Diabetes Mellitus and Incidence of Bladder and Kidney Cancer: An Exposure-Control Matched Study

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Abstract

Background: Diabetes mellitus (DM), one of the most common metabolic diseases worldwide, is associated with malignancies at many sites. The relationship between DM and bladder or kidney cancer is still controversial. We investigated the associations between DM and bladder or kidney cancer in a population-based exposure-control matched study.

Method: Using the Korean National Health Insurance System sample cohort database, we identified patients who were diagnosed as having DM between January 2006 and December 2010. A control group was also selected from the database using propensity score matching to adjust for age and sex. An exposure-control matched study was conducted until December 2015. The two groups were compared for baseline characteristics and bladder or kidney cancer incidence. Cox's proportional hazard regression analyses were performed to investigate associations between bladder or kidney cancer and each clinical variable.

Results: In total, 132,570 patients with DM were identified. In addition, 132,570 patients without DM matched by age and sex (control group) were selected. The mean age was 54 years, and the male-to-female ratio was 1:1. During the follow-up period, 619 patients in the DM group and 511 in the control group were diagnosed as having bladder cancer. Of those diagnosed as having kidney cancer, 419 patients were in the DM group and 285 were in the control group. Adjusted Cox's proportional hazard regression analysis revealed that DM is associated with bladder and kidney cancer.

Conclusions: DM is associated with bladder and kidney cancer. Older men are at an increased risk for both cancers.

Background

Diabetes mellitus (DM) is one of the most common metabolic diseases worldwide. In the US, 34.2 million people have DM, comprising 10.5% of the country's population. [1] In South Korea, DM prevalence has increased during last 10 years from 9.6–10.8%. [2] DM is associated with numerous complications including cardiovascular disease, neuropathy, nephropathy, and retinopathy. In genitourinary systems, DM is known to be a risk factor for bladder dysfunction, sexual dysfunction, and urinary tract infections. [3] In addition, DM is known to directly increase the risk of urolithiasis. [4]

DM is also associated with malignancies at many sites. Patients with DM have high risks for cancers of the liver, pancreas, colon, and stomach. [5] Multiple factors including hyperglycemia, hyperinsulinemia, and insulin-like growth factor I are considered to contribute to oncogenesis. [6] However, the relationship between DM and prostate cancer is not currently understood. [7]

Bladder cancer is a fourth major cancer type newly diagnosed in men in the US. In 2020, 81,400 people were diagnosed bladder cancer in the US. Among newly diagnosed cancers in the US, kidney cancer is the sixth common cancer in men and the seventh in women. [8]

Risk factors for bladder cancer has been widely studied. Smoking is the most common risk factor of this cancer. In addition, occupational exposure to aromatic amines has been suggested as an important risk factor. [9] Kidney cancer was known to be associated with smoking, excessive body weight, and hypertension. [10]

The relationship between DM and bladder cancer has been previously reported. However, DM as a risk factor for bladder cancer is still in debate. In addition, although DM is regarded as a risk factor for kidney cancer, its independent effect without obesity and hypertension is still unclear. [10]

In this study, we investigated the associations of DM and bladder or kidney cancer using data from the Korean National Health Insurance Service (NHIS). In addition, we investigated other risk factors for bladder or kidney cancer using a sample cohort database.

Methods

This study was approved by the Institutional Review Board (NHIMC 2018-09-002). This study used National Sample Cohort data, provided by NHIS. We retrieved data from NHIS - National Sample Cohort (NHIS-NSC) from 2006 to 2015. The NHIS-NSC included on a million people each year. The database included the following information for each patient: disease diagnosis with the corresponding International Classification of Diseases (ICD) 10 code, age, sex, body mass index (BMI), socioeconomic status, smoking/drinking status, and results of a blood test performed at the national health check-up for citizens once every two years.

We identified patients from the NHIS-NSC who were diagnosed as having DM between January 2006 and December 2010. The control group was also selected from the NHIS-NSC using propensity score matching to adjust for age, sex, residence and income quantile. An exposure-control matched study was performed from January 2006 until December 2015. We compared both groups for incidence of bladder cancer or kidney cancer. Patients who diagnosed bladder cancer or kidney cancer before 2006 were excluded. In addition, we analyzed characteristics of each group and investigated differences using Student’s t-test and the chi-square test.

