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Interaction patterns amongst risk factors for bladder cancer in adults with type 2 diabetes managed in primary care

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ABSTRACT

Background

Previous studies have shown that patients with type 2 diabetes have a higher risk of developing bladder cancer than the general population. However, little is known about how different risk factors interact to influence the risk of bladder cancer among diabetes patients.

Aim

To explore the interaction patterns among factors associated with the risk of bladder cancer incidence among patients who received diabetes management in primary care.

Design and Setting

A retrospective cohort study was performed using territory-wide electronic health records of Hong Kong. Patients who received diabetes care in general outpatient clinics between 2010 and 2019 without cancer history were included and followed up until December 2019.

Method

The interaction patterns among factors associated with the risk of bladder cancer incidence were examined using conditional inference survival tree analysis.

Results

A total of 382,770 patients were included. During a median follow-up of 6.2 years, 644 patients developed bladder cancer. Age (≤74 vs >74 years) and sex emerged as primary and secondary factors in differentiating the risk of bladder cancer sequentially. Among middle-old males (62 to 74 years) and youngest males (≤58 years), smoking (aHR for ever vs never smoker: 1.96, 95%CI 1.49-2.58) and chronic kidney disease (aHR for presence vs absence: 2.92, 95%CI 1.21-7.02) appeared as dominant risk factor for bladder cancer respectively.

Conclusion

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This study identified the interaction patterns among age, sex, smoking, and chronic kidney disease on the risk of bladder cancer incidence, providing potential targets for public health cancer prevention strategies in primary care for patients with type 2 diabetes.

Keywords: bladder cancer; diabetes; primary health care; interaction; public health; survival analysis

HOW THIS FITS IN

Prior research shows that type 2 diabetes is associated with an increased risk of bladder cancer. While older age, male sex, and smoking are known risk factors for bladder cancer, little is known about how different risk factors interact in the presence of diabetes and other lesser known factors on bladder cancer risk. Findings of the study suggest that among younger males aged less than 75 years, smoking and the presence of chronic kidney disease appear as key risk factors in subgroups of patients. These imply the differential risk patterns across age-sex subgroups and the importance of tobacco control and renal health in bladder cancer prevention in primary care for patients with type 2 diabetes.

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INTRODUCTION

Globally, bladder cancer is the ninth most commonly diagnosed cancer.[1] Prior research has shown that patients with type 2 diabetes have a 24% elevated risk of developing bladder cancer, when compared to those without diabetes.[2] The major etiological factor for bladder cancer is tobacco smoking.[3] Other risk factors for bladder cancer include older age, male sex, and occupational exposure to carcinogens.[4] Some evidence also suggests a potential association between chronic kidney disease (CKD) and bladder cancer.[5]

Age, male sex, and smoking are established risk factors for bladder cancer. Previous research has shown that males are four times likely to be diagnosed with bladder cancer than females,[6] and active smoking contributes to approximately 50% of bladder cancer risk.[7] On the other hand, emerging evidence suggests that CKD could be potentially linked to urinary tract cancers such as bladder cancer.[5] However, most studies focus on patients with advanced CKD who need dialysis or renal transplant.[5] It remains less clear whether CKD at less severe levels is also associated with bladder cancer.[5]

Nevertheless, little is known about how these known (or potential) risk factors interact in the presence of other lesser known factors to collectively influence the risk of bladder cancer. For example, active smoking itself may contribute to the development of metabolic disorders[8] and type 2 diabetes.[9] However, it is less clear about how the co-existence of smoking exposure and diabetes may influence the course of bladder cancer development. While active smoking is an independent risk factor for bladder cancer across both sexes,[7] there are potentially substantial differences in smoking prevalence between sexes. It remains less certain about the relative importance of smoking on bladder cancer in comparison with other factors across different subgroups with varying smoking prevalence and cumulative exposure. Moreover, it remains largely unknown whether there are other lesser known factors which may play a key role in differentiating the risk of bladder cancer amongst certain subgroups. Furthermore, the presence of CKD could be associated with diabetes-associated microangiopathy. Nevertheless, it could also be driven by other underlying causes, such as ageing,[10] immunity, vascular system, toxicity, infection, mechanics, and genetics.[11] In addition, despite diabetes patients being at greater risk of developing bladder cancer, studies examining on factors associated with the risk of bladder cancer or their interactions among diabetes patients remain rare.

