all the subjects in the ATBC cohort with information on alcohol consumption and dietary intake (n = 27,111) at baseline.

Case Identification. Cases were identified through the Finnish Cancer Registry, which provides almost 100% of case ascertainment (24). The medical records of all potential RCCs were collected from hospitals and pathology laboratories and a study physician reviewed them to confirm the cancer diagnosis. Deaths were identified from the Registry of Causes of Death in Finland.

Baseline Data Collection. At baseline, subjects completed a questionnaire regarding background characteristics and

medical history. Height, weight, and blood pressure were measured, and a blood sample was drawn and stored at −70°C. The participants also completed a self-administered food frequency questionnaire, which was used to measure the total amount and type of alcohol (beer, wine, and spirits) consumed. Of the entire ATBC cohort, 27,111 men (93%) completed the dietary questionnaire with information on alcohol consumption and were included in the study. Using a color picture booklet as an aid, participants were asked to report their usual frequency of consumption over the previous 12 months and portion sizes for over 270 common food items, including specific alcoholic beverages. This dietary instrument was evaluated for reproducibility and validity (25). For reproducibility, Pearson correlation coefficients varied from 0.54 (vitamin A) to 0.9 (alcohol). For validity, dietary intake from food frequency questionnaires was compared with diet records as the gold standard, and Pearson correlation coefficients ranged from 0.4 (selenium) to 0.8 (alcohol; ref. 25). Dietary nutrient intake was estimated using food composition data available from the National Public Health Institute of Finland (26). Total alcohol intake was converted into grams of ethanol per day, whereas grams of intake of the specific alcoholic beverages were also assessed. The alcohol content was calculated as 12.8 g for a glass of beer, 14.0 g for a drink of liquor, and 11.3 g for a glass of wine.

Statistical Analysis. We did a cohort analysis of the subjects who developed RCC between 1985 and 1999 (median, 12.2 years follow-up) among the 27,111 trial participants. Cox proportional hazards models, using follow-up time as the underlying metric, were used to estimate multivariate adjusted relative risks (RR) and 95% confidence intervals (CI) of incident RCC cases with alcohol consumption. We evaluated the association between alcohol intake and incident RCC through categorical indicators for the quartiles of alcohol intake among the study population using the first quartile (lowest intake) as the reference category. We used the lowest quartile of intake as the reference because at least 10% of the cohort reported drinking no alcohol and it is quite probable that this group of men may have included not only teetotalers but also those consuming small amounts of alcohol infrequently. In a sub-analysis, we excluded all the men who reported drinking no alcohol and used the lowest quartile of drinkers as the reference category. Both total ethanol intake and ethanol intake from spirits and beer were assessed. We could not assess wine drinking and risk of RCC because too few people in our study drank wine. The variables used in the basic multivariate model were selected based on biological plausibility and their association with RCC in the literature. Other variables that resulted in a ≥10% change in the β coefficients of the alcohol variables of the basic model were also included in the final multivariate model. All dietary variables were energy-adjusted using the residual method. The basic multivariate model included age, BMI, supplement group, total energy (excluding energy from alcohol sources), blood pressure, years of smoking, total number of cigarettes smoked per day, fruits, and vegetables. A number of other covariates, such as education, region where the participants lived, leisure time and occupational physical activity, serum cholesterol, fat, and various dietary nutrients, were also tested but were not included in the final model. The tests for linear trend were calculated by assigning the median alcohol intake in categories treated as continuous variables. Potential interactions between alcohol and other risk factors for RCC were tested by entering the cross-product term for alcohol and each of these factors along with the main effects term for alcohol intake in the multivariate model. We also ran models stratified by age, BMI, and smoking. All reported *P* values are two tailed. All analyses were done using Statistical Analysis System software release 8.02 (SAS Institute, Cary, NC).