Baseline characteristics included age, sex, height, weight, smoking, drinking, economic status, residence and presence of hypertension. Residence was classified as metropolitan, large city, small city, or rural areas according to the administrative region. The capital city (Seoul) was defined as metropolitan while other metropolitan cities were considered large cities. Other smaller cities and counties were classified as small cities and rural areas, respectively. Economic status was sectioned by income from low to very high using 10 quantiles. The first and second income quantiles were classified as very high, third to fifth quantiles as high, sixth to eighth quantiles as middle, and ninth and tenth quantiles as low. Smoking/drinking status was classified according to a questionnaire patients completed at the national health check-up. Smoking status was categorized as non-smoker, ex-smoker and current smoker. Drinking status was categorized as none, mild, moderate, or heavy drinker. Criteria for determining drinking status are displayed in Supplementary Tables 1 and 2.

We performed Cox's proportional hazard regression analyses to investigate the associations between bladder or kidney cancer and each clinical variable. We analyzed the relationships between DM and each clinical variable including the presence of DM, age, sex, smoking/drinking status, BMI, and presence of hypertension. Univariate and multivariable regression analyses for DM were conducted. Multivariable regression analyses were adjusted with sex, age, smoking, drinking, BMI, presence of hypertension, residence and income quantile. All analyses were performed using SAS Enterprise Guide 7.13 software (SAS Institute, Cary, NC, USA).

Results

In total, 132,570 patients with DM were identified from the NHIS-NSC from 2006 to 2010. In addition, 132,570 patients without DM matched by age and sex (control group) were selected from the NHIS-NSC. Baseline characteristics are displayed in Table 1. The mean age was 54 years and male-to-female ratio was 1:1. In both groups, patients older than 60 comprised 41% of the total number of patients. DM group were diagnosed with hypertension more than control group.

Table 1
Baseline characteristics

		DM		Control		p value
		N = 132,570		N = 132,570		
		N	%	N	%	
Sex	Male	66,302	50.01	66,265	49.98	0.886
	Female	66,268	49.99	66,305	50.02	
Age (year)	Mean	54.58 ± 14.90 (SD)		54.59 ± 14.91 (SD)		
	20–39	17,366	13.37	17,366	13.37	1
	40–59	59,248	45.63	59,248	45.63	
	≥ 60	53,237	41.00	53,237	41.00	
Hypertension		83,677	63.12	48,877	35.36	< .001
Residence	Metropolitan	28,606	21.58	28,119	21.21	0.003
	Large city	32,632	24.61	32,726	24.69	
	Small city	55,924	42.18	55,764	42.06	
	Rural	15,408	11.62	15,961	12.04	
Income quantile	Very high	21,069	15.89	21,087	15.91	0.861
	High	31,393	23.68	31,482	23.75	
	Middle	41,079	30.99	41,172	31.06	
	Low	39,029	29.44	38,829	29.29	
Smoking	Non-smokers	57,748	43.56	57,561	43.42	< .001
	Ex-smokers	8,812	6.65	8,177	6.17	
	Current smokers	16,717	12.61	16,698	12.60	
Drinking	None	52,286	39.44	50,697	38.24	< .001
	Mild	25,028	18.88	26,461	19.96	
	Moderate	2,470	1.86	2,341	1.77	
	Heavy	3,249	2.45	2,740	2.07	
Body mass index	< 23	72,089	54.38	80,816	60.96	< .001

		DM		Control		p value
		N = 132,570		N = 132,570		
		N	%	N	%	
(kg/m2)	23 ~ 24.9	22,408	16.90	22,959	17.32	
	≥ 25	38,073	28.72	28,795	21.72	
Bladder cancer		619	0.47	511	0.39	
Kidney cancer		412	0.31	285	0.21	
*SD: Standard deviation						

Table 2
Cox's s proportional hazard regression analysis for bladder cancer

		Crude HR		p value	Adjusted HR*		p trends adjusted
		HR	95% CI		HR	95% CI	(pivot trend)
DM	None	1(Reference)			1 (Reference)		
	Presence	1.24	1.103–1.395	< .001	1.204	1.030–1.408	0.020
Sex	Female	1 (Reference)			1 (Reference)		
	Male	2.686	2.357–3.061	< .001	3.458	2.856–4.186	< .001
Age	20–39	1 (Reference)			1 (Reference)		
	40–59	3.596	2.330–5.550	< .001	3.906	2.067–7.381	< .001
	≥ 60	12.514	8.195–19.110	< .001	13.755	7.325–25.829	< .001
Hypertension	None	1 (Reference)			1 (Reference)		
	Presence	1.240	1.103–1.395	< 0.001	1.556	1.311–1.847	< .001
Smoking	Non-smokers	1 (Reference)			1 (Reference)		
	Ex-smokers	1.882	1.540–2.299	< .001	1.201	0.967–1.492	0.098
	Current smokers	1.375	1.154–1.639	< .001	1.094	0.898–1.333	0.373
Drinking	None	1 (Reference)			1 (Reference)		
	Mild	1.029	0.877–1.208	0.725	0.853	0.715–1.019	0.080
	Moderate	1.735	1.230–2.448	< .001	1.189	0.836–1.693	0.336

