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Alcohol consumption and risk of upper-tract urothelial cancer

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ABSTRACT

Background: Upper-tract urothelial cancer (UTUC), which includes renal pelvic cancer and ureter cancer, is a rare cancer and its prognosis is poor. Smoking and high-risk occupations (e.g., printing and dyestuff working which involves exposure to aniline dyes) are well-known risk factors for UTUC. However, the risk of alcohol consumption in UTUC remains unclear. This study aimed to determine whether alcohol consumption is an independent risk factor for UTUC.

Methods: The study was a case–control study which used the nationwide clinical inpatient database of the Rosai Hospital group in Japan. We identified 1569 cases and 506,797 controls between 1984 and 2014. We estimated the odds ratio (OR) and 95% confidence interval (95%CI) of alcohol consumption for UTUC – never, up to 15 g/day, >15–30 g/day, or >30 g/day – using unconditional logistic regression. We adjusted for the following covariates: age, sex, study period, hospital, history of smoking, and high-risk occupation.

Results: The risk of UTUC was significantly higher in ever-drinkers compared with never-drinkers (OR = 1.23, 95%CI, 1.08–1.40; $P = 0.001$). Compared with never-drinkers, the risk threshold for UTUC was >15 g of alcohol consumption per day (equivalent to 6 ounces of Japanese sake containing 23 g of alcohol). A dose-response was observed ($P < 0.001$).

Conclusion: Alcohol consumption may be an independent risk factor for UTUC, with a low-risk threshold of 15 g of alcohol per day.

1. Introduction

Upper-tract urothelial cancer (UTUC) includes renal pelvic cancer and ureter cancer stemming from the mucosa of the urinary tract; it excludes renal-cell cancer arising from cells of the proximal convoluted renal tubules. UTUC is a rare urinary tract cancer [1]; it is often detected at an advanced stage, and its prognosis is usually poor [2,3].

Smoking is an established risk factor for urinary tract cancer, including UTUC and bladder cancer [1,4–8]. Certain occupations, such as printing and dyestuff working, have also been established as risk factors for urinary tract cancer (primarily bladder cancer) because of exposure of the workers to aniline dyes and other chemicals [9,10].

Attention has focused on alcohol consumption as a potential risk factor for urinary tract cancer [11]. Alcohol consumption was reported to be an independent risk factor for bladder cancer in the Netherlands and Japan, even after smoking (the major confounder) was controlled with stratification or adjustment of the status and amount of smoking [12,13]. This study aimed to examine the association between drinking and the risk of UTUC using a nationwide, hospital-based, case–control study.

2. Materials and methods

2.1. Data

Cases and controls were identified from the inpatient database of the Rosai Hospital group, which is run by the Japan Organization of Occupational Health and Safety. Details of the database have been described previously [13,14]. In brief, the Rosai Hospital group consists of 34 general hospitals in the main urban areas in Japan. The hospitals have maintained electronic medical records since 1984. The database includes the following information: patients' background (such as sex, age, hospital of admission, and admission date); discharge diagnoses coded according to the International Classification of Diseases and Related Health Problems, 9th

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Revision (ICD-9) or 10th Revision (ICD-10); and lifestyle-related information (alcohol consumption, smoking, and occupational history); the information was obtained from questionnaires that were completed at the time of admission. The occupational history included current and up to three former jobs with their durations. The jobs were coded to the Japan Standard Industrial Classification for industry and the Japan Standard Occupational Classification for occupation, which correspond to the International Standard Industrial Classification and International Standard Occupational Classification, respectively. Since 2002, pathological diagnoses have been coded according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). Written informed consent was obtained from the patients before they completed the questionnaires.

We obtained a de-identified dataset under the research agreement between the authors and the Japan Organization of Occupational Health and Safety. The study was approved by the Research Ethics Committees of the Graduate School of Medicine, The University of Tokyo, Tokyo (Protocol Number: 3890-3), and Kanto Rosai Hospital, Kanagawa, Japan (Protocol Number: 2014-38).

2.2. Cases and controls

We included patients aged 20 years or older who were admitted between January 1984 and March 2014. We excluded those who did not provide information at admission (31%) – mostly because of emergency admission – and those with incomplete data (22%).

