RESEARCH ARTICLE

Risk Factors for Upper and Lower Urinary Tract Cancer Death in a Japanese Population: Findings from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study)

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Abstract

Background: The incidence of bladder cancer is lower in Asian than in Western countries. However, the crude incidence and mortality of bladder cancer have recently increased in Japan because of the increased number of senior citizens. We have already reported risk factors for urothelial cancer in a large population-based cohort study in Japan (JACC study). However, we did not evaluate the cancer risk in the upper and lower urinary tract separately in our previous study. Materials and Methods: Here we evaluated the risk of cancer death in the upper and lower urinary tracts, separately, using the database of the JACC study. The analytic cohort included 46,395 males and 64,190 females aged 40 to 79 years old. The Cox proportional hazard model was used to determine hazard ratios and their 95% confidence intervals. Results: Current smoking increased the risk of both upper and lower urinary tract cancer deaths. A history of kidney disease was associated with an increased risk of bladder cancer death, even after controlling for age, sex and smoking status. Conclusions: The present study confirmed that current smoking increases the risk of both upper and lower urinary tract cancer deaths and indicated the possibility that a history of kidney disease may be a risk factor for bladder cancer death in the Japanese population.

Keywords: Risk factor - renal pelvic and ureter cancer - bladder cancer - smoking - Japanese

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Introduction

The urinary system consists of kidneys, ureters and bladder. Bladder cancer arises from mucosa of the lower urinary tract (Kogevinas et al., 2008). On the other hand, in adults, renal cell carcinoma, which represents 80 to 90% of kidney cancer, arises from cells from the proximal convoluted renal tubules (Cho et al., 2008) while renal pelvic cancer, which represents the rest of the kidney cancer, arises from mucosa of the upper urinary tract (Cho et al., 2008).

The incidences of bladder cancer and kidney cancer are lower in Asian countries than in Western countries (WHO, 2003). However, the incidences of bladder cancer (Kakehi et al., 2010) and kidney cancer (Toma, 2003) have been increasing in Japan. Furthermore, the mortalities of bladder cancer and kidney cancer have increased in Japan (Japanese Mistry of Health, Labour and Welfare, 2016). We have already reported several findings on the risk of urothelial cancer (i.e., renal pelvic, ureter and bladder cancer) death in a Japanese population (Sakauchi et al., 2004). However, we did not evaluate the urothelial cancer risk in the upper urinary tract (UUT) and bladder, separately. Therefore, in the present study, we evaluated the risk of urothelial cancer death in the UUT and bladder, separately.

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Materials and Methods

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC study) is a nationwide collaborative prospective cohort study of the various risks and preventive factors influencing cancer mortality and incidence (Tamakoshi et al., 2013). Study methods and ethical issues have been described elsewhere (Sakauchi et al., 2004; Tamakoshi et al., 2013).

Briefly, the cohort was established from 1988 to 1990, with 110,585 residents (46,395 males and 64,190 females) ranging in age from 40 to 79 years in 45 areas across Japan (Sakauchi et al., 2004; Tamakoshi et al., 2013). In most regions, informed consent was obtained individually and directly from members of the cohort, while in several areas, informed consent was obtained at the community level after the purpose of the study and confidentiality of the data have been explained to community leaders and mayors. Most of participants were people who had received a municipal health checks. The participants completed a self-administrated questionnaire containing questions on their medical history, height, weight and lifestyle factors such as smoking and drinking.

In most areas, follow-ups on mortalities and causes of death were completed at the end of 2009 (Tamakoshi et al., 2013). Death from bladder cancer was defined as code ' C67' in the ICD-10 (International Statistic Classification of Diseases and Health Problems, Tenth Revision) while death from the UUT cancer (i.e., renal pelvic and ureter cancer) was defined as code ' C65 and C66' in the ICD-10 (Sakauchi, et al., 2004; Tamakoshi et al., 2013). Eligible subjects included 46,395 males and 64,190 females with 707,136 and 1,025,703 person-year follow-up, respectively. During the follow-up period, 166 participants (115 males and 51 females) died from bladder cancer and 61 participants (40 males and 21 females) died from UUT cancer.

Smoking status at baseline was classified into two categories: current smokers and non-smokers. Drinking status at baseline was also classified into two categories: current drinkers and non-drinkers.

The body mass index (BMI) was calculated as the reported weight divided by the square of the reported height (kg/m2). Obesity was defined as a high BMI (BMI > 25.0 kg/m2). 'Diabetes mellitus (DM) subjects' were defined as subjects who had a history of DM while 'normal subjects' were defined as those without a history of DM or obesity.

All statistical analyses were conducted using the Statistical Analysis System (SAS) package (SAS institute Inc. Cary, NC, USA) package. The hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated with Cox's proportional hazard model. Age was treated as a continuous variable while indicator valuables were used for other factors. P-values of less than 0.05 were considered to indicate statistical significance.