*Adjusted with sex, age, smoking, drinking, body mass index, presence of hypertension, residence and income quantile

**CI;Confidence Interval, DM;Diabetes Mellitus, HR;Hazard Ratio

		Crude HR		p value	Adjusted HR*		p trends adjusted
		HR	95% CI		HR	95% CI	(pivot trend)
	Heavy	1.318	0.925–1.877	0.126	0.787	0.544–1.140	0.205
Body mass index	< 23	1 (Reference)			1 (Reference)		
(kg/m2)	23 ~ 24.9	1.114	0.956–1.298	0.166	1.074	0.895–1.290	0.442
	≥ 25	0.925	0.802–1.066	0.279	0.948	0.796–1.130	0.553
*Adjusted with sex, age, smoking, drinking, body mass index, presence of hypertension, residence and income quantile							
**CI;Confidence Interval, DM;Diabetes Mellitus, HR;Hazard Ratio							

Table 3
Cox's s proportional hazard regression analysis for kidney cancer

		Crude HR		p value	Adjusted HR*		p trends adjusted
		HR	95% CI		HR	95% CI	(pivot trend)
DM	None	1 (Reference)			1 (Reference)		
	Presence	1.483	1.275–1.725	< .001	1.521	1.247–1.857	< .001
Sex	Female	1			1 (Reference)		
	Male	1.919	1.642–2.243	< .001	2.068	1.642–2.604	< .001
Age	20–39	1 (Reference)			1 (Reference)		
	40–59	4.363	2.672–7.124	< .001	5.187	2.434–11.050	< .001
	≥ 60	7.991	4.92-12.979	< .001	9.701	4.552–20.675	< .001
Hypertension	None	1 (Reference)			1 (Reference)		
	Presence	2.677	2.269–3.160	< 0.001	1.847	1.481–2.304	< .001
Smoking	Non-smokers	1 (Reference)			1 (Reference)		
	Ex-smokers	1.541	1.180–2.013	0.002	1.136	0.845–1.526	0.399
	Current smokers	1.277	1.022–1.595	0.031	1.136	0.878–1.470	0.332
Drinking	None	1 (Reference)			1 (Reference)		
	Mild	1.1	0.904–1.340	0.341	0.948	0.757–1.188	0.644
	Moderate	0.782	0.416–1.469	0.444	0.609	0.321–1.156	0.129

*Adjusted with sex, age, smoking, drinking, body mass index, presence of hypertension, residence and income quantile

**CI;Confidence Interval, DM;Diabetes Mellitus, HR;Hazard Ratio

		Crude HR		p value	Adjusted HR*		p trends adjusted
		HR	95% CI		HR	95% CI	(pivot trend)
	Heavy	1.325	0.851–2.064	0.213	0.882	0.550–1.414	0.601
Body mass index	< 23	1 (Reference)			1 (Reference)		
(kg/m2)	23 ~ 24.9	1.197	0.983–1.458	0.074	1.107	0.872–1.406	0.405
	≥ 25	1.188	0.999–1.412	0.051	1.107	0.889–1.38	0.363
*Adjusted with sex, age, smoking, drinking, body mass index, presence of hypertension, residence and income quantile							
**CI;Confidence Interval, DM;Diabetes Mellitus, HR;Hazard Ratio							

During the follow-up period, 619 patients in the DM group and 511 patients in the control group were diagnosed as having bladder cancer. Of those who were diagnosed as having kidney cancer, 419 patients were in the DM group and 285 were in the control group.

The distribution of residence was different between the two groups; however, the distribution of economic status was similar. The DM group had more smokers (both current and ex-) and more moderate and heavy drinkers than in the control group. The DM group also had a significantly higher population with a BMI greater than 25 kg/m^2. Hypertension was more diagnosed in the DM group.