Cases were patients with the diagnosis of renal pelvic cancer or ureter cancer (C65 or C66 in ICD-10; 189.1 or 189.2 in ICD-9). Our controls were patients with no history of the following tobacco- or alcohol-related diseases: all other cancers, all cardiovascular diseases, all respiratory diseases, and all digestive diseases [13]. Among the controls, we also excluded patients who were hospitalized for accidental diseases (e.g., injury and other external causes) because alcohol consumption might be higher among these patients than in the general population. The distribution of diagnoses among the controls is shown in Table 1.

2.3. Alcohol consumption and smoking

Alcohol consumption was categorized as follows: alcohol consumption status (never versus ever) and the average amount of alcohol intake per day (never, up to 15 g/day, >15–30 g/day, or >30 g/day) [13]. We assumed that one 180-mL cup (equivalent to 6 ounces) of Japanese sake, one 500-mL bottle (equivalent to 17 ounces) of beer, one 180-mL glass (equivalent to 6 ounces) of wine, and one 60-mL cup (equivalent to 2 ounces) of whisky contained 23 g of alcohol. We also created a continuous variable of the average amount of alcohol intake per day.

Smoking habits were categorized as follows: smoking status (never, former, or current) and pack-years (never, up to 20 pack-years, >20–40 pack-years, or >40 pack-years) [13]. Ever-smokers were defined as those who had some experience of smoking during their lifetime [15].

2.4. High-risk occupations

People involved in high-risk occupations – related to aniline dyes, aromatic solvents, diesel exhaust, or other chemicals – based on previous literature included the following: printing workers; painters; manufacturers of chemical, textile, leather, or rubber products; mechanics or repairers of transportation equipment; electricians; barbers, hairdressers, or beauticians; laundry or cleaning service workers; and truck drivers [9,10,16]. High-risk occupations also included hotel service employment (although in previous studies it was uncertain what particular exposure increased the risk) [10]. We assumed that cases or controls had a risk in their occupational experience if one of their jobs included these high-risk occupations, and if the duration of the high-risk occupation was 10 years or longer [10,16].

2.5. Changes in diagnostic procedure

According to changes and updates in the ICD-9 and ICD-10 coding procedures, which might affect the diagnoses in cases and controls, we divided the study into four periods (1984–1989, 1990–2002, 2003–2012, and 2013–2014).

2.6. Statistical methods

Percentages were compared with chi-square tests, and means were compared with *t*-tests between cases and controls.

We estimated odds ratios (ORs) and 95% confidence intervals (95%CIs) of alcohol consumption for UTUC, using unconditional logistic regression. We adjusted for the following covariates: age, sex, study period, admitting hospital, smoking, and experience of working in a high-risk occupation. In addition to a dose-response risk of alcohol consumption for UTUC with a trend test, we also plotted ORs and 95%CIs for the continuous dose of daily alcohol consumption in a spline curve, which was estimated by a generalized additive model. We did not use data beyond the 99th percentile point level of the dose (92 g/day, equivalent to four standard units of daily alcohol consumption) to maintain stability of the spline curve. We did not include an interaction term between alcohol consumption and smoking for the risk of UTUC in

Table 1
Distribution of diagnoses among controls for upper-tract urothelial cancer cases.

Diagnoses	ICD-9 and ICD-10 codes	Percentage
Musculoskeletal system and connective tissue disease	410–739, M00–M99	23%
Eye, adnexa, ear, and mastoid process disease	360–389, H00–H95	16%
Benign neoplasm	209–229, 235–239, D10–D49	14%
Pregnancy, childbirth, and the puerperium	630–679, O00–O99	13%
Genitourinary system disease	580–629, N00–N99	11%
Nervous system disease	320–359, G00–G99	5.1%
Endocrine, metabolic, and immune mechanism disease	240–279, D80, D99, E00–E99	4.4%
Infectious and parasitic disease	1–136, A00–B99	3.9%
Symptoms, signs, and abnormal findings	780–799, R00–R99	2.5%
Skin and subcutaneous tissue disease	680–709, L00–L99	2.4%
Mental and behavioral disorders	290–319, F00–F99	1.3%
Other diseases [a]		3.9%

Percentages may not total 100 because of rounding.
[a] All other cancers (140–208, 230–234, C00–C99, D00–D09), cardiovascular diseases (390–459, I01–I99), respiratory diseases (460–519, J00–J99), digestive diseases (520–579, K00–K99), and injury, poisoning, and other external causes (800–999, S00–T98) were excluded.

Table 2
Characteristics of upper tract urothelial cancer cases and controls.