This investigation was approved by the Ethical Boards of Nagoya University (no. 227), Hokkaido University (no. 14-044) and Kyoto Prefectural University of Medicine (no. MCHS-200).

Results

Table 1 shows adjusted HRs of UUT cancer death in relation to smoking and drinking habits, medical histories and obesity. Compared with non-smokers, current smokers showed an increased age and sex adjusted risk of UUT cancer death. On the other hand, drinking alcohol failed to show any meaningful association with the risk of UUT cancer death after controlling for age, sex and smoking although current drinking showed a non-significantly

Table 1. Adjusted Hazard Ratios of Upper Urinary Tract Cancer Death in Relation to Smoking and Drinking Habits, Medical Histories and Obesity

Factors	Number of subjects	Person-years	Number of deaths	Age and sex adjusted HR(95%CI)	Age, sex and smoking adjusted HR(95%CI)
Smoking tobacco					
Non-smokers	73,115	1,196,939	26	1.00	
Current smokers	26,510	416,760	27	2.32(1.22-4.40)*	Not available
Drinking alcohol					
Non-drinkers	55,026	880,613	16	1.00	1.00
Current drinkers	47,421	773,263	36	1.87(0.95-3.71)#	1.64(0.82-3.28)
Medical histories					
History of kidney disease					
No	82,511	1,338,678	42	1.00	
Yes	4,271	62,419	1	0.55(0.08-4.00)	Not available
History of hypertension					
No	76,248	1,275,447	36	1.00	1.00
Yes	22,531	332,186	14	1.24(0.66-2.33)	1.37(0.71-2.66)
Obesity and diabetes mellitus					
Normal subjects	68,059	1,121,681	36	1.00	1.00
Obesity without diabetes mellitus	18,127	305,964	9	0.99(0.48-2.02)	0.87(0.39-1.95)
Diabetes mellitus	5,283	71,125	3	0.98(0.30-3.15) P for trend=0.929	0.73(0.18-3.02) P for trend=0.878

HR(95%CI): Hazard ratio(95% confidence interval), *:p<0.05, #: p<0.1; Obesity: those with high body mass index (25.0 kg/m^2 or greater), Normal subjects: those without diabetes mellitus or obesity

Table 2. Adjusted Hazard Ratios of Bladder Cancer Death in Relation to Smoking and Drinking Habits, Medical Histories and Obesity

Factors	Number of subjects	Person-years	Number of deaths	Age and sex adjusted HR(95%CI)	Age, sex and smoking adjusted HR(95%CI)
Smoking tobacco					
Non-smokers	73,115	1,196,939	89	1.00	
Current smokers	26,510	416,760	70	1.98(1.37-2.84)*	Not available
Drinking alcohol					
Non-drinkers	55,026	880,613	74	1.00	1.00
Current drinkers	47,421	773,263	90	01.11(0.77-1.44)	0.99(0.69-1.44)
Medical histories					
History of kidney disease					
No	82,511	1,338,678	109	1.00	1.00
Yes	4,271	62,419	11	2.24(1.21-4.17)*	2.49(1.33-4.64)*
History of hypertension					
No	76,248	1,275,447	111	1.00	1.00
Yes	22,531	332,186	40	0.90(0.63-0.57)	0.87(0.59-1.23)
Obesity and diabetes mellitus					
Normal subjects	68,059	1,121,681	98	1.00	1.00
Obesity without diabetes mellitus	18,127	305,964	22	0.92(0.59-1.44)	0.85(0.53-1.38)
Diabetes mellitus	5,283	71,125	3	0.31(0.10-0.96)* P for trend=0.143	0.33(0.11-1.03)# P for trend=0.129

HR(95%CI): Hazard ratio(95% confidence interval), *:p<0.05, #: p<0.1; Obesity: those with high body mass index (25.0 kg/m^2 or greater), Normal subjects: those without diabetes mellitus or obesity

increased age and sex adjusted risk of UUT cancer death compared with non-drinkers. For medical histories and obesity, either hypertension, kidney disease, DM, or obesity without DM did not show any meaningful association with the risk of UUT cancer death.

Table 2 illustrates adjusted HRs of bladder cancer death in relation to smoking and drinking habits, medical histories and obesity. Compared with non-smokers, current smokers showed an increased risk of bladder cancer death. On the other hand, compared with non-drinkers, current drinkers showed no meaningful relation to the risk of bladder cancer death. For medical histories and obesity, kidney disease increased the risk of bladder cancer death even after controlling for age, sex and smoking status, while hypertension showed no association with the risk of bladder cancer death. Compared with normal subjects, DM-subjects showed a significantly decreased age and sex-adjusted risk of bladder cancer death. Furthermore, DM showed a non-significantly decreased risk of bladder cancer death even after additional controlling for smoking status. On the other hand, obesity without DM showed no meaningful association with the risk of bladder cancer death.