To identify targets for public health cancer prevention strategies, this study aims to examine the interaction patterns among factors associated with the risk of bladder cancer incidence among patients who received diabetes management in primary care using a conditional inference survival tree approach.

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METHODS

Methods is described in Appendix 1.

RESULTS

Of the 382,770 patients included, 644 patients developed bladder cancer during follow-up (median 6.2, IQR 3.3-8.0years). The overall bladder cancer incidence was 0.30 per 1000 person-years. The incidence among females and males was 0.13 and 0.47 per 1000 person-years respectively. The tree model first broadly divided patients by age (≤74 vs >74years), followed by sex. Among younger males aged 74 years or below, smoking and CKD emerged as key risk factors for bladder cancer in middle-old and youngest males respectively (Figure 1). Among younger males, the prevalence of smoking and CKD were 52.63% and 16.91% respectively, whereas the corresponding prevalence for their female counterparts were 6.05% and 12.07% (Table 1).

Age and sex

The tree model first identified age at 74 years as a primary factor in differentiating the risk of bladder cancer within the study diabetes cohort. Among oldest patients aged 74 years above, males tended to have a higher risk of developing bladder cancer than females (aHR 3.89,95%CI=3.00-5.04), adjusting for age and duration of diabetes (Table 2). Younger males were further partitioned into several age groups characterized by different dominant risk factors for bladder cancer (Figure 1). On the other hand, young females aged 74 years or below generally had the lowest risk of bladder cancer regardless of metformin use (Figures 1 and 2A;Table 2).

Age, male sex, and smoking

Among middle-old males (62 to 74years), smoking was identified as a dominant risk factor for bladder cancer (Figure 1). Ever smokers had an increased risk of developing bladder cancer when compared to never smokers (aHR 1.96,95%CI=1.49-2.58), controlling for age and duration of diabetes (Table 2;Figure 2B).

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Age, male sex, and chronic kidney disease

Among youngest males (≤58years), CKD appeared as a key risk factor for bladder cancer (Figure 1). Those with CKD had an elevated risk of developing bladder cancer when compared to those without CKD (aHR 2.92,95%CI=1.21-7.02), adjusting for age and duration of diabetes (Table 2). Nevertheless, those with CKD tended to have a shorter follow-up when compared to those without CKD (median: 3.1 vs 6.9years). Those with CKD reached a plateau level of cumulative bladder cancer incidence at 3.9 years. The cumulative incidence for those without CKD reached the same level 4.5 years later (at 8.4years) (Figure 2C).

Model performance

The AUCs at 2, 5, and 7 years were 0.813(95%CI=0.813-0.813), 0.778(95%CI=0.777-0.779), and 0.782(95%CI=0.781-0.783) respectively.

DISCUSSION

Summary

The current study showed that despite older age, male sex, and smoking being established risk factors for bladder cancer, these factors may play differential roles in influencing the risk of bladder cancer among subgroups of patients who received diabetes management in primary care. The survival tree model broadly partitioned patients into several subgroups to differentiate their risk of bladder cancer according to age and sex, and identified predominant factors associated with bladder cancer risk within age-sex subgroups. Findings of the study suggested a notable increased risk of bladder cancer among patients who had reached 75 years at baseline. In addition, among younger males aged 74 years or below, smoking exposure and the presence of CKD appeared as important risk factor for bladder cancer for those aged 62 to 74 years and aged 58 years or below respectively.