Results

During 281,074 person-years of follow-up, we documented 195 incident cases of RCC. Baseline characteristics of the study participants according to level of alcohol consumption are presented in Table 1. Men with higher alcohol intakes had slightly higher BMI, smoked more cigarettes daily, had higher systolic and diastolic blood pressure, and consumed less total fat. There were no appreciable differences in serum cholesterol by level of alcohol intake.

As shown in Table 2, the age-adjusted RRs and 95% CI for RCC in increasing categories of total alcohol intake were 1.0, 0.94 (0.66-1.35), 1.01 (0.71-1.45), and 0.63 (0.42-0.96), respectively (*P* value for trend = 0.03). After adjustment for BMI, supplement group, energy intake (excluding energy from alcohol), smoking, blood pressure, and fruit and vegetable intake, the RRs of RCC in increasing categories of total alcohol intake were 1.0, 0.91 (0.62-1.33), 0.94 (0.64-1.38), and 0.53 (0.34-0.83), respectively (*P* value for trend = 0.005).

We also assessed possible differences in the association of beverage type with RCC. The age-adjusted RRs and 95% CI of RCC in increasing categories of spirit intake were 1.0, 0.97

Table 1. Baseline characteristics according to increasing categories of total alcohol consumption among male Finnish smokers

	Alcohol intake categories (ethanol, g/d)			
	1	2	3	4
Range (median), g/d	0-2.5 (0.4)	2.6-11.0 (6.2)	11.1-25.6 (17.3)	25.7-278.5 (39.1)
Characteristics				
Participants (*n*)	6,777	6,782	6,774	6,778
Age, y	58.3 ± 5.3	57.5 ± 5.1	56.7 ± 4.8	56.1 ± 4.7
BMI, kg/m^2	26.0 ± 3.8	26.2 ± 3.6	26.3 ± 3.8	26.5 ± 3.9
Years of smoking	36.8 ± 8.7	35.7 ± 8.7	35.6 ± 8.3	35.5 ± 7.9
Cigarettes smoked per day	18.8 ± 8.5	19.2 ± 8.2	20.5 ± 8.4	23.1 ± 9.4
Diastolic blood pressure, mm Hg	85.6 ± 10.6	86.7 ± 10.6	87.9 ± 10.7	90.1 ± 10.8
Systolic blood pressure, mm Hg	140.1 ± 19.4	140.9 ± 19.3	141.9 ± 19.2	144.8 ± 19.3
Serum cholesterol, mmol/L	6.2 ± 1.2	6.3 ± 1.2	6.3 ± 1.2	6.2 ± 1.1
Daily dietary intake*				
Total energy, kcal/d†	2753 ± 793	2684 ± 758	2677 ± 764	2640 ± 793
Total dietary fat, g/d	109.3 ± 15.9	108.6 ± 14.9	106.4 ± 14.8	97.9 ± 16.8
Fruits, g/d	92.7 ± 82.5	94.8 ± 80.2	88.9 ± 76.8	78.5 ± 75.4
Vegetable, g/d	150.5 ± 110.0	170.2 ± 113.2	171.5 ± 114.2	169.5 ± 118.4

NOTE: All variables (except age) are standardized to the age distribution of the cohort.
*Nutrients are adjusted for total energy intake.
† Excludes energy from alcohol sources.

Table 2. Relative risk of RCC in relation to alcohol consumption among male Finnish smokers