Characteristics	Controls (n = 506,797)	Cases (n = 1569)	*P* value
Sex, women, n (%)	297,547 (59)	498 (32)	<0.001
Age, mean (SD), years	54 (18.0)	70 (10.5)	<0.001
Period, n (%)			
1984–1989	71,430 (14)	107 (6.8)	<0.001
1990–2002	227,718 (45)	551 (35)	
2003–2012	191,500 (38)	810 (52)	
2013–2014	16,149 (3.2)	101 (6.4)	
Alcohol consumption, ever-drinkers, n (%)	201,122 (40)	859 (55)	<0.001
Ethanol intake per day, mean (SD), g/day	14.4 (25.2)	19.7 (23.8)	<0.001
Ethanol intake per day, g/day, n (%)			
Never	305,675 (60)	710 (45)	<0.001
>0 to ≤15	9398 (1.8)	40 (2.6)	
>15 to ≤30	112,942 (22)	455 (29)	
>30	78,782 (16)	364 (23)	
Smoking, n (%)			
Never	313,315 (62)	639 (41)	<0.001
Former	54,156 (11)	317 (20)	
Current	139,326 (27)	613 (39)	
Pack-years, n (%)			
Never	313,315 (62)	639 (41)	<0.001
>0 to ≤20	85,041 (17)	171 (11)	
>20 to ≤40	63,590 (13)	328 (21)	
>40	44,851 (8.8)	431 (27)	
Experience of high-risk occupations, n (%)	22,583 (4.5)	114 (7.3)	<0.001

Percentages may not total 100 because of rounding.
Values for each hospital are not shown to maintain patient anonymity ($P < 0.001$).

the final model because the interaction term was not significant in *a priori* analysis ($P = 0.26$). We did not attempt multiple imputations because most of the incomplete data were missing alcohol consumption (66%).

For sensitivity analysis, we performed subgroup analysis of cases and controls who were admitted to hospital after 2002 using pathological information. In subgroup analysis, we limited the cases to patients who received a complete pathological diagnostic code of ICD-O-3 for urinary tract cancer [17].

Alpha was set at 0.05 and all *P* values were two-sided. Data were analyzed using STATA/MP13.1 (Stata-Corp LP, College Station, TX) and R.

3. Results

A total of 2446 cases and 1,045,326 controls aged 20 years or older were admitted to hospital between 1984 and 2014. Among them, 477 cases (20%) and 310,745 controls (30%) did not provide questionnaire information, mostly because of emergency admission. Furthermore, the data on 400 cases (16%) and 227,784 controls (22%) were incomplete. The study patients thus included 1569 cases and 506,797 controls. The distribution of age and sex and the proportion of cases did not differ between patients who were included in the study and those who were excluded. The prevalence of alcohol consumption in the excluded controls (never, 53%; <15 g/day, 2.0%; >15–30 g/day, 23%; and >30 g/day, 22%) was similar to that in the study controls.

The demographic and clinical characteristics of the patients are shown in Table 2. The prevalence of ever-drinkers was higher in cases than in controls ($P < 0.001$). The amount of daily alcohol consumption was also higher in cases than in controls ($P < 0.001$).

The results of unconditional logistic regression are shown in Table 3. The risk of UTUC in ever-drinkers was significantly elevated, with an OR of 1.23 (95%CI, 1.08–1.40; $P = 0.001$). The risk of UTUC was significantly elevated at alcohol consumption >15 g/day. The dose-response was significant ($P < 0.001$), and a linear increase in the risk was observed at light to moderate daily alcohol consumption levels (Fig. 1). The risk of UTUC in former smokers and current smokers was significantly elevated, with ORs of 1.29 (95%CI, 1.10–1.53; $P = 0.002$) and 2.24 (95%CI, 1.95–2.58; $P < 0.001$), respectively. The risk of UTUC became significant before 20 pack-years. The risk of UTUC was significantly elevated with a high-risk occupation.

The results of subgroup analysis are shown in Table 4. We analyzed 320 pathologically completed cases and 197,806 controls in unconditional logistic regression. The risk of UTUC in ever-

Table 3
Odds ratios of upper-tract urothelial cancer estimated with 1569 cases and 506,797 controls by unconditional logistic regression. .