Cox's proportional hazard regression analyses were performed to investigate the association between each clinical variable and the incidence of bladder and kidney cancer. Male sex and older age were associated with a higher incidence of bladder cancer. In addition, smoking (including ex-smokers and current smokers) and moderate drinking were risk factors for bladder cancer. However, BMI was not related to bladder cancer.

Presence of hypertension was significantly associated with bladder cancer. In addition, DM was associated with the incidence of bladder cancer (crude hazard ratio [HR], 1.24; 95% confidence interval [CI)], 1.103–1.395). After adjusting for age, sex, economic status, smoking, drinking, BMI, and hypertension, DM was significantly associated with bladder cancer incidence. Furthermore, male sex and older age were significantly associated with bladder cancer after applying similar adjustments.

The same analyses were performed for kidney cancer. Male sex, older age, and smoking experience were related to greater risks of having kidney cancer. However, drinking and BMI were not associated with kidney cancer incidence. Presence of hypertension and DM were significantly related to kidney cancer

incidence. After adjusting for age, sex, economic status, smoking, drinking, BMI, and hypertension, kidney cancer was associated with age, sex, hypertension and DM.

Discussion

In this study, we investigated the association between DM and bladder and kidney cancer in a population-based exposure-control matched study. We assessed the relationships of bladder and kidney cancer with not only DM but also other factors including smoking, drinking, and presence of hypertension.

Previous studies have investigated the relationships between DM and malignancies. DM was associated with an increased risk of hepatocellular carcinoma or endometrial cancer. [11, 12] By contrast, patients with DM had a reduced risk of prostate cancer diagnosis. [7] Nonetheless, DM or obesity has been considered as the risk factor for cancer in multiple sites. Multiple factors of DM contributed to the development or progression of cancer in complex ways. Hyperinsulinemia, insulin-like growth factor I, hyperglycemia, and other factors may contribute to cancer biology. [13]

The relationship between DM and bladder or kidney cancer varied by study. Inoue M. et al performed a population-based cohort study in Japan. They concluded patients with DM had an increased risk of liver, pancreatic, and kidney cancer in men; however, kidney cancer or bladder cancer was not related to DM in women. [5] However, bladder or kidney cancer was detected in small numbers from the cohort population, making it difficult to draw conclusions. Larsson SC et al also reported in their prospective study that DM was not associated with the risk of bladder cancer. [14] In a large cohort study by Newton C.C et al, no associations were found between DM and the risk of bladder cancer overall; however, patients with DM for more than 15 years and those using insulin had a higher risk of bladder cancer than those without DM. [15] Using the Taiwan National Insurance Database, Tseng CH concluded that patients with DM had a higher risk of bladder cancer. [16] However, they had a relatively short follow-up period from 2003 to 2005. Woolcott CG et al found that a self-reported diagnosis of DM is associated with an increased risk of urothelial cancer, which is higher in women, whites, and African Americans. [17]

An association of kidney cancer and DM is still controversial. In an aforementioned study, kidney cancer was associated with DM in men. [5] In another study by Lai GY et al, DM showed a positive association with kidney cancer. [18] However, in a study by Lai SW, DM was not correlated with the risk of kidney cancer. [19]

A recent meta-analysis reported that DM was associated with bladder cancer in men, not in women. [20] However, more studies with more heterogeneity are needed to make conclusions. In addition, information for Asian populations, including South Korea is still limited.

This study suggests that DM is associated with bladder cancer and kidney cancer. It used the NHIS-NSC that contributed by one million people per year with relatively long periods that minimum 5 years follow-up. This may be helpful for considering DM as a risk factor for bladder or kidney cancer. In addition, the database by KNHIS also includes diagnostic information and medications/prescription of all Korean

individuals. In subsequent studies, we can investigate other risk factors including hypertension or other metabolic syndrome for other malignancies.

This study had several limitations. In the basic characteristics, DM and control group were different statistically in some variants including smoking and others. Although we performed adjusted regression study, more precise propensity score matching would be necessary. In addition, other patient data such as cancer stages or personal medications were not analyzed in this study. This study lacked an analysis for subgroups, so further studies are needed to complete this analysis.

Nevertheless, this study demonstrated that the risk of bladder or kidney cancer increases with DM and other factors, including age, hypertension and smoking.

Conclusion

DM is associated with bladder and kidney cancer. In addition, older age and the male sex are risk factors for these cancers.