Variable	Alcohol intake categories*				*P*, trend
	1†	2	3	4	
Total alcohol (g/d)					
Range (median), ethanol	0-2.5 (0.4)	2.6-11.0 (6.2)	11.1-24.0 (17.3)	24.1-278.5 (39.1)	
Cases	56	52	53	34	
Person-years	69,170	70,907	70,901	70,096	
Age-adjusted RR (95% CI)	1	0.94 (0.66-1.35)	1.01 (0.71-1.45)	0.63 (0.42-0.96)	0.03
Multivariate RR (95% CI)‡	1	0.91 (0.62-1.33)	0.94 (0.64-1.38)	0.53 (0.34-0.83)	0.005
Spirits (g/d)					
Range (median), ethanol	0-0.4 (0)	0.5-5.3 (1.7)	5.4-15.9 (8.0)	16.0-160 (22.8)	
Cases	62	42	56	35	
Person-years	70,485	69,705	70,838	70,046	
Age-adjusted RR (95% CI)	1	0.97 (0.66-1.41)	0.90 (0.64-1.27)	0.65 (0.43-0.97)	0.06
Multivariate RR (95% CI)‡	1	0.93 (0.63-1.39)	0.84 (0.58-1.20)	0.55 (0.36-0.85)	0.02
Beer (g/d)					
Range (median), ethanol	0 (0)	0.01-1.9 (1.2)	2.0-7.4 (4.0)	7.5-242.6 (14.8)	
Cases	65	53	45	32	
Person-years	69,796	69,513	71,287	70,479	
Age-adjusted RR (95% CI)	1	1.20 (0.85-1.70)	0.84 (0.58-1.21)	0.58 (0.38-0.88)	0.002
Multivariate RR (95% CI)‡	1	1.22 (0.85-1.76)	0.83 (0.57-1.22)0.55 (0.36-0.85)		0.002

*Alcohol categorized by quartile of ethanol intake.
†The first quartile is the reference group.
‡The multivariate model included the following variables: age, BMI, supplement group, calories (excluding energy from alcohol sources), blood pressure, years of smoking regularly, total number of cigarettes smoked per day, smoking inhalation, and fruits and vegetables.

(0.66-1.41), 0.90 (0.64-1.27), and 0.65 (0.43-0.97), respectively (*P* value for trend = 0.06) (Table 2). In the multivariate model, the RRs and 95% CI of RCC in increasing categories of spirit intake were 1.0, 0.93 (0.63-1.39), 0.84 (0.58-1.20), and 0.55 (0.36-0.85), respectively (*P* value for trend = 0.02). We observed almost similar decreases in risk of RCC with consumption of beer. In the multivariate model, the RRs and 95% CI of RCC in increasing categories of beer intake were 1.0, 1.22 (0.85-1.76), 0.83 (0.57-1.22), and 0.55 (0.36-0.85), respectively (*P* value for trend = 0.002) (Table 2).

We did not find any evidence for significant interactions between total alcohol (Table 3) or beer intake (Table 4) or spirit intake (Table 5) within strata defined by age, BMI, or cigarettes smoked per day.

We also conducted a sub-analysis in which individuals who reported drinking no alcohol were excluded. In this analysis, the associations for total alcohol, beer intake, and spirits were statistically similar to the overall findings, except the multivariate RR of the highest quartile of spirits, and the spirits trend. The multivariate RRs and 95% CI of RCC in increasing quartiles of total alcohol intake were 1, 0.88 (0.54-1.42), 0.61 (0.38-1.04), and 0.51 (0.29-0.89), respectively (*P* value for trend = 0.01). For beer, the RRs were 1, 1.02 (0.81-1.28), 0.83 (0.69-0.99), and 0.82 (0.71-0.95), respectively (*P* value for trend = 0.006). In the multivariate model, the RRs for increasing categories of spirit intake were 1, 0.97 (0.76-1.25), 1.00 (0.85-1.19), and 0.89 (0.77-1.03), respectively (*P* value for trend = 0.26).

Discussion

In this large prospective cohort study among male smokers, we found that increased total alcohol intake was associated with decreased risk of RCC. We also found that all forms of alcoholic beverages (spirits and beer) assessed were associated with decreased risk of RCC in this cohort. These associations persisted after controlling for established or suspected independent risk factors for RCC, such as cigarette smoking, BMI, and blood pressure.

