

Risk of Alcohol Consumption in Bladder Cancer: Case-Control Study from a Nationwide Inpatient Database in Japan

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Bladder cancer is common in Western countries, but not in Japan. Established risk factors are smoking and high-risk jobs such as printing and manufacturing. The risk of alcohol consumption in bladder cancer has been the recent focus; however, available literature on alcohol consumption and bladder cancer has been limited from Japanese population, thought to have a weak genetic tolerance to acetaldehyde. We aimed to determine whether alcohol consumption is an independent risk factor for bladder cancer among Japanese. The study was a matched case-control study from the nationwide Japanese clinical database administered by the Rosai Hospital group. We identified 739 cases of bladder cancer diagnosed between 2005 (when the database was established) and 2014 and 7,196 controls matched by sex, age, hospital, and admission period. We estimated the odds ratio of alcohol consumption for bladder cancer adjusted for the amount of smoking, high-risk occupations, and comorbidities (hypertension, hyperlipidemia, diabetes, hyperuricemia, and obesity) with conditional logistic regression. The risk of bladder cancer was significantly higher in ever drinkers than in never drinkers (odds ratio, 1.33; 95% confidence interval, 1.06 to 1.66). Furthermore, the risk threshold for alcohol consumption was more than 15 g of alcohol intake per day (one, 180-mL cup equivalent to 6 ounces of Japanese sake containing 23 grams of alcohol). Among Japanese, alcohol consumption may be an independent risk factor for bladder cancer, with a lower risk threshold.

Keywords: acetaldehyde; alcohol consumption; bladder cancer; case-control study; Japanese
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Introduction

Bladder cancer is common among Western countries, but not in Asia including Japan. Worldwide, in 2012, the estimated incidence was 429,800, and the estimated annual death rate was 165,100 (Torre et al. 2015). Bladder cancer occurs mainly in men (Siegel et al. 2015; Torre et al. 2015).

In addition to the established risk factors for bladder cancer of smoking and high-risk jobs (such as printing, manufacturing, and trade workers) (Malaker et al. 1987; Samanic et al. 2008; Freedman et al. 2011), a more recent focus has been on the risk imparted by alcohol consumption. The components of alcoholic beverages and their metabolic products are voided through the urinary tract. In particular, acetaldehyde, the major toxic product of alcohol that damages DNA, is classified as carcinogenic and is detected in the urine (Tsukamoto et al. 1993; Boffetta and Hashibe 2006; Secretan et al. 2009).

Preceding meta-analyses have found that alcohol consumption was not associated with bladder cancer (Bagnardi

et al. 2001, 2015; Pelucchi et al. 2012; de Menezes et al. 2013). However, a cohort study in the Netherlands found an elevated risk of bladder cancer in current heavy drinkers (Zeegers et al. 2001). A recent study from US cohorts also suggested that moderate alcohol consumption was associated with overall cancer risk (Cao et al. 2015). Possible risk of alcohol consumption in bladder cancer still needs to be examined. Especially for Asian population, available literature on alcohol consumption and bladder cancer was limited (Murata et al. 1996; Wakai et al. 2004), and one-third of East Asians are thought to have weak genetic tolerance to acetaldehyde on encoding acetaldehyde dehydrogenase, which detoxifies acetaldehyde (Yokoyama and Omori 2005). We therefore investigated the risk of alcohol consumption in bladder cancer further for Japanese people, who have a weak genetic tolerance to acetaldehyde.

Here, we aimed to determine whether alcohol consumption is an independent risk factor for bladder cancer using a large, nationwide dataset in Japan.

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Materials and Methods

The study was approved by the Research Ethics Committees of Graduate School of Medicine, The University of Tokyo, Tokyo (Protocol Number 3890-3), and Kanto Rosai Hospital, Kanagawa, Japan (Protocol Number 2014-38). Written informed consent for the use of the data was obtained in advance to patients completing the questionnaire. De-identified data were provided under the research agreement between the authors and the Japan Labour Health and Welfare Organization.

