Diabetologia (2011) 54:2009–2015
DOI 10.1007/s00125-011-2171-z

ARTICLE

Diabetes and risk of bladder cancer: a study using the National Health Insurance database in Taiwan

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Received: 10 January 2011 / Accepted: 4 April 2011 / Published online: 5 May 2011

Abstract
Aims/hypothesis Studies on the link between diabetes and bladder cancer in Asians are rare. We investigated the association between diabetes and incidence of bladder cancer by using a large national insurance database.
Methods A random sample of 1,000,000 individuals covered by the National Health Insurance was recruited. A total of 495,199 men and 503,748 women for all ages and 187,609 men and 189,762 women ≥40 years old and without bladder cancer at recruitment were followed from 2003 to 2005. Cox regression evaluated the adjusted relative risk for all ages and for age ≥40 years old.
Results The results were similar for all ages and for age ≥40 years. In Cox models, patients with diabetes consistently showed a significantly higher relative risk ranging from 1.36 to 1.51 after adjustment for age, sex and other potential confounders. Age, male sex, nephropathy, urinary tract diseases (infection and stone) and statin use were associated with bladder cancer, but occupation, hypertension, stroke, ischaemic heart disease, peripheral arterial disease, eye disease, dyslipidaemia and medications (oral glucose-lowering agents including sulfonylurea, metformin, acarbose and thiazolidinediones, insulin, fibrates, ACE inhibitors/angiotensin receptor blockers and calcium channel blockers) were not. Chronic obstructive pulmonary disease and living in regions other than Metropolitan Taipei were associated with lower risk.
Conclusions Patients with diabetes have a higher risk of bladder cancer. The association with urinary tract diseases suggests a complex scenario in the link between bladder cancer and diabetes at different disease stages.

Keywords Bladder cancer · Diabetes mellitus · Incidence · Relative risk · Taiwan

Abbreviation
NHI National Health Insurance

Introduction

The association between diabetes and bladder cancer has been inconsistently reported. A meta-analysis of 16 studies (seven case–control studies, three cohort studies and six studies with cohorts of diabetic patients) published in 2006 concluded that diabetes was significantly associated with a higher risk (24%) of bladder cancer [1]. In the meta-analysis, compared with risk in the control population, a significant risk was noted in the case–control and cohort studies, but not in the studies with cohorts of diabetic patients [1]. A publication bias against studies with small sample sizes and against reporting a low relative risk is possible, and may have resulted in an overestimation of the relationship between diabetes and bladder cancer [1]. Other limitations of the meta-analysis include a mixture of studies with case–control and cohort designs, a mixture of incident and dead cases of bladder cancer, small case numbers of bladder cancer in most studies, potential selection bias due to different sources of participants, and lack of differentiation between cases of type 1 and type 2 diabetes.

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Studies published after this meta-analysis also yielded inconsistent results. A prospective study in Swedish men did not find an association between bladder cancer and diabetes [2], but a case–control study performed in the USA showed a significant association between bladder cancer and diabetes, with a trend related to diabetes duration [3]. Postmenopausal women in the prospective Iowa Women's Health Study showed a significant 2.46-fold higher risk of bladder cancer in participants with diabetes [4]. However, in these recent studies, the presence of diabetes was self-reported by the participants, and subtypes of diabetes were not defined [2–4].

Most studies included in the meta-analysis were conducted in Western countries, and only one study was performed in the Asian population in Korea [1]. This Korean study showed a significantly higher risk (32%) of bladder cancer incidence (but not mortality) in men with diabetes, but no data were available for women [5]. A later Japanese case–control study did not confirm the association in men, and could not estimate the association in women because of the lack of bladder cancer cases in women [6]. Therefore the association of diabetes and bladder cancer in Asian women has not been investigated, and a common limitation in these Asian studies is the failure to identify cases by diabetes subtype. Furthermore, the association in different age groups is worthy of investigation, but has not been investigated. This study used the National Health Insurance (NHI) database to evaluate the association between diabetes and the incidence of bladder cancer.