Table 3. Relative risk of RCC in relation to total alcohol consumption in subgroups defined by selected variables among male Finnish smokers

Variable	No. cases	Alcohol intake categories*				*P*, trend	*P*, interaction
		1†	2	3	4		
Range (median), g/d		0-2.5 (0.4)	2.6-11.0 (6.2)	11.1-24.0 (17.3)	24.1-278.5 (39.1)		
Age, y							
≤55	76	1	0.96 (0.52-1.78)	0.60 (0.31-1.18)	0.57 (0.29-1.12)	0.06	
56-59	44	1	0.36 (0.14-0.91)	0.67 (0.32-1.39)	0.34 (0.14-0.81)	0.06	
>59	75	1	1.35 (0.74-2.47)	1.78 (0.97-3.29)	0.63 (0.27-1.49)	0.33	0.73
BMI							
≤24	40	1	0.61 (0.25-1.45)	0.83 (0.36-1.91)	0.56 (0.21-1.47)	0.37	
25-29	119	1	1.16 (0.70-1.93)	1.28 (0.77-2.13)	0.72 (0.40-1.28)	0.20	
>30	36	1	0.63 (0.27-1.45)	0.47 (0.19-1.15)	0.22 (0.07-0.63)	0.006	0.30
No. cigarettes/d							
≤15	57	1	1.26 (0.63-2.52)	1.57 (0.78-3.15)	0.86 (0.34-2.13)	0.82	
16-24	71	1	0.80 (0.42-1.52)	0.98 (0.52-1.85)	0.51 (0.24-1.10)	0.12	
≥25	67	1	0.76 (0.39-1.47)	0.59 (0.30-1.17)	0.39 (0.20-0.78)	0.008	0.14

NOTE: The multivariate model included the following variables: age, BMI, supplement group, calories (excluding energy from alcohol sources), blood pressure, years of smoking regularly, total number of cigarettes smoked per day, smoking inhalation, and fruits and vegetables.
*Alcohol categorized by quartile of ethanol intake.
†The first quartile is the reference group.

Table 4. Relative risk of RCC in relation to beer consumption in subgroups defined by selected variables among male Finnish smokers

Variable	No. cases	Beer intake categories*				*P*, trend	*P*, interaction
		1†	2	3	4		
Range (median), g/d		0 (0)	0.1-1.9 (1.2)	2.0-7.4 (4.0)	7.5-242.6 (14.8)		
Age, y							
≤55	76	1	2.14 (1.15-3.98)	1.17 (0.60-2.27)	0.58 (0.27-1.24)	0.002	
56-59	44	1	0.57 (0.25-1.32)	0.64 (0.30-1.39)	0.40 (0.16-0.97)	0.31	
>59	75	1	1.04 (0.58-1.87)	0.75 (0.40-1.40)	0.76 (0.39-1.47)	0.53	0.07
BMI							
≤24	40	1	1.36 (0.58-3.21)	0.77 (0.30-2.01)	1.08 (0.45-2.57)	0.85	
25-29	119	1	1.18 (0.72-1.91)	1.07 (0.67-1.71)	0.55 (0.31-0.98)	0.02	
>30	36	1	1.24 (0.59-2.62)	0.27 (0.09-0.82)	0.19 (0.06-0.68)	0.008	0.08
No. cigarettes/d							
≤15	57	1	1.00 (0.51-1.97)	0.87 (0.43-1.73)	0.69 (0.30-1.57)	0.25	
16-24	71	1	1.95 (1.08-3.25)	0.79 (0.40-1.59)	0.59 (0.27-1.28)	0.06	
≥25	67	1	0.78 (0.39-1.57)	0.89 (0.47-1.65)	0.48 (0.24-0.94)	0.04	0.90

NOTE: The multivariate model included the following variables: age, BMI, supplement group, calories (excluding energy from alcohol sources), blood pressure, years of smoking regularly, and total number of cigarettes smoked per day.
*Alcohol categorized by quartile of ethanol intake.
†The first quartile is the reference group.