Comparison with existing literature

In the present study, smoking emerged as a dominant factor in determining the risk of bladder cancer among middle-old males (62 to 74 years) with diabetes. Prior research has shown that active smoking itself is associated with an increased risk of metabolic disorders[8] and type 2 diabetes.[9] One possible mechanism linking

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smoking to metabolic abnormalities is that nicotine exposure may impair insulin sensitivity and promote insulin resistance.[12-13] On the other hand, smoking is also a known risk factor for bladder cancer.[3] Possible mechanisms include direct exposure to carcinogens in tobacco and indirect exposure to a chronic low-grade inflammatory environment conducive to carcinogenesis.[14-15] The epidemiological association between smoking and bladder cancer has been observed across both sexes.[7] Nevertheless, in the present study cohort, there exists a large gap in smoking prevalence between two sexes (male: 53 to 55% vs female: 6 to 7%). The relatively low prevalence of smoking among females in the study cohort may partially contribute to smoking being a less important factor in differentiating the risk of bladder cancer among females. In addition, a recent review[16] has summarized that there are potential biological differences in carcinogenesis of the bladder between two sexes, potentially accounting for the differential incidence rates and outcomes between sexes. Some potential key factors include differences in anatomical, immunological, sex hormonal, epigenetic and genetic characteristics.[16] Furthermore, the emergence of smoking being a dominant factor in differentiating the risk of bladder cancer among middle-old males could be due to cumulative exposure over the life course. A previous meta-analysis[17] has quantified the dose-response association between tobacco smoking exposure and bladder cancer risk, demonstrating the gradual increased risk with smoking exposure up to 50 pack-years and a risk plateau afterwards, as well as a general increasing trend with smoking duration up to 60 years. Findings of the study are generally consistent with the effects of cumulative exposure to smoking on bladder cancer risk found in the literature.[17]

Moreover, CKD emerged as a key factor in differentiating the risk of bladder cancer among youngest males (≤58 years) with diabetes. Those with CKD generally had a higher risk of developing bladder cancer up to 8.4 years when compared to those without CKD. The plateau reached by those with CKD early at 3.9 years could be in part due to small number of bladder cancer cases (n=7), and lower life expectancy resulting in shorter follow-up. In the literature, emerging evidence suggests that the presence of CKD could be potentially associated with an elevated risk of bladder cancer.[5] Nevertheless, whether renal dysfunction at a less severe stage is associated with bladder cancer risk remains controversial.[5,18-19] For example, Lowrance et al. found that only patients with eGFR <30 ml/min per 1.73m^2 demonstrated an increased risk of bladder cancer.[18] On the other hand, a meta-analysis summarized that reduced renal function is only associated with urinary tract cancers among dialysis patients.[19] In addition, the kidney is a target organ of microangiopathy under diabetes condition.[20] The presence of CKD could be a complication of diabetes resulted from progression of diabetes, potentially indicating a more advanced stage over the course of diabetes progression. Given diabetes as a common risk factor for both CKD and cancer,[5] the presence of CKD under diabetes condition may accelerate carcinogenesis of bladder cancer. A

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previous study[21] showed that the coexistence of CKD and diabetes may exert additive positive effects on the risk of cancer mortality. Potential pathophysiological mechanisms linking CKD and bladder cancer include underlying cystic kidney disease, accumulation of toxins as a consequence of renal dysfunction under different underlying causes, chronic inflammation, and oxidative stress.[5] Moreover, CKD is an age-related condition.[22] Previous research suggests that a healthy 75-year-old individual only has half the nephrons he had at 25 years old.[11] It is also suggested that patients with CKD are physiologically five years older than their actual age.[10] The presence of CKD may imply premature aging[22] among younger individuals. Furthermore, the unique emergence of CKD as key factor among males but not females among the study cohort could be due to differences between sexes in CKD prevalence, life expectancy, declining rates of renal functioning, sex hormones, risk preferences for CKD treatment.[23] Possible mechanisms linking sex differences to CKD include direct effects of sex hormones, differences in nitric oxide metabolism and oxidative stress in the kidneys potentially due to interactions with sex hormones, as well as differential lifestyle factors between genders.[23]

