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                                                                 | 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 proportional hazard regression analysis for bladder cancer

|                | Crude HR |          | p value | Adjusted HR* | Adjusted HR* | p trends adjusted |
|----------------|----------|----------|---------|--------------|--------------|-------------------|
|                | HR       | 95% CI   |         | HR           | 95% CI       |                   |
| 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 (Reference)          | 1        |         | 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
|                  | Crude HR                  |      | Adjusted HR*                  |      | p trends adjusted |
|------------------|---------------------------|------|-------------------------------|------|------------------|
|                  | HR                        | 95% CI| HR                           | 95% CI|                  |
| DM               | None                      | 1 (Reference) | 1 (Reference) |                  |
|                  | Presence                  | 1.483| 1.275–1.725 | < .001 | 1.521 | 1.247–1.857 | < .001 |
|                  | Sex                       | Female | 1 | (Reference) | 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) | 0.983–1.458 | 0.074   | 1.107        | 0.872–1.406    | 0.405            |
| (kg/m²)                  | 23 ~ 24.9|                |         |              |                |                  |
| ≥ 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/m². 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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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

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**Supplementary Files**

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