Data on the alcohol-RCC association from cohort studies are limited. Cohort studies published in the 1970s (16-19) reported no association between alcohol consumption and RCC mortality, however, these studies were limited because they were restricted to alcoholics, and their findings were based on small numbers of cases. In a more recent study from Sweden (20), a cohort of 8,340 men and 1,013 women discharged with a diagnosis of alcoholism who were followed for an average of 8 years also reported no association between alcohol intake and risk of RCC, but these results were based on a very small number of cases (20 cases in men and 2 in women). A total of eight case-control studies (10-15, 21, 22) have reported on the alcohol-RCC association, six (10-15) found no association, whereas two large studies (21, 22) reported that alcohol consumption was associated with a significant reduction of risk for RCC in women, but not men. Moreover, investigators using data from a large cohort of Iowa women recently reported a reduction in risk of kidney cancer associated with alcohol consumption (9).

Whereas our findings of risk reduction for alcohol in RCC may be due to chance, the consistent trends found with total alcohol, spirits, and beer lessen this possibility.

Our study had certain limitations and strengths. Because the cohort consisted exclusively of male smokers, the results may not be generalizable to nonsmokers or to women. Data on alcohol consumption was limited. We had no data on drinking patterns, only usual level, and alcohol use was self-reported from a single point in time, precluding assessment of lifelong alcohol use, intake earlier in life, or changes in alcohol usage over the 12-year study period. It is quite possible that participants may have changed their drinking habits over time. It is also possible that smoking status may have changed during the follow-up. However, these features apply to most cohort studies and are not unique to the current study.

To our advantage, our study has the largest number of prospective cases to date evaluating the risk of alcohol and RCC and it is the largest prospective study in males. Additionally, we had detailed information on many variables such as BMI, smoking, blood pressure, and diet, which enabled us to control for potential confounding. Although our study consisted of all smokers, this can also be considered a unique strength. Due to smoking being a common exposure to all subjects, it allowed us to assess the relationship between alcohol and RCC in a group that does not generally practice desirable health behaviors. Smokers are believed to be at increased risk for RCC (7, 8). We found that alcohol consumption is associated with deceased risk of RCC in middle-aged heavy smokers.

Table 5. Relative risk of RCC in relation to spirit consumption in subgroups defined by selected variables among male Finnish smokers

Variable	No. cases	Spirit intake categories*				*P*, trend	*P*, interaction
		1†	2	3	4		
Range (median), g/d		0-0.4 (0)	0.5-5.3 (1.7)	5.4-15.9 (8.0)	16.0-160 (22.8)		
Age, y							
≤55	76	1	1.06 (0.57-1.99)	0.68 (0.36-1.26)	0.52 (0.27-1.02)	0.05	
56-59	44	1	0.34 (0.11-1.01)	0.64 (0.31-1.31)	0.48 (0.21-1.05)	0.28	
>59	75	1	1.19 (0.64-2.20)	1.16 (0.65-2.05)	0.63 (0.29-1.38)	0.34	0.68
BMI							
≤24	40	1	0.39 (0.14-1.03)	0.55 (0.25-1.18)	0.29 (0.10-0.88)	0.11	
25-29	119	1	1.15 (0.69-1.89)	0.95 (0.59-1.54)	0.64 (0.37-1.12)	0.13	
>30	36	1	1.25 (0.46-3.41)	0.97 (0.40-2.31)	0.70 (0.27-1.79)	0.46	0.54
No. cigarettes/d							
≤15	57	1	1.10 (0.55-2.22)	1.12 (0.58-2.15)	0.58 (0.25-1.47)	0.27	
16-24	71	1	0.52 (0.25-1.09)	0.76 (0.42-1.36)	0.56 (0.29-1.10)	0.54	
≥25	67	1	1.36 (0.70-2.63)	0.70 (0.36-1.37)	0.52 (0.26-1.05)	0.02	0.07

NOTE: The multivariate model included the following variables: age, BMI, supplement group, calories (excluding energy from alcohol sources), blood pressure, years of smoking regularly, total number of cigarettes smoked per day, and fruits and vegetables.
*Alcohol categorized by quartile of ethanol intake.
†The first quartile is the reference group.