Data source

Cases and controls were identified from a nationwide inpatient clinical database at the Rosai Hospital group run by the Japan Labour Health and Welfare Organization. Rosai hospitals were established nationwide by the Ministry of Labour of Japan in and after 1949 for the working population, and later the hospital group was transferred from public to an independent administrative agency, the Japan Labour Health and Welfare Organization. Currently, the Rosai Hospital group consists of 34 general hospitals in main urban areas in Japan, providing health services for the general population as well as for the working population. Since 1984, the hospitals have gathered information on inpatient treatment from medical records, including information on alcohol consumption, smoking, and occupation from questionnaires completed at admission. In addition, since 2005, hospitals have been collecting information on comorbidities, including hypertension, hyperlipidemia, and diabetes. The data center in the Japan Labour Health and Welfare Organization assembles all the information electronically from all 34 Rosai Hospitals. At the end of 2013, the database contained data from about 6 million inpatients.

The database contains the following information for each patient: 1) a personal identification code; 2) hospital of admission; 3) sex; 4) age; 5) admission date; 6) International Classification of Diseases, 9th Revision (ICD-9) code or 10th Revision (ICD-10) diagnostic code for diseases; 7) International Classification of Diseases for Oncology, Third Edition (ICD-O-3) code for pathology; 8) details of alcohol consumption; 9) details of smoking; 10) details of current and up to three former jobs; and 11) details of comorbidities (hypertension, hyperlipidemia, diabetes mellitus, hyperuricemia, and obesity) collected at an annual health checkup.

The data are entered into the database by professional registrars, and the questionnaire is self-administered or completed during a face-to-face interview with a nurse or a registrar or both. Job information is coded with the 4-digit Japan Standard Industrial Classification (JSIC) code for industry and the 3-digit Japan Standard Occupational Classification (JSOC) code for occupation, which correspond to the International Standard Industrial Classification and International Standard Occupational Classification, respectively (Ministry of Internal Affairs and Communications 2009). The job codes are updated to the latest version of JSIC (Revision 13th) and the latest version of JSOC (Revision 5th) by the Japan Labour Health and Welfare Organization. The organization also updates the codes as needed and converts old codes to the most similar new ones.

Study design

As the incidence of bladder cancer was low and the numbers of bladder cancer were small in previous large cohort studies, we performed a matched case-control study (Inoue et al. 2005; Ros et al. 2011).

We limited our sampling frame to patients age 20 years and older and excluded those who did not provide information at admission, mostly emergency patients; those not asked about comorbidities; and those with incomplete data for smoking, alcohol consumption, occupation, comorbidities, sex, age, hospital, and admission dates.

Cases were defined as patients with urothelial carcinoma (C67 in ICD-10, 188 in ICD-9) confirmed by pathologists at each Rosai Hospital (Freedman et al. 2011). Urothelial carcinoma in ICD-O-3 was defined in accordance with our previous study (Zaitzu et al. 2015). Controls were patients with no history of the following tobacco- or alcohol-related diseases: all cancers (C00 to 97 in ICD-10, 140 to 208 in ICD-9), all cardiovascular diseases (I01 to I99 in ICD-10, 390 to 459 in ICD-9), all respiratory diseases (J00 to 99 in ICD-10, 460 to 519 in ICD-9), and all digestive diseases (K00 to K93 in ICD-10, 520 to 579 in ICD-9) (Katanoda et al. 2008; Samanic et al. 2008). The control patients had other diseases such as infectious disease or musculoskeletal system disease, except the tobacco- or alcohol-related diseases listed above.

Matching

Controls for each bladder cancer case were matched by sex, age (in the same 5-year age category), admitting hospital, and admission date (in the same of three admission periods). For each case, we then randomly sampled 10 controls from the total number of matched controls for the each case. The matching process, however, generated less than 10 controls for some cases.

Alcohol drinking and smoking

Data on alcohol consumption (never or ever) and the average amount of alcohol (including any type of alcohol beverage such as Japanese sake, beer, wine, or liquor) consumed per day were abstracted from the database. The amount of alcohol was converted to the average Japanese sake consumption, assuming that one, 180-mL cup of Japanese sake contains 23 grams of alcohol (Inoue et al. 2005). In accordance to a preceding study with some modification based on our own data, alcohol intake per day was then divided into four categories: never, up to 15 g/day, more than 15 to 30 g/day, and more than 30 g/day (Zeegers et al. 2001). Never drinkers were defined as those reporting less than 1 year of alcohol consumption anytime during their lifetime.