Declarations

Ethics approval and consent to participate

All procedures in our study involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. Data were collected after approval from Institutional Review Board of National Health Insurance Ilsan Hospital. (NHIMC 2018-09-002).

Consent for publication

Not applicable.

Availability of data and material

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

There are no competing interests in conducting the current research.

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There was no funding provided in the current research.

Acknowledgements

Not applicable.

Abbreviations

BMI Body Mass Index

CI Confidence Interval

DM Diabetes Mellitus

HR Hazard Ratio

ICD International Classification of Diseases

NHIS National Health Insurance Service

NSC National Sample Cohort

References

1. National Diabetes Statistics Report, 2020.
2. Shin J-Y. Trends in the prevalence and management of diabetes in Korea: 2007–2017. Epidemiol Health. 2019;41(0):e2019029-2019020.
3. Brown JS, Wessells H, Chancellor MB, Howards SS, Stamm WE, Stapleton AE, Steers WD, Van Den Eeden SK, McVary KT: Urologic complications of diabetes. *Diabetes Care* 2005, 28(1):177–185.
4. Liu LH, Kang R, He J, Zhao SK, Li FT, Zhao ZG. Diabetes mellitus and the risk of urolithiasis: a meta-analysis of observational studies. Urolithiasis. 2015;43(4):293–301.
5. Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med. 2006;166(17):1871–7.
6. Gallagher EJ, LeRoith D. Obesity and Diabetes: The Increased Risk of Cancer and Cancer-Related Mortality. Physiol Rev. 2015;95(3):727–48.
7. Fall K, Garmo H, Gudbjornsdottir S, Stattin P, Zethelius B. Diabetes mellitus and prostate cancer risk; a nationwide case-control study within PCBaSe Sweden. Cancer Epidemiol Biomarkers Prev. 2013;22(6):1102–9.
8. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. Cancer J Clin. 2020;70(1):7–30.
9. Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, Kassouf W, Kiemeney LA, La Vecchia C, Shariat S, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013;63(2):234–41.

10. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. Nat Rev Urol. 2010;7(5):245–57.
11. Yang WS, Va P, Bray F, Gao S, Gao J, Li HL, Xiang YB. The role of pre-existing diabetes mellitus on hepatocellular carcinoma occurrence and prognosis: a meta-analysis of prospective cohort studies. PloS one. 2011;6(12):e27326.
12. Liao C, Zhang D, Mungo C, Tompkins DA, Zeidan AM. Is diabetes mellitus associated with increased incidence and disease-specific mortality in endometrial cancer? A systematic review and meta-analysis of cohort studies. Gynecol Oncol. 2014;135(1):163–71.
13. Lohmann AE, Goodwin PJ, Chlebowski RT, Pan K, Stambolic V, Dowling RJ. Association of Obesity-Related Metabolic Disruptions With Cancer Risk and Outcome. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2016;34(35):4249–55.
14. Larsson SC, Andersson SO, Johansson JE, Wolk A. Diabetes mellitus, body size and bladder cancer risk in a prospective study of Swedish men. European journal of cancer (Oxford England: 1990). 2008;44(17):2655–60.
15. Newton CC, Gapstur SM, Campbell PT, Jacobs EJ. Type 2 diabetes mellitus, insulin-use and risk of bladder cancer in a large cohort study. Int J Cancer. 2013;132(9):2186–91.
16. Tseng CH. Diabetes and risk of bladder cancer: a study using the National Health Insurance database in Taiwan. Diabetologia. 2011;54(8):2009–15.
17. Woolcott CG, Maskarinec G, Haiman CA, Henderson BE, Kolonel LN. Diabetes and urothelial cancer risk: the Multiethnic Cohort study. Cancer Epidemiol. 2011;35(6):551–4.
18. Lai GY, Park Y, Hartge P, Hollenbeck AR, Freedman ND. The association between self-reported diabetes and cancer incidence in the NIH-AARP Diet and Health Study. J Clin Endocrinol Metab. 2013;98(3):E497–502.
19. Lai SW, Liao KF, Lai HC, Tsai PY, Sung FC, Chen PC. Kidney cancer and diabetes mellitus: a population-based case-control study in Taiwan. Ann Acad Med Singapore. 2013;42(3):120–4.
20. Xu Y, Huo R, Chen X, Yu X. Diabetes mellitus and the risk of bladder cancer: A PRISMA-compliant meta-analysis of cohort studies. Medicine. 2017;96(46):e8588.

Supplementary Files

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