Methods

Study population According to the Ministry of the Interior, Taiwan, in 2005, >98.0% of the Taiwanese population (22,770,383: 11,562,440 men and 11,207,943 women) was covered by the NHI. A random sample of 1,000,000 people insured by the NHI in 2005 was created by the National Health Research Institute for academic research. The National Health Research Institute is the only institute approved, as per local regulations, for conducting sampling of a representative sample of the whole population for the year 2005 with a predetermined sample size of 1,000,000 individuals. The reimbursement databases of these sampled individuals were retrieved and could be provided for academic research after approval. The identification information was scrambled for the protection of the privacy of the sampled individuals. The reimbursement databases from 1996 onward were available. Sex, birth date, medications and diagnostic codes based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM; www.icd9data.com/2007/Volume1/240-279/250-259/250/default.htm) were retrieved for analyses in this study. Diabetes was coded 250.1–250.9, and bladder cancer was coded 188.

Because bladder cancer is rare in young populations, we analysed data for individuals of all ages and for those aged ≥40 years (the number of bladder cancer cases in individuals aged <40 years was very small). Figure 1 shows a flow chart used for selecting cases in this study. After exclusion of individuals with type 1 diabetes (in Taiwan, patients with type 1 diabetes were issued a 'Severe Morbidity Card' after certified diagnosis), individuals for whom the living region was not known, individuals diagnosed as having bladder cancer before 2003, 495,199 men and 503,748 women of all ages, and 187,609 men and 189,762 women aged ≥40 years and without bladder cancer were followed from 1 January 2003 to 31 December 2005.

Statistical analyses Age, diabetes status, diabetes duration and other covariates found in the NHI reimbursement databases were determined as a status or a diagnosis on or before 1 January 2003. Bladder cancer was only counted in cases in which incidence occurred within the 3 year period from 1 January 2003 to 31 December 2005.

Cox proportional hazards regression analysis was performed to calculate the adjusted relative risks for individuals of all ages and those aged ≥40 years. Bladder cancer was the dependent variable, and the seven selected independent risk factors (models I to VII, respectively) included diabetes, diabetes duration (no diabetes and diabetes for <1, 1–3, 3–5, and ≥5 years), glucose-lowering therapy (no diabetes, diabetes without therapy, diabetes and therapy with oral glucose-lowering agents only, and therapy involving insulin with or without oral agents), nephropathy (ICD-9-CM codes: 580–589), urinary tract diseases (590–599), urinary tract infection (590, 595, 597) and urinary tract stone (592, 594). The common confounders adjusted for in all models were age, sex, comorbidities, medications, living region and occupation. Comorbidities included hypertension (401–405), chronic obstructive pulmonary disease (490–496, a surrogate for smoking), stroke (430–438), ischaemic heart disease (410–414), peripheral arterial disease (250.7, 785.4, 443.81, and 440–448), eye disease (250.5, 362.0, 369, 366.41, and 365.44) and dyslipidaemia (272.0–272.4). Medications included statins, fibrates, ACE inhibitors and/or angiotensin receptor blockers, and calcium channel blockers. Insured individuals were classified according to their occupation (a surrogate for socioeconomic status). The living region served as a surrogate for geographical distribution of some environmental exposure. Occupation was categorised into class I (civil servants, teachers, employees of governmental or private businesses, professionals and technicians), class II (people without a specific employer, self-employed people or seamen), class III (farmers or fishermen) and class IV (low-income