Smoking status of never, former, and current was recorded in the database. The average number of cigarettes smoked per day, and the age of the patient when starting and stopping smoking were recorded as well. Smoking intensity in former and current smokers was converted to pack-years by multiplying the average number of cigarettes smoked per day by the number of years the patient smoked to the nearest full year and dividing the product by 20, the number of cigarettes in a pack. In accordance to preceding studies with some modification based on our own data, we categorized pack-years into six categories: never, up to 10 pack-years, more than 10 to 20 pack-years, more than 20 to 40 pack-years, more than 40 to 50 pack-years, and more than 50 pack-years (Baris et al. 2009; Kurahashi et al. 2009). Ever smokers were defined as those who reported smoking more than 100 cigarettes anytime during their lifetime (Freedman et al. 2011).

Occupational information, age, and admission dates

From the thousands of detailed JSIC and JSOC classifications, we considered the following to be high-risk for bladder cancer: print-

ing and related workers; electrical, natural gas, and heating and air conditioning workers; sanitation workers; hotel service employees; heavy manufacturing; and skilled tradesmen (Malaker et al. 1987; Samanic et al. 2008). We then assumed that patients were at a higher risk for bladder cancer if one of their jobs was high-risk, without considering the duration. Age was divided into 5-year categories (such as 20 to 25, 26 to 30). Hospital admission dates were divided into three admission periods: April 2005 through March 2008, April 2008 through March 2011, and April 2011 through March 2014.

Statistical methods

We used conditional logistic regression to estimate odds ratio (OR) and 95% confidence interval (95% CI) for alcohol consumption as a risk factor for bladder cancer. These estimates were adjusted for smoking (status and pack-years), occupation (higher-risk vs. no risk), and comorbidities (hypertension, hyperlipidemia, diabetes mellitus, hyperuricemia, and obesity). We adjusted comorbidities because these were possible risk factors for bladder cancer (Wyszynski et al. 2014). While the synergy effect between alcohol drinking and smoking has been demonstrated (Murata et al. 1996), we did not set the interaction term for the synergy effect in the final models because the interaction term was not a significant predictor in the current study.

In the main analysis, for all matched patients (including never, former, and current smokers), we estimated the overall ORs of alcohol consumption and smoking, as well as the ORs for the daily amount of alcohol consumed and the number of pack-years of smoking.

Because bladder cancer risk was different between former and current smokers against never smokers, in the first subgroup analyses, we estimated the ORs for all patients minus current smokers and, in the second subgroup analysis, for all patients minus former smokers. In the subgroup analyses, we did not estimate the OR for the daily amount of alcohol consumed but estimated the overall ORs of alcohol consumption (never or ever). The number of bladder cancer case is smaller in the subgroup analyses than in the main analysis. This reduction resulted in some strata containing no cases of bladder cancer when stratifying by the daily amount of alcohol consumed and the other variables. We could not estimate robust ORs without cases in some strata. Percentages were compared with chi-square tests.

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).

Results

We initially included 434,415 patients aged 20 years and older admitted to the hospitals between April, 2005 and March, 2014. We then excluded 152,662 patients who did not provide information, 181,614 patients not asked about comorbidities, and 24,324 patients with incomplete data; the rest of 75,815 patients were matched. The study subjects consisted of 7,935 matched patients: 739 cases and 7,196 controls. Of the 739 cases, 696 had 10 matched controls per each case; the remaining 43 cases had less than 10 matched controls per case.

The distributions of sex, age, hospital, and dates were well balanced between groups (Table 1). The percentage of ever drinkers was larger in cases than in controls (74.7% vs. 69.7% respectively; $P = 0.005$). The distribution of daily

alcohol intake differed between groups ($P = 0.02$). Likewise, the percentage of ever smokers was larger in cases than in controls (78.1% vs. 68.7%, respectively; $P = 0.001$), and the distribution of pack-years of smoking also differed ($P < 0.001$). The distributions of high-risk occupations or comorbidities, however, did not differ between groups.