Overall, findings of the current study add to the literature by identifying the potential interaction patterns among age, sex, smoking, and CKD on bladder cancer risk among patients who received routine diabetes management in primary care. Prior research suggests that by the age of 75 years, a healthy individual would have lost half of his nephrons he had at the age of 25 years.[11] The emergence of age at 75 years as identified optimal cutoff for elevated bladder cancer risk coincides with the expected half-life of total renal mass during natural ageing. While smoking and renal dysfunction is a known risk factor or potential risk factor for bladder cancer, in the presence of diabetes, smoking and CKD emerged as key risk factor for middle-old males and youngest males respectively. Active smoking itself may contribute to the onset of type 2 diabetes,[9] and the concurrent presence of smoking exposure and diabetes later in life may collectively influence the course of bladder cancer development. On the other hand, the presence of CKD is often considered as a sign of accelerated aging,[22] or underlying comorbid conditions in diabetes such as microvascular and macrovascular complications.[20] The premature aging of kidneys in diabetes, likely in the presence of multiple comorbidities, may ultimately aggravate carcinogenesis of the bladder along the urinary tract. Furthermore, the emergence of smoking and CKD as important risk factors in younger males below 75 years may attribute to the differences in smoking prevalence across sexes in the study cohort, and differential CKD patterns across sexes.[23]

Implications for research and practice

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There are several public health implications of the present study. First, age-sex subgroups with differential risk profiles for bladder cancer among the diabetes cohort were identified. For patients with type 2 diabetes in the absence of bladder cancer symptoms, older males, middle-old male ever smokers, and youngest males with CKD, could be at higher risk of developing bladder cancer. Closer monitoring of potential bladder cancer symptoms during routine follow-up for diabetes management in primary care may help identify bladder cancer cases early. Second, while smoking is a well-established risk factor for bladder cancer, smoking is a particularly dominant risk factor among middle-old males (62 to 74 years) with diabetes. Smoking prevention in primary care targeted at the broader general population, in particular before the onset of type 2 diabetes, may help reduce the risk of bladder cancer. Third, the presence of CKD could be potentially associated with an elevated risk of bladder cancer and act as key risk factor among youngest males (≤58 years) with diabetes. Preventing renal dysfunction through regular monitoring and potential dietary intervention[10] (for example, protein restriction[10] and plant-based diet)[24] during routine diabetes management in primary care may help lower the risk of developing bladder cancer. Specifically, under diabetes condition, management of blood pressure, glucose, and lipids, as well as lifestyle modifications may potentially help reduce the risk of developing diabetes-associated kidney disease.[20] Furthermore, prior research suggests that patients with CKD are biologically older than their chronological age.[10] The presence of CKD may indicate a suboptimal general health status. Specifically, the presence of CKD in diabetes is considered as a marker of underlying comorbid conditions, such as other diabetes-associated microvascular and macrovascular complications.[20] Fourth, the emergence of several dominant risk factors among males may highlight differences in epidemiology and support the potential differential underlying mechanisms between two sexes. Different sex-specific bladder cancer prevention strategies may help tailor to the differential needs of two sexes. Fifth, compared to the general population, it is unclear among the study diabetes cohort, to what extent the onset of type 2 diabetes attributes to active smoking, and to the coexistence of smoking and a cluster of unhealthy behaviors[25] that may collectively promote type 2 diabetes. It is also uncertain to what extent the presence of renal dysfunction is associated with diabetes alone, other underlying causes,[11] or a combination of factors. Future research is warranted to compare findings to patients without diabetes in the general population.

Strengths and limitations

Strengths of the study include a large diabetes cohort with regular follow-up in GOPCs, relative comprehensive assessment at baseline to capture the clinical profile of individual patients with type 2 diabetes,

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the homogenous profile of patients who receive diabetes care in GOPCs, and the linkage across datasets in the electronic health records system to capture clinical information of patients. However, several limitations may exist in the current study. First, information on some potential confounders such as dosage of smoking exposure (age of smoking initiation or pack-years of smoking), occupation, and dietary exposure was not available. Second, severity of CKD was not differentiated. Patients with more advanced stages of CKD may not survive long enough to experience the event of bladder cancer diagnosis. Nevertheless, patients with CKD appeared to have a higher risk of developing bladder cancer up to 8.4 years of follow-up. Further studies are needed to examine at which stage of CKD the risk of bladder cancer may potentially increase. Third, the underlying causes of CKD within the diabetes cohort were not distinguishable. Lastly, given type 2 diabetes as an age-related chronic disease,[26] the role of smoking in metabolic disorders[8] and type 2 diabetes,[9] as well as diabetes-associated kidney disease as a renal manifestation of microangiopathy under diabetes condition,[20] future research is warranted to examine generalizability of the findings to other diabetes populations and the broader general population. In addition, the optimality of the identified cutoffs for age among the study diabetes population may also need further verification in other populations.