Characteristics	Odds ratio (95%CI)[a]	Odds ratio (95%CI)[b]
Women (versus men)	0.56 (0.49–0.65)	0.61 (0.53–0.71)
Age (continuous)	1.07 (1.07–1.08)	1.07 (1.06–1.07)
Period (versus 1984–1889)		
1990–2002	1.26 (1.02–1.55)	1.23 (0.99–1.51)
2003–2012	1.75 (1.42–2.16)	1.62 (1.31–1.99)
2013–2014	2.41 (1.82–3.20)	2.20 (1.66–2.91)
Alcohol consumption (versus never-drinkers)		
Ever	1.23 (1.08–1.40)	
> 0 to ≤ 15 (g/day)		1.12 (0.80–1.56)
> 15 to ≤ 30 (g/day)		1.21 (1.05–1.39)
> 30 (g/day)		1.26 (1.08–1.47)
Smokers (versus never-smokers)		
Former	1.29 (1.09–1.52)	
Current	2.24 (1.94–2.57)	
>0 to ≤20 (pack-year)		1.24 (1.03–1.50)
>20 to ≤40 (pack-year)		1.80 (1.53–2.12)
>40 (pack-year)		2.41 (2.06–2.82)
High-risk occupations (versus not experienced)	1.24 (1.02–1.50)	1.24 (1.02–1.51)

[a] Odds ratios for upper-tract urothelial cancer adjusted for alcohol consumption status and smoking status by an unconditional logistic regression, adjusted for age, sex, period, hospitals, and experience of high-risk occupations.
[b] Odds ratios for upper-tract urothelial cancer adjusted for alcohol consumption intensity and smoking intensity by an unconditional logistic regression, adjusted for age, sex, period, hospitals, and experience of high-risk occupations.

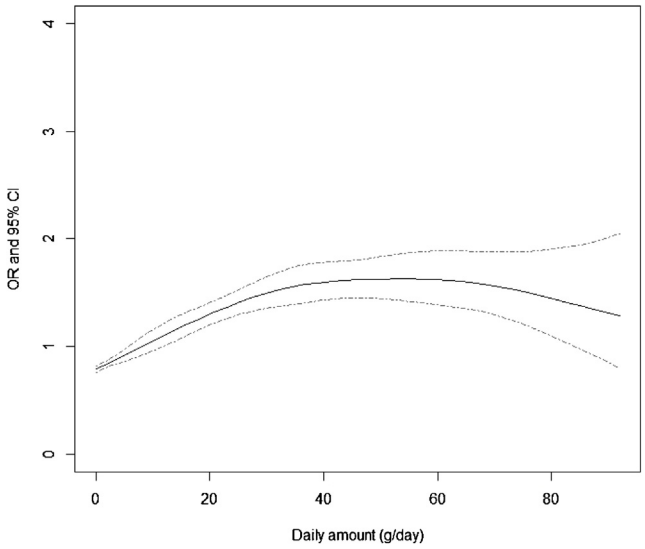

Fig. 1. Dose-response association between alcohol consumption and the risk of upper-tract urothelial cancer. Spline curves demonstrate odds ratios (OR) (solid line) and 95% confidence intervals (CI) (dashed lines) of upper-tract urothelial cancer for continuous alcohol consumption dosage (g/day) estimated by a generalized additive model.

drinkers was significantly elevated, with an OR of 1.38 (95%CI, 1.03–1.84; $P = 0.03$), and the risk of UTUC was significantly elevated beyond 15 g/day (Table 4). The dose-response of alcohol consumption was significant ($P < 0.001$). A matched design analysis showed similar results (data not shown).

4. Discussion

We found that alcohol consumption was related to UTUC with a dose-response trend. The risk of UTUC in ever-drinkers was 1.2–1.5 times higher than that in never-drinkers. A linear increase in the risk of UTUC was observed at light to moderate alcohol doses. The risk threshold of alcohol intake was apparently >15 g/day. Smoking was also associated with an increased risk of UTUC, with a threshold of >20 pack-years. High-risk occupations also tended to increase the risk of UTUC.

A strength of our study is the large sample size. Because our study, which was based on a nationwide dataset, was larger than a previous population-based study in the USA, we had more statistical power to detect differences in risk [4]. The fact that our study was based on a Japanese population may have also contributed to our ability to detect an association. The Japanese (in common with other East Asian groups) are genetically more susceptible to the toxic effects of acetaldehyde because of lower acetaldehyde dehydrogenase enzyme levels [18,19]. However, the point estimate of the risk of UTUC from alcohol consumption in our study (OR approximately 1.2–1.4) was similar to that reported in the USA (OR approximately 1.1–1.5), as well as the pooled estimate from a systematic review of risk factors for whole urinary tract cancer (summary OR 1.2) [4,11].