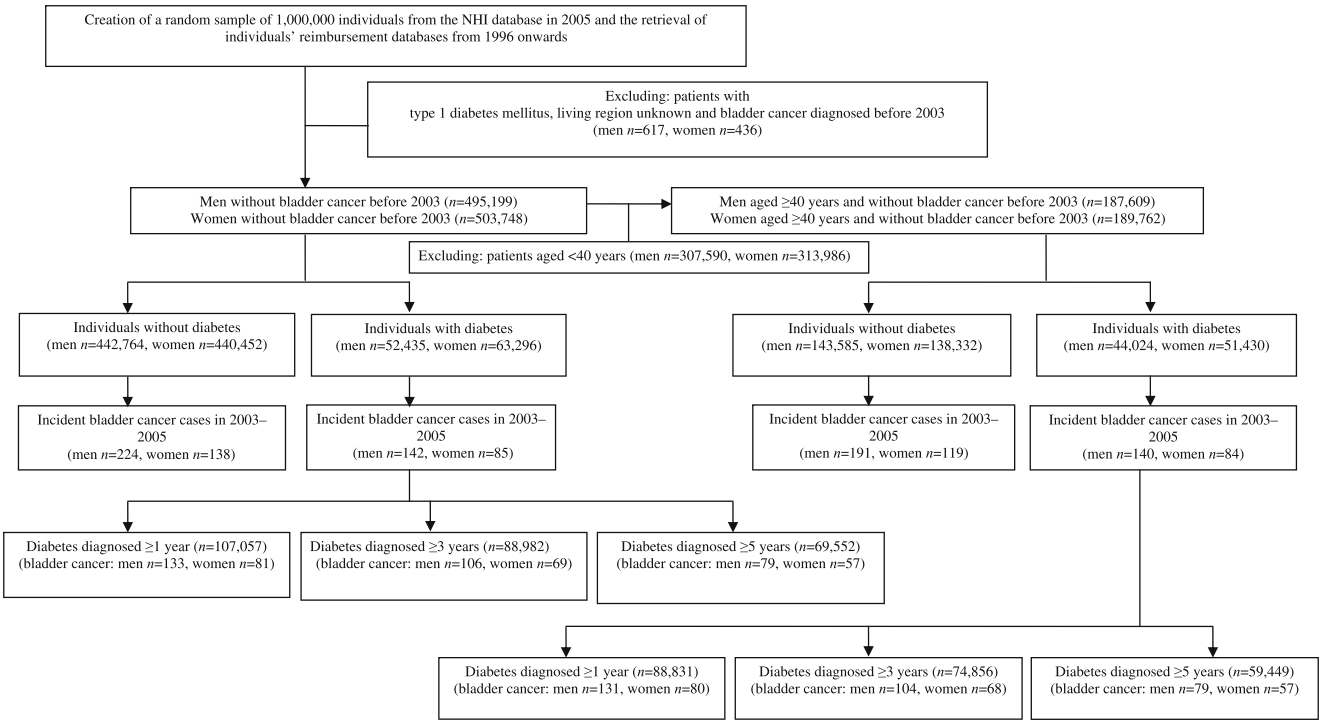

Fig. 1 Flow chart showing the procedures involved in the calculation of incidence of bladder cancer from 2003 to 2005

families supported by social welfare, or veterans). Living regions were classified as Taipei, Northern, Central, Southern, and Kao-Ping and Eastern.

Because insulin use may increase with the duration of diabetes, mutually adjusted relative risks for diabetes duration and glucose-lowering therapy were also determined for diabetic patients considering the confounders mentioned above (model VIII).

Additional multivariable models were created for estimating the adjusted relative risks for age, sex, diabetes, nephropathy, urinary tract diseases, comorbidities, living region, occupation, the above-mentioned medications, and glucose-lowering drugs (sulfonylurea, metformin, acarbose, thiazolidinedione and insulin).

Analyses were conducted using SAS statistical software, version 9.1 (SAS Institute, Cary, NC, USA). $p<0.05$ was considered statistically significant.

Results

Table 1 shows the adjusted relative risks for the selected risk factors. No remarkable differences were observed between people of all ages and those aged ≥40 years. Diabetes was associated with a 50% increased risk (model I), and diabetes duration showed a non-linear increase in the risk (model II). For those with diabetes for <1 year, an insignificant 40% increased risk was observed. The risk was significant for diabetes diagnosed >1 year, but it decreased with increasing diabetes duration (model II). The increased risk was significant in diabetic patients who were undergoing different therapies, with insulin users having the highest relative risk (model III). This finding is partially attributable to a confounding effect of a longer diabetes duration in insulin users, and not completely to insulin per se, because when diabetes duration was additionally adjusted for in the model including diabetic patients only, the relative risks for insulin users increased by 43%, which was not significantly different (model VIII). Nephropathy (model IV) and urinary tract diseases (model V), including infection (model VI) and stones (model VII), were consistently associated with a higher risk.