The mechanism of action by which alcohol consumption affects RCC risk in men is unknown. Alcohol consumption has been associated with decreased risk of type 2 diabetes mellitus in large-scale epidemiologic studies (27, 28), possibly through a mechanism involving decreased insulin resistance (29, 30), and diabetes mellitus is positively related to RCC in prospective cohort studies (31, 32). In addition, moderate alcohol consumption may lower blood pressure (33-35), increase high-density lipoprotein cholesterol and its subfractions (36, 37), decrease platelet aggregation (38, 39), and increase fibrinolytic activity (40). Thus, it is possible that alcohol consumption might prevent or limit renal fibrosis and chronic renal failure via improved vascular function. Due to moderate alcohol intake being shown to decrease levels of insulin-like growth factor I (41, 42), it is possible that the decrease risk of RCC associated with alcohol intake may be mediated by insulin-like growth factor I.

However, based on alcohol metabolism and the production of reactive oxygen species (43), alcohol would be expected to increase the risk of RCC. In our postmenopausal women alcohol feeding study, we found that one or two drinks per day for 8 weeks had no effect on DNA damage assessed by 5-hydroxymethyl-2-deoxyuridine autoantibodies, but increased isoprostane levels.[4,5] Other studies have also reported paradoxical inverse correlations between alcohol consumption and oxidative DNA (44, 45). Alcohol may also interfere with folate absorption, transport, and metabolism, potentially limiting folate stores in tissues (46). This could contribute to RCC via abnormal DNA methylation (47), but is unclear (48) because of evidence that the presence of DNA methylation does not always contribute to the loss of expression of tumor suppressor genes in human RCC cells (49).

In this large prospective cohort study, we found evidence that alcohol consumption was associated with decreased risk of RCC. Because most of the risk reductions were seen at the highest quartile of alcohol intake, these data should be interpreted with caution. However, the association was consistent when we examined the risk of RCC with total alcohol, spirits, and beer intake after multivariate adjustment for several known or suspected confounding factors, thus providing support for a true association. Owing to alcohol consumption being deleterious for a number of cancers particularly among smokers, these results should be interpreted with caution. There is a need for additional studies to solidify alcohol as a consistent and believable RCC risk factor before including it in risk algorithm.