In the main analysis, the OR (95% CI) of ever drinkers having bladder cancer was 1.33 (1.06 to 1.66), and the OR became statistically significant after 15 g/day (Table 2). The ORs (95% CI) of former smokers and current smokers were 1.70 (1.33 to 2.18) and 2.71 (2.10 to 3.50), respectively, and the OR of bladder cancer risk became significant after 10-pack years. The ORs for occupation and comorbidities indicated no increased risk (Table 2).

In the first subgroup analysis, the OR (95% CI) of ever drinkers adjusted for smoking status was 1.40 (1.05 to 1.86), and the OR of ever drinkers adjusted for pack-years was 1.43 (1.07 to 1.90) (Table 3). The OR of former smokers was 1.76 (1.35 to 2.29). The OR of cancer was significantly higher after more than 10 pack-years. The ORs for occupation and the five comorbidities were again not statistically significant (Table 3).

In the second subgroup analysis, the OR (95% CI) of ever drinkers adjusted for smoking status was 1.37 (1.01 to 1.86), and the OR of ever drinkers adjusted for pack-years was 1.41 (1.03 to 1.91) (Table 4). The OR of current smoker was 2.61 (1.96 to 3.49). The OR of cancer became statistically significant after more than 20 pack-years. The ORs for occupation and the five comorbidities were still not statistically significant (Table 4).

Discussion

We found that alcohol consumption was an independent risk factor for bladder cancer. Alcohol consumption modestly but significantly increased the risk. The OR for ever drinkers was 1.3 to 1.4 times as high as that for never drinkers. The risk threshold of alcohol intake was more than 15 g/day. In addition, the risk threshold of smoking was more than 10 pack-years.

As compared to other studies, the uniqueness of this study is that we first found that alcohol increased the risk of bladder cancer in East Asian population. The fact that we studied Japanese patients, having weak genetic features on acetaldehyde detoxification as a whole, may explain why we found the risk. In addition, because we analyzed a large, nationwide dataset, the number of bladder cancer case was much larger than previous case-control studies and cohort studies (Murata et al. 1996; Wakai et al. 2004; Inoue et al. 2005; Ros et al. 2011), which provided efficient statistical power to detect the risk. Moreover, we tried to prevent possible confounding by simultaneous controlling for detailed information on smoking, occupational background, and comorbidity, as well as major patient baseline characteristics. Thus, we believe that our finding of alcohol as a risk factor for bladder cancer is robust.

Table 1. Demographic and Clinical Characteristics of Patients with Bladder Cancer and Controls Matched on by Sex, Age, Hospital, and Admission Period.

Characteristic	Bladder cancer cases	Matched controls
Sample size, n	739	7,196
Sex, n (%)		
Men	614 (83.1)	5,972 (83.0)
Women	125 (16.9)	1,224 (17.0)
Age, mean (SD), years	70.1 (9.4)	70.7 (9.6)
Admission period, n (%)		
April 2005 to March 2008	261 (35.3)	2,532 (35.2)
April 2008 to March 2011	270 (36.5)	2,654 (36.9)
April 2011 to March 2014	208 (28.2)	2,010 (27.9)
Alcohol use, n (%)		
Never	187 (25.3)	2,181 (30.3)
Ever	552 (74.7)	5,015 (69.7)
Ethanol intakes (ever)		
> 0 to ≤ 15 (g/day)	42 (5.7)	445 (6.2)
> 15 to ≤ 30 (g/day)	260 (35.2)	2,440 (33.9)
> 30 (g/day)	250 (33.8)	2,130 (29.6)
Smoking, n (%)		
Never	162 (21.9)	2,250 (31.3)
Former	320 (43.3)	3,216 (44.7)
Current	257 (34.8)	1,730 (24.0)
Pack-years (former and current)		
> 0 to ≤ 10 (pack-year)	51 (6.9)	663 (9.2)
> 10 to ≤ 20 (pack-year)	71 (9.6)	807 (11.2)
> 20 to ≤ 40 (pack-year)	190 (25.7)	1,677 (23.3)
> 40 to ≤ 50 (pack-year)	115 (15.6)	742 (10.3)
> 50 (pack-year)	150 (20.3)	1,057 (14.7)
High-risk occupational experience, n (%)		
No	556 (75.2)	5,383 (74.8)
Yes	183 (24.8)	1,813 (25.2)
Hypertension, n (%)		
No	234 (31.7)	2,489 (34.6)
Yes	505 (68.3)	4,707 (65.4)
Hyperlipidemia, n (%)		
No	583 (78.9)	5,671 (78.8)
Yes	156 (21.1)	1,525 (21.2)
Diabetes mellitus, n (%)		
No	532 (72.0)	5,085 (70.7)
Yes	207 (28.0)	2,111 (29.3)
Hyperuricemia, n (%)		
No	677 (91.6)	6,639 (92.3)
Yes	62 (8.4)	557 (7.7)
Obesity, n (%)		
No	578 (78.2)	5,552 (77.2)
Yes	161 (21.8)	1,644 (22.8)