Table 2 shows the adjusted relative risks in the multivariable models (for all ages and for age ≥40 years) including age, sex, diabetes, nephropathy, urinary tract diseases, sulfonylurea, metformin, acarbose, thiazolidinediones, insulin, hypertension, chronic obstructive pulmonary disease, stroke, ischaemic heart disease, peripheral arterial disease, eye disease, dyslipidaemia, statin, fibrate, ACE inhibitor/angiotensin receptor blocker, calcium channel blocker, living region and occupation. Age, male sex, diabetes, nephropathy and urinary tract diseases were associated with a higher risk, while chronic obstructive pulmonary disease and living regions other than Taipei were associated with a lower risk. Statin use was associated with a higher risk, which was borderline significant in

Table 1 Adjusted relative risks for bladder cancer for selected risk factors derived from Cox proportional hazards models in all individuals (models I to VII) and in diabetic patients only (model VIII) (the adjusted variables are shown in the footnote)

Variable	Interpretation	All ages		Age ≥40 years	
		RR (95% CI)	*p* value	RR (95% CI)	*p* value
All subjects (models I to VII)					
Model I: diabetes	Yes vs no	1.49 (1.23–1.80)	<0.01	1.51 (1.25–1.83)	<0.01
Model II: diabetes duration	<1 year vs no diabetes	1.42 (0.82–2.47)	0.22	1.45 (0.83–2.53)	0.19
	1–3 years vs no diabetes	1.98 (1.41–2.76)	<0.01	2.01 (1.44–2.81)	<0.01
	3–5 years vs no diabetes	1.69 (1.20–2.38)	<0.01	1.60 (1.12–2.28)	<0.01
	≥5 years vs no diabetes	1.32 (1.05–1.66)	0.02	1.36 (1.08–1.71)	<0.01
Model III: glucose-lowering drugs	No drugs vs no diabetes	1.46 (1.16–1.85)	<0.01	1.49 (1.17–1.88)	<0.01
	OGLA only vs no diabetes	1.46 (1.14–1.87)	<0.01	1.47 (1.15–1.89)	<0.01
	Insulin with/without OGLA vs no diabetes	1.89 (1.22–2.93)	<0.01	1.95 (1.26–3.02)	<0.01
Model IV: nephropathy	Yes vs no	2.38 (1.92–2.96)	<0.01	2.31 (1.85–2.89)	<0.01
Model V: urinary tract diseases	Yes vs no	2.59 (2.19–3.07)	<0.01	2.50 (2.09–2.98)	<0.01
Model VI: urinary tract infection	Yes vs no	1.92 (1.57–2.34)	<0.01	1.88 (1.53–2.31)	<0.01
Model VII: urinary tract stone	Yes vs no	2.00 (1.59–2.52)	<0.01	1.90 (1.49–2.41)	<0.01
Diabetic patients only (model VIII)					
Diabetes duration	1–3 years vs <1 year	1.40 (0.75–2.62)	0.29	1.40 (0.75–2.62)	0.30
	3–5 years vs <1 year	1.21 (0.64–2.28)	0.56	1.12 (0.59–2.12)	0.73
	≥5 years vs <1 year	0.95 (0.53–1.70)	0.87	0.95 (0.53–1.69)	0.86
Glucose-lowering drugs	OGLA only vs no drugs	1.03 (0.77–1.36)	0.85	1.02 (0.76–1.35)	0.92
	Insulin with/without OGLA vs no drugs	1.43 (0.90–2.26)	0.13	1.43 (0.90–2.26)	0.13

All models are adjusted for age, sex, hypertension, chronic obstructive pulmonary disease, stroke, ischaemic heart disease, peripheral arterial disease, eye disease, dyslipidaemia, living regions, occupation and use of statin, fibrate, ACE inhibitor/angiotensin receptor blockers, calcium channel blockers

OGLA, oral glucose-lowering agents

individuals of all ages (p=0.05) and statistically significant in individuals aged ≥40 years (p=0.04). Use of other medications (including insulin) was not significantly predictive of bladder cancer.

Discussion

Consistent with the hypothesis that westernisation of lifestyle increases the risk of bladder cancer [7], people living in the Metropolitan Taipei region were at higher risk than the rest of the country (Table 2). Furthermore, consistent with the risk factors described in other studies [8–12], age, male sex, urinary tract infection or stones, and nephropathy were significant risk factors (Tables 1 and 2). A recent population-based matched case–control study performed in the USA suggested a reduced risk of bladder cancer in women, but not in men, with a history of urinary tract infection [13]. Actually, when men and women were analysed separately, nephropathy and urinary tract diseases including infection and stones remained significant in both sexes (data not shown). The discrepancy between men and women in the study performed in the USA and between the study performed in the USA and the present study is attributable to the inherent limitations of the case–control design of the USA study or to the different ethnicities of the individuals in the respective studies. Therefore the lower risk in the US women with urinary tract infection [13] requires confirmation.