CONCLUSIONS

The current study demonstrated the interaction patterns among age, sex, smoking, and CKD on the risk of bladder cancer incidence among patients who received routine diabetes care at GOPCs. Consistent to the findings in the general population, the risk of bladder cancer generally increases with age. Males are more predisposed to bladder cancer development than females. Among the study diabetes cohort, there is a marked elevated risk once patients reach 75 years. While smoking and CKD are known risk factor or potential risk factor for bladder cancer among the general population, in the study cohort, these two factors emerge as important risk factor in particular to middle-old males (62 to 74 years) and youngest males (≤58 years) respectively. Findings of the study may provide potential targets for public health cancer prevention strategies in primary care for patients with type 2 diabetes.

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Data availability: Data is not available for sharing due to access restriction.

Competing interests: None declared.

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Table 1. Baseline characteristics of patients by age and sex.

Characteristics	Female, ≤74 years (n=151,157)		Male, ≤74 years (n=169,692)		Female, >74 years (n=36,564)		Male, >74 years (n=25,357)	
Number of bladder cancer cases during follow-up, n (%)	63	(0.04%)	308	(0.18%)	82	(0.22%)	191	(0.75%)
Demographics								
Age at assessment in year, mean±SD	59.43	±9.17	58.52	±9.24	80.39	±4.30	79.75	±4.02
Duration of diabetes in year, median (IQR)	3	(1-8)	3	(1-8)	7	(2-14)	6	(1-13)
Medical history								
Chronic kidney disease, n (%)	18,245	(12.07%)	28,695	(16.91%)	6,195	(16.94%)	5,303	(20.91%)
Cirrhosis, n (%)	2,722	(1.80%)	3,987	(2.35%)	506	(1.38%)	371	(1.46%)
Ischemic heart disease, n (%)	5,429	(3.59%)	14,567	(8.58%)	3,963	(10.84%)	3,936	(15.52%)
Cerebrovascular disease, n (%)	6,047	(4.00%)	9,941	(5.86%)	4,063	(11.11%)	3,639	(14.35%)
Heart failure, n (%)	1,668	(1.10%)	2,880	(1.70%)	1,890	(5.17%)	1,332	(5.25%)
Hypertension, n (%)	124,728	(82.52%)	141,511	(83.39%)	35,172	(96.19%)	24,060	(94.89%)
Chronic obstructive pulmonary disease, n (%)	203	(0.13%)	1,280	(0.75%)	323	(0.88%)	967	(3.81%)
Pneumonia, n (%)	2,692	(1.78%)	4,786	(2.82%)	2,238	(6.12%)	2,275	(8.97%)
Family history of diabetes, n (%)	79,070	(52.31%)	85,672	(50.49%)	10,178	(27.84%)	5,931	(23.39%)
Medication use								
Anti-diabetic drugs								
Metformin, n (%)	62,255	(41.19%)	67,027	(39.50%)	16,084	(43.99%)	9,801	(38.65%)
Sulfonylurea, n (%)	38,260	(25.31%)	44,963	(26.50%)	12,146	(33.22%)	8,206	(32.36%)
Insulin, n (%)	8,561	(5.66%)	11,457	(6.75%)	2,085	(5.70%)	1,769	(6.98%)
Dipeptidyl peptidase-4 inhibitors, n (%)	5,029	(3.33%)	7,167	(4.22%)	1,383	(3.78%)	1,141	(4.50%)
Sodium-glucose cotransporter-2 inhibitors, n (%)	321	(0.21%)	662	(0.39%)	28	(0.08%)	31	(0.12%)
Glucagon-like peptide-1 receptor agonists, n (%)	76	(0.05%)	117	(0.07%)	2	(0.01%)	2	(0.01%)
Glucosidase inhibitors, n (%)	594	(0.39%)	652	(0.38%)	169	(0.46%)	136	(0.54%)
Glitazone, n (%)	66	(0.04%)	648	(0.38%)	95	(0.26%)	10	(0.04%)
Meglitinide, n (%)	594	(0.39%)	52	(0.03%)	15	(0.04%)	75	(0.30%)
Any of the above, n (%)	77,318	(51.15%)	89,206	(52.57%)	21,252	(58.12%)	14,013	(55.26%)
Aspirin, n (%)	20,761	(13.73%)	36,798	(21.69%)	12,191	(33.34%)	10,050	(39.63%)
Non-steroidal anti-inflammatory drugs, n (%)	90,056	(59.58%)	84,165	(49.60%)	20,170	(55.16%)	11,882	(46.86%)
Anti-coagulants, n (%)	4,277	(2.83%)	9,756	(5.75%)	2,510	(6.86%)	2,320	(9.15%)
Anti-platelets, n (%)	6,282	(4.16%)	14,630	(8.62%)	3,376	(9.23%)	3,303	(13.03%)
Anti-hypertensive drugs, n (%)	98,839	(65.39%)	110,888	(65.35%)	31,687	(86.66%)	21,314	(84.06%)
Statins, n (%)	74,006	(48.96%)	84,071	(49.54%)	19,196	(52.50%)	13,130	(51.78%)
Behaviors								
Current drinker/ ex-drinker, n (%)	17,812	(11.78%)	80,882	(47.66%)	2,710	(7.41%)	9,520	(37.54%)
Current smoker/ ex-smoker, n (%)	9,139	(6.05%)	89,304	(52.63%)	2,472	(6.76%)	13,885	(54.76%)
Anthropometric measurements								
Body mass index in kg/m^2, mean±SD	26.26	±4.45	26.29	±4.07	25.16	±3.83	24.92	±3.30
Waist-to-hip ratio, mean±SD	0.92	±0.06	0.95	±0.06	0.94	±0.07	0.96	±0.06
Laboratory measurements								
HbA_{1c} in %, mean±SD	7.36	±1.39	7.46	±1.59	7.07	±1.12	7.12	±1.24
Fasting glucose in mmol/L, mean±SD	7.65	±2.24	7.75	±2.38	7.22	±1.89	7.22	±1.90
Low-density lipoprotein cholesterol in mmol/L, mean±SD	2.77	±0.85	2.64	±0.81	2.61	±0.82	2.47	±0.76
High-density lipoprotein cholesterol in mmol/L, mean±SD	1.35	±0.34	1.18	±0.30	1.37	±0.36	1.23	±0.34
Triglycerides in mmol/L, mean±SD	1.62	±1.09	1.67	±1.35	1.53	±0.84	1.34	±0.81
Serum creatinine in μmol/L, mean±SD	67.69	±31.46	89.89	±45.65	84.51	±36.70	106.99	±44.74