The risk of UTUC associated with alcohol is biologically plausible because acetaldehyde is carcinogenic and has been detected in human urine [18,20]. Alcohol consumption is also a risk factor for cancer of the bladder, which connects with the upper urinary tract and shares the same urothelial epithelium [12,13]. Additionally, the risk of alcohol is associated with polymorphisms in genes encoding acetaldehyde dehydrogenase [21].

The main risk factor for UTUC remains smoking habits. The risk threshold of smoking was >20 pack-years according to a previous study [4], which is consistent with our results. The association between alcohol consumption and UTUC may have been residually confounded by smoking status (i.e., drinkers are more likely to also be smokers). From the perspective of prevention, smoking remains more strongly associated with urinary tract cancer. Therefore, promotion of smoking cessation remains a priority.

There are some limitations to our study. First, confounding (in either direction – away from the null or towards the null) may have been inadvertently introduced as a result of the selection criteria for our hospital controls. In sensitivity analysis including all controls, regardless of their medical history or accidental disease, the result was the same as that for controls when exclusion criteria were applied; the OR of ever-drinkers was 1.21 (95%CI, 1.06–1.37)

Table 4
Odds ratios of upper-tract urothelial cancer estimated with 320 pathologically completed cases and 197,806 controls by unconditional logistic regression.

Characteristics	Odds ratio (95%CI)[a]	Odds ratio (95%CI)[b]
Women (versus men)	0.72 (0.52–0.99)	0.82 (0.59–1.15)
Age (continuous)	1.08 (1.07–1.09)	1.07 (1.06–1.08)
Period (versus 2002)		
2003–2012	5.08 (2.39–10.8)	5.05 (2.38–10.7)
2013–2014	8.79 (3.94–19.6)	8.65 (3.88–19.3)
Alcohol consumption (versus never-drinkers)		
Ever	1.38 (1.03–1.84)	
>0 to ≤15 (g/day)		1.22 (0.69–2.17)
>15 to ≤30 (g/day)		1.38 (1.01–1.90)
>30 (g/day)		1.44 (1.01–2.07)
Smokers (versus never-smokers)		
Former	1.44 (1.03–2.03)	
Current	2.36 (1.69–3.30)	
>0 to ≤20 (pack-year)		1.12 (0.74–1.70)
>20 to ≤40 (pack-year)		2.07 (1.44–2.98)
>40 (pack-year)		2.47 (1.71 −3.56)
High-risk occupation (versus not experienced)	1.09 (0.71–1.69)	1.10 (0.71–1.70)

[a] Odds ratios for upper-tract urothelial cancer adjusted for alcohol consumption status and smoking status by an unconditional logistic regression, adjusted for age, sex, period, hospitals, and experience of high-risk occupations.
[b] Odds ratios for upper-tract urothelial cancer adjusted for alcohol consumption intensity and smoking intensity by an unconditional logistic regression, adjusted for age, sex, period, hospitals, and experience of high-risk occupations.

and the risk of UTUC was elevated beyond 15 g/day. However, the prevalence of daily alcohol consumption in our controls was higher than that in the general population in Japan – the prevalence of habitual drinking, i.e., drinking more than one standard unit of alcohol (23 g/day) 3 times or more per week, was 21% [22]. Second, case–control studies are susceptible to information bias because the recall of exposure necessarily postdates the disease onset. If the exposure classification is non-differential (i.e., recall of drinking habits is randomly misclassified among cases and controls), then the bias will be toward the null. However, if patients with UTUC differentially misremembered their alcohol intake compared with controls, this may have biased our estimates either toward or away from the null (depending on the systematic error in the direction of recalled intake). Third, although our classification of high-risk occupations was based on standard criteria with the duration of working in different occupations, we did not inquire about specific chemical exposure. This likely resulted in the marginally significant associations that we observed. Fourth, because of the small number of confounding variables in the present study, there might have been some residual confounding by insufficient adjustment for certain risk factors. These risk factors include information on shochu (Japanese distilled spirit) [15], preventable dietary/nutrition factors (e.g., fresh fish and fruits) [8], and socioeconomic status [23].

In summary, alcohol consumption may be a modest risk factor for UTUC, with a threshold of daily alcohol intake of >15 g per day.

Conflicts of interest

None declared.

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Author contributions

Dr. Zaitsu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final version to be published.

Study concept and design: Zaitsu.

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