The risk of current smokers was about three to four times as high as that of never smokers (Freedman et al. 2011; Inoue et al. 2012). Our result was the same trend. The most effective strategy for preventing bladder cancer is

smoking cessation; however, informing the patient of the risk of smoking is insufficient (Strope and Montie 2008). Efforts to encourage smoking cessation are still needed.

Our study has several limitations. First, as in any hos-

Table 2. Results of Logistic Regression Analysis for Factors Associated with a Risk of Bladder Cancer among 7,935 Cases and Controls Matched on Sex, Age, Hospital, and Hospitalization Dates.

Characteristics	Odds Ratio (95% CI) [†]	Odds Ratio (95% CI) [‡]
Alcohol drinking		
Never	Reference	
Ever	1.33 (1.06 to 1.66)	
Ethanol intakes		
Never		Reference
> 0 to ≤ 15 (g/day)		1.20 (0.83 to 1.73)
> 15 to ≤ 30 (g/day)		1.33 (1.04 to 1.70)
> 30 (g/day)		1.41 (1.10 to 1.82)
Smoking		
Never	Reference	
Former	1.70 (1.33 to 2.18)	
Current	2.71 (2.10 to 3.50)	
Pack-years		
Never		Reference
> 0 to ≤ 10 (pack-year)		1.32 (0.93 to 1.89)
> 10 to ≤ 20 (pack-year)		1.56 (1.12 to 2.17)
> 20 to ≤ 40 (pack-year)		2.02 (1.54 to 2.64)
> 40 to ≤ 50 (pack-year)		2.88 (2.12 to 3.90)
> 50 (pack-year)		2.62 (1.96 to 3.48)
Higher-risk job experience		
Yes (vs. No)	0.96 (0.81 to 1.15)	0.98 (0.82 to 1.18)
Hypertension		
Yes (vs. No)	1.13 (0.94 to 1.36)	1.11 (0.92 to 1.33)
Hyperlipidemia		
Yes (vs. No)	1.05 (0.87 to 1.28)	1.05 (0.86 to 1.27)
Diabetes mellitus		
Yes (vs. No)	0.95 (0.79 to 1.14)	0.94 (0.78 to 1.13)
Hyperuricemia		
Yes (vs. No)	1.11 (0.84 to 1.47)	1.07 (0.81 to 1.42)
Obesity		
Yes (vs. No)	1.00 (0.83 to 1.22)	0.97 (0.80 to 1.18)

[†]Odds ratios for bladder cancer for all patients adjusted for alcohol status (ever vs. never), smoking status (ever vs. never), occupation, and comorbidities by a conditional logistic regression.

[‡]Odds ratios for bladder cancer for all patients adjusted for alcohol intensity (never, > 0 to ≤ 15 g/day, > 15 to ≤ 30 g/day, and > 30 g/day), smoking intensity (never, > 0 to ≤ 10 pack-year, > 10 to ≤ 20 pack-year, > 20 to ≤ 40 pack-year, > 40 to ≤ 50 pack-year, and > 50 pack-years), occupation, and comorbidities by a conditional logistic regression.