Abbreviation: HbA_{1c}, glycated hemoglobin.

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Table 2. Comparisons in adjusted hazard ratios of selected split variables between sibling nodes.

Node	Characteristics	Comparison i, Metformin use in young female	Comparison ii, Chronic kidney disease in youngest male	Comparison iii, Smoking in middle-old male	Comparison iv, Male sex in the oldest
Node 4	{Female, age ≤74 years, metformin use}	1			
Node 5	{Female, age ≤74 years, no metformin use}	1.13 (0.67-1.91)			
Node 9	{Male, age ≤58 years, no chronic kidney disease}		1		
Node 10	{Male, age ≤58 years, chronic kidney disease}		**2.92 (1.21-7.02)**		
Node 13	{Male, age between 62 to 74 years, never smoker}			1	
Node 14	{Male, age between 62 to 74 years, current/ex-smoker}			**1.96 (1.49-2.58)**	
Node 16	{Female, age >74 years}				1
Node 17	{Male, age >74 years}				**3.89 (3.00-5.04)**

Note 1: Comparisons were made with adjustment of age and duration of diabetes.
Note 2: Adjusted hazard ratios are presented in 95% confidence interval.

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Figure 1. Survival tree diagram for bladder cancer incidence among patients with type 2 diabetes.
Figure 2. Cumulative bladder cancer incidence A) across age-sex subgroups; B) across ever and never smokers among males aged 62 to 74 years; C) across males aged 58 years or below in the presence or absence of chronic kidney disease. CKD, chronic kidney disease.

