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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.