pital-based, case-control study, selection bias might affect external validity. The controls were, however, selected from the patients whose diseases were little associated with exposure to alcohol, so that this limitation may be negligible. In addition, even in a large cohort, the number of bladder cancer incidence is small; therefore, a matched case-control method by nationwide clinical big-data would be more appropriate. Second, we had no information on the types of alcoholic beverages consumed, so that we could only detect the risk on the amount of ethanol intake. The amount of ethanol intake is thought to be associated with carcinogenesis (Zeegers et al. 2001); however, the risk of

the types and ingredients of alcohol beverages should be explored further. In addition, although some studies conducted from the same database were published (Kaneko et al. 2015), we need more robust validations of the questionnaire, especially with regards to questions on alcohol consumption, to improve the quality of assessment in the database. Third, we had no information on the genetic tolerance to acetaldehyde or no other genetic factors associated to bladder cancer for each individual level (Kaisary et al. 1987). These unmeasured individual genetic factors may not affect our conclusion due to the large sample size; nevertheless, we need further studies focusing on the individual

Table 3. Results of Logistic Regression Analysis for Former Smokers as Risk Factors for Bladder Cancer among 5,948 Cases and Controls Matched on Sex, Age, Hospital, and Hospitalization Dates.

Characteristics	Case/Control, n	Odds Ratio (95% CI) by smoking status [†]	Odds Ratio (95% CI) by smoking intensity [‡]
Alcohol consumption			
Never	148/1,875	Reference	Reference
Ever	334/3,591	1.40 (1.05 to 1.86)	1.43 (1.07 to 1.90)
Smoking			
Never	162/2,250	Reference	
Former	320/3,216	1.76 (1.35 to 2.29)	
Pack-years (former and never)			
Never	162/2,250		Reference
> 0 to ≤ 10 (pack-year)	44/575		1.36 (0.92 to 2.01)
> 10 to ≤ 20 (pack-year)	54/644		1.49 (1.03 to 2.17)
> 20 to ≤ 40 (pack-year)	109/1,052		1.83 (1.34 to 2.51)
> 40 to ≤ 50 (pack-year)	48/369		2.40 (1.61 to 3.59)
> 50 (pack-year)	65/576		2.05 (1.43 to 2.95)

[†]Odds ratios for bladder cancer adjusted for smoking status, as well as for alcohol drinking status, occupation, and comorbidity by conditional logistic regression analysis.

[‡]Odds ratios for bladder cancer adjusted for smoking intensity, as well as for alcohol drinking status, occupation, and comorbidity by conditional logistic regression analysis.

These data do not include those for current smokers.

Table 4. Results of Logistic Regression Analysis for Current Smokers as Risk Factors for Bladder Cancer among 4,399 Cases and Matched Controls.

Characteristic	Case/Control, n	Odds Ratio (95% CI) by smoking status [†]	Odds Ratio (95% CI) by smoking intensity [‡]
Alcohol consumption			
Never	143/1,662	Reference	Reference
Ever	276/2,318	1.37 (1.01 to 1.86)	1.41 (1.03 to 1.91)
Smoking			
Never	162/2,250	Reference	
Current	257/1,730	2.61 (1.96 to 3.49)	
Pack-years (current and never)			
Never	162/2,250		Reference
> 0 to ≤ 10 (pack-year)	7/88		1.22 (0.53 to 2.81)
> 10 to ≤ 20 (pack-year)	17/163		1.77 (0.98 to 3.21)
> 20 to ≤ 40 (pack-year)	81/625		2.33 (1.63 to 3.34)
> 40 to ≤ 50 (pack-year)	67/373		3.36 (2.26 to 5.01)
> 50 (pack-year)	85/481		3.19 (2.21 to 4.60)

[†]Odds ratios for bladder cancer adjusted for smoking status, as well as for alcohol drinking status, occupation, and comorbidities by conditional logistic regression analysis.

[‡]Odds ratios for bladder cancer adjusted for smoking intensity, as well as for alcohol drinking status, occupation, and comorbidities by conditional logistic regression analysis.

These data do not include those for former smokers.

risk for preventing bladder cancer.

In summary, among Japanese, alcohol consumption may be an independent risk factor for bladder cancer with the risk threshold of more than 15 g/day, even though the magnitude of risk was modest.

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Conflict of Interest

The authors declare no conflict of interest.

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