Appendix 1. Methods

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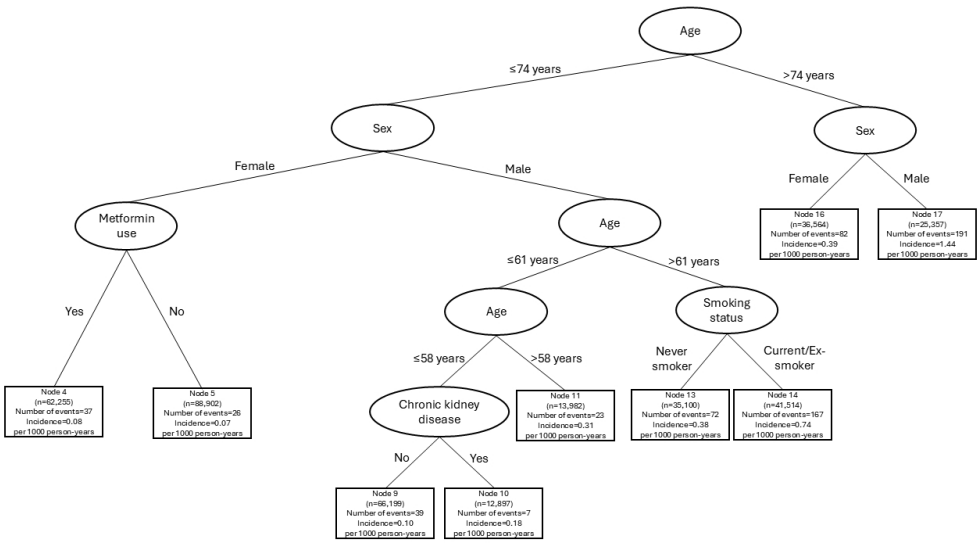

Figure 1. Survival tree diagram for bladder cancer incidence among patients with type 2 diabetes.

855x481mm (38 x 38 DPI)

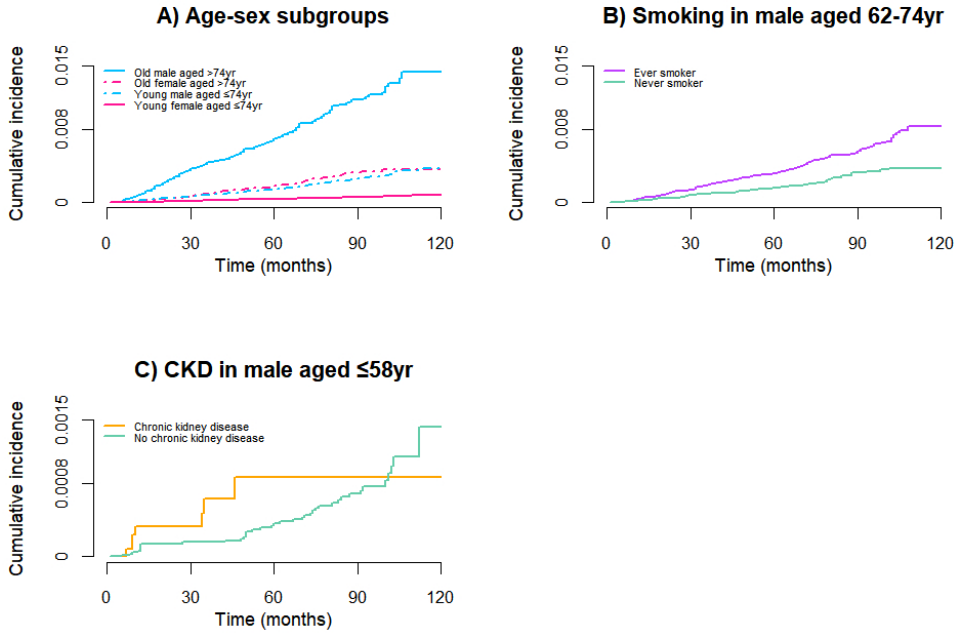

Figure 2. Cumulative bladder cancer incidence A) across age-sex subgroups; B) across ever and never smokers among males aged 62 to 74 years; C) across males aged 58 years or below in the presence or absence of chronic kidney disease. CKD, chronic kidney disease.

476x337mm (52 x 52 DPI)