Discussion

In the present study, 61 out of 227 (26.9%) urothelial cancer deaths were deaths from UUT cancer (not shown in the table), which was greater than the proportion of UUT cancer patients among newly diagnosed urothelial cancer patients (19 out of 123, 15.4%) (Sakauchi et al., 2005) in our previous study within the JACC study (26.9% vs. 15.4%, p<0.05). These findings suggest that fatality rate may be higher among UUT cancer patients than bladder cancer patients, which is consistent with the report by Korkes et al. (2006). They reported that most patients with bladder cancer were in the early stage at diagnosis while a high proportion of UUT cancer patients were found at advanced stages at diagnosis (Korkes et al., 2006).

Cigarette smoking is the most important cause of bladder cancer (Kogevinas et al., 2008). Tobacco smoking is associated with an increased risk of malignancies of organs in direct contact with smoke, such as lungs, as well as organs not in direct contact with smoke, such as kidneys, ureters and bladder. In the JACC study, smoking increased the risk of urothelial cancer death (Sakauchi et al., 2004). In the present study, smoking increased the risk of both UUT cancer death and bladder cancer death.

Obesity increases the risk of kidney, colon, endometrium, and breast cancer (Ballard-Barbash et al., 2006). Insulin-resistance, which is common in obesity and leads to elevated levels of insulin-like growth factor type 1, is suggested to increase the risk of cancer (Ballard-Barbash et al., 2006). However, obesity did not showed any meaningful association with either the risk of UUT cancer death or the risk of bladder cancer death in the present study.

DM is suggested to increase the risk of bladder cancer (Cantiello et al., 2015; Noto et al., 2013). Type 2 DM patients are typically obese and live sedentary lives, both of which contribute to insulin-resistance and increase the risk of cancer (Cantiello et al., 2015). On the other hand, usage of metformin, which is the first choice drug for Type 2 DM patients to treat hyperglycemia, is reported to decrease the risk of cancer (Noto et al., 2013). Recently, Zhu et al. (2013) carried out a meta-analysis of cohort studies and reported that DM increased the risk of bladder cancer. In the present study, however, DM decreased the age- and sex-adjusted risk of bladder cancer death. Even after additional adjustment of smoking status, DM tended to decrease the risk of dying from bladder cancer.

The reasons why DM subjects showed a decreased risk of bladder cancer death may be explained in the following ways. First, DM patients may receive urinary

examination regularly at DM clinics. Since malignancies of urinary system are detected in up to 5% of patients with microscopic hematuria and in up to 30 to 40% of those with gross hematuria (Sharp et al., 2013), bladder cancer may be more likely to be detected at the early stage among DM patients than non-DM subjects. Second, DM patients, who receive operation for bladder cancer at the early stage and have a good prognosis, may die not from bladder cancer, but from heart diseases or cancers other than bladder cancer. Kubota et al. (2015) reported that cardiovascular disease (30.5%) was the first leading cause of death among 3,851 participants with DM in the JACC study while Shibata et al. (2003) reported that DM increased the risk of liver cancer death for both males (HR=2.91; 95%CI=2.13-3.97) and females (HR=4.52; 95%CI=2.68-7.63) in the JACC study.

Urinary stones of the renal pelvis, which may cause chronic irritation and infection, is a medical condition with an increased risk of urothelial cancer (Kogevinas et al., 2008). Cyclophosphamide, which is used for glomerulonephritis and nephrotic syndrome (Appel et al., 2008 ; Nachman et al., 2008), increases the risk of urothelial cancer (Kogevinas et al., 2008). In the present study, a history of kidney disease increased the risk of bladder cancer death but failed to show an increased risk of UUT cancer death although both bladder cancer and UUT cancer are urothelial cancers. These findings may be partly explained by the small number of UUT cancer deaths in the present study.

Hypertension is an established risk factor for kidney cancer (WHO, 2003) while it is still a matter of the debate whether or not hypertension is associated with an increased risk of bladder cancer (Cantiello et al., 2015). In our previous studies within the JACC study, a history of hypertension increased the risk of renal cancer death (Washio et al., 2005). In contrast with renal cell cancer death, a history of hypertension did not increase the risk of either UUT cancer death or bladder cancer death in the present study.

In summary, the present study showed that smoking increased the risk of UUT cancer death as well as the risk of urinary bladder cancer death while a history of kidney disease increased the risk of bladder cancer mortality but did not increase the risk of UUT cancer death. The advantage of our study was that our population-based cohort study was a large-scale prospective study among the Japanese population (Sakauchi et al., 2004; Tamakoshi et al., 2013). However, we had limited potential to evaluate the risk of UUT cancer death because there were only small number of UUT cancer deaths (i.e., 61 deaths) in the present study despite of the large-scale of the cohort study. Further studies may be needed to evaluate risk factors for UUT cancer death in Japan.

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