References

1. Chow W-H, Devesa S, Warren J, Fraumeni J. Rising incidence of renal cell cancer in the United States. JAMA 1999;281:1628–31.
2. Black R, Bray F, Ferlay J, Parkin D. Cancer incidence and mortality in the European Union: cancer registry data and estimates of national incidence for 1990. Eur J Cancer 1997;33:1075–107.
3. Liu S, Semenciw R, Morrison H, Schanzer D, Mao Y. Kidney cancer in Canada: the rapidly increasing incidence of adenocarcinoma in adults and seniors. Can J Public Health 1997;88:99–104.
4. Parkin D, Pisani P, Ferlay, J. Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer 1999;80:827–41.
5. McLaughlin J, Blot W, Devesa S, Fraumeni J. Renal cancer. In: Schottenfeld D, Fraumeni JF, editors. Cancer Epidemiology and Prevention. 2nd ed. New York: Oxford University Press; 1996. p. 1142–55.
6. Landis S, Murray T, Bolden S, Wingo P. Cancer statistics, 1999. CA Cancer J Clin 1999;49:8–31.
7. Yuan J, Castelao J, Gago-Dominguez M, Yu M, Ross R. Tobacco use in relation to renal cell carcinoma. Cancer Epidemiol Biomarkers Prev 1998;7:429–33.
8. Moyad M. Review of potential risk factors for kidney (renal cell) cancer. Semin Urol Oncol 2001;19:280–93.
9. Nicodemus K, Sweeney C, Folsom A. Evaluation of dietary, medical and lifestyle risk factors for incident kidney cancer in postmenopausal women. Int J Cancer 2004;108:115–21.
10. Yu M, Mack T, Hanisch R, et al. Cigarette smoking, obesity, diuretic use, and coffee consumption as risk factors for renal cell carcinoma. J Natl Cancer Inst 1986;77:351–6.
11. Brownson R. A case-control study of renal cell carcinoma in relation to occupation, smoking, and alcohol consumption. Arch Environ Health 1988;43:238–41.
12. Maclure M, Willett W. A case-control study of diet and risk of renal adenocarcinoma. Epidemiol 1990;1:430–40.
13. McLaughlin J, Gao Y, Gao R, et al. Risk factors for renal-cell cancer in Shanghai, China. Int J Cancer 1992;52:562–5.
14. Benhamou S, Lenfant M-P C, Flamant R. Risk factors for renal cell carcinoma in a French case-control study. Int J Cancer 1993;55:32–6.
15. Kreiger N, Marrett L, Dodds L, et al. Risk factors for renal cell carcinoma: results from a population-based case-control study. Cancer Causes Control 1993;4:101–10.
16. Schmidt W, de Lint J. Causes of death of alcoholics. QJ Stud Alcohol 1972;33:171–85.
17. Pell S, D'Alonzo C. A five-year mortality study of alcoholics. J Occup Med 1973;15:120–5.
18. Monson R, Lyon J. Proportional mortality among alcoholics. Cancer 1975;36:1077–9.
19. Jensen O. Cancer morbidity and causes of death among Danish brewery workers. Int J Cancer 1979;23:454–63.
20. Adami H-O, McLaughlin J, Hsing A, et al. Alcoholism and cancer risk: a population-based cohort study. Cancer Causes Control 1992;3:419–29.
21. Wolk A, Gridley G, Niwa S, et al. International renal cell cancer study. VII. Role of diet. Int J Cancer 1996;65:67–73.
22. Parker A, Cerhan J, Lynch C, Ershow A, Cantor K. Gender. Alcohol consumption, and renal cell carcinoma. Am J Epidemiol 2002; 155:455–62.
23. The ATBC Cancer Prevention Study Group. The α-tocopherol, β-carotene lung cancer prevention study: design, methods, participant characteristics, and compliance. Ann Epidemiol 1994;4:1–10.
24. Korhonen P, Malila N, Pukkala E, Teppo L, Albanes D, Virtamo J. The Finnish Cancer Registry as follow-up source of a large trial cohort. Acta Oncologica 2002;41:381–8.
25. Pietinen P, Hartman A, Haapa E, et al. Reproducibility and validity of dietary assessment instruments. I. A self-administered food use questionnaire with a portion size picture booklet. Am J Epidemiol 1988;128:655–66.
26. National Public Health Institute of Finland, Food Composition Database Fineli, 2004. Available from:http://www.ktl.fi/fineli.
27. Ajani U, Hennekens C, Spelsberg A, Manson J. Alcohol consumption and risk of type 2 diabetes mellitus among US male physicians. Arch Intern Med 2000;160:1025–50.
28. Rimm E, Chan J, Stampfer M, Colditz G, Willett W. Prospective study of cigarette smoking, alcohol use and the risk of diabetes in men. BMJ 1995;310:555–9.
29. Onishi Y, Honda M, Ogihara T, et al. Ethanol feeding induces insulin resistance with enhanced PI 3-kinase activation. Biochem Biophys Res Commun 2003;303:788–94.
30. Bell R, Mayer-Davis E, Martin M, D'Agostino RB Jr, Haffner S. Associations between alcohol consumption and insulin sensitivity and cardiovascular disease risk factors. Diabetes Care 2000;23:1630–6.
31. Lindbald P, Chow W, Chan J, et al. The role of diabetes mellitus in the aetiology of renal cell cancer. Diabetologia 1999;42:107–12.
32. Wideroff L, Gridley G, Mellemkjaer L, et al. Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. J Natl Cancer Inst 1997;89:1360–5.
33. MacMahon S. Alcohol consumption and hypertension. Hypertension 1987;9:111–21.
34. Beilin L, Puddey I, Burke V. Alcohol and hypertension—kill or cure? J Hum Hypertens 1996;10:S1–5.
35. Gillman M, Cook N, Evans D, Rosner B, Hennekens C. Relationship of alcohol intake with blood pressure in young adults. Hypertension 1995;25:1106–10.
36. Gaziano J, Buring J, Breslow J, et al. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. N Engl J Med 1993;329:1829–34.
37. Hulley S, Gordon S. Alcohol and high-density lipoprotein cholesterol: causal inference from diverse study designs. Circulation 1981;64:III57–63.
38. Rubin R, Rand M. Alcohol and platelet function. Alcohol Clin Exp Res 1994;18:105–10.
39. Renaud S, Beswick A, Fehily A, Elwood P. Alcohol and platelet aggregration: the Caerphilly Prospective Heart Disease Study. Am J Clin Nutr 1992;55:1012–7.
40. Ridker P, Vaughan D, Stampfer M, Glynn R, Hennekens C. Association of moderate alcohol consumption and plasma concentration of endogenous tissue-type plasminogen activator. JAMA 1994;272:929–33.
41. Rojdmark S, Rydvald Y, Aquilonius A, Brismar K. Insulin-like growth factor (IGF)-1 and IGF binding protein-1 concentrations in serum of normal subjects after alcohol ingestion: evidence for decreased IGF-1 bioavailability. Clin Endocrinol (Oxf) 2000;52:313–8.
42. Teramukai S, Rohan T, Eguchi H, Oda T, Shinchi K, Kono S. Anthropometric and behavioral correlates of insulin-like growth factor I

[4] T.J. Hartman, et al. Moderate alcohol comsumption and levels of antioxidant vitamins and isoprostane in postmenopausal women, unpublished data.
[5] S. Mahabir, et al. No association between alcohol supplementation and autoantibodies to DNA damage in postmenopausal women in controlled feeding study, unpublished data.

and insulin-like growth factor binding protein 3 in middle-aged Japanese men. Am J Epidemiol 2002;156:344–8.
43. Badger T, Ronis M, Seitz H, Albano E, Ingelman-Sundberg M, Lieber C. Alcohol metabolism: role in toxicity and carcinogenesis. Alcohol Clin Exp Res 2003;27:336–47.
44. Yoshida R, Shioji I, Kishida A, Ogawa Y. Moderate alcohol consumption reduces urinary 8-hydroxygdeoxyguanosine by inducing of uric acid. Ind Health 2001;39:322–9.
45. Bianchini F, Jaeckel A, Vineis P, et al. Inverse correlation between alcohol consumption and lymphocyte levels of 8-hydroxyguanosine in humans. Carcinogenesis 2001;22:885–90.
46. Hillman R, Steinberg S. The effect of alcohol on folate consumption. Annu Rev Med 1982;33:345–54.
47. Hoffman R. Altered methionine metabolism. DNA methylation and oncogene expression in carcinogenesis. A review and synthesis. Biochim Biophys Acta 1984;738:49–87.
48. Baylin S, Belinsky S, Herman J. Aberrant methylation of gene promoters in cancers—concepts, misconcepts, and promise. J Natl Cancer Inst 2000;92:1460–1.
49. Kawakami T, Okamoto K, Ogawa O, Okada Y. Multipoint methylation and expression analysis of tumor suppressor genes in human renal cancer cells. Urology 2003;61:226–30.