We consistently observed a higher risk of bladder cancer in the diabetic patients (Tables 1 and 2). In a recent case–control study in the USA, the risk in diabetic patients increased with increasing risk seen in patients with diabetes for a longer duration and in patients using oral glucose-lowering agents; this risk was calculated after adjustment for age, sex, smoking, body mass index and urinary tract infection [3]. In contrast, in this study, we observed a decrease in the relative risks associated with diabetes for a longer duration; the highest relative risks in insulin users was also decreased after adjustment for diabetes duration and other covariates (model VIII in Table 1). When the effect of glucose-lowering therapies is evaluated, diabetes duration should be adjusted

Table 2 Adjusted relative risks for bladder cancer in the multivariable models using Cox regression

Variable	Interpretation	All ages		Age ≥40 years	
		RR (95% CI)	*p* value	RR (95% CI)	*p* value
Age	Every 1-year increment	1.06 (1.05–1.07)	<0.01	1.05 (1.04–1.06)	<0.01
Sex	Men vs women	1.92 (1.62–2.28)	<0.01	1.88 (1.57–2.25)	<0.01
Diabetes	Yes vs no	1.36 (1.10–1.68)	<0.01	1.39 (1.12–1.72)	<0.01
Nephropathy	Yes vs no	1.98 (1.59–2.45)	<0.01	1.93 (1.55–2.42)	<0.01
Urinary tract diseases	Yes vs no	2.39 (2.02–2.84)	<0.01	2.30 (1.92–2.75)	<0.01
Sulfonylurea	Yes vs no	1.03 (0.70–1.52)	0.88	1.00 (0.68–1.49)	0.99
Metformin	Yes vs no	0.96 (0.63–1.47)	0.86	0.99 (0.65–1.53)	0.98
Acarbose	Yes vs no	1.08 (0.46–2.56)	0.86	1.08 (0.46–2.56)	0.86
Thiazolidinediones	Yes vs no	0.80 (0.34–1.90)	0.62	0.80 (0.34–1.90)	0.61
Insulin	Yes vs no	0.57 (0.21–1.57)	0.28	0.58 (0.21–1.59)	0.29
Hypertension	Yes vs no	0.93 (0.75–1.16)	0.52	0.96 (0.77–1.20)	0.74
Chronic obstructive pulmonary disease	Yes vs no	0.79 (0.65–0.96)	0.02	0.81 (0.66–0.98)	0.03
Stroke	Yes vs no	0.85 (0.66–1.09)	0.19	0.88 (0.68–1.13)	0.31
Ischaemic heart disease	Yes vs no	1.00 (0.81–1.25)	0.99	1.03 (0.82–1.28)	0.81
Peripheral arterial disease	Yes vs no	1.10 (0.82–1.48)	0.53	1.12 (0.83–1.50)	0.47
Eye disease	Yes vs no	0.88 (0.52–1.49)	0.64	0.84 (0.49–1.44)	0.53
Dyslipidaemia	Yes vs no	0.98 (0.78–1.25)	0.89	0.95 (0.74–1.20)	0.65
Statin	Yes vs no	1.36 (0.99–1.86)	0.05	1.38 (1.01–1.88)	0.04
Fibrate	Yes vs no	0.96 (0.70–1.30)	0.77	0.92 (0.67–1.26)	0.61
ACE inhibitor/angiotensin receptor blocker	Yes vs no	0.98 (0.72–1.33)	0.88	0.94 (0.68–1.28)	0.69
Calcium channel blocker	Yes vs no	0.90 (0.66–1.23)	0.50	0.90 (0.65–1.23)	0.49
Living region	Northern region vs Taipei	0.65 (0.49–0.86)	<0.01	0.67 (0.50–0.90)	0.01
	Central region vs Taipei	0.70 (0.55–0.90)	<0.01	0.73 (0.56–0.95)	0.02
	Southern region vs Taipei	0.71 (0.55–0.93)	0.01	0.74 (0.56–0.97)	0.03
	Kao-Ping and Eastern region vs Taipei	0.72 (0.57–0.92)	<0.01	0.78 (0.61–1.01)	0.06
Occupation	II vs I	0.90 (0.70–1.15)	0.39	0.84 (0.64–1.10)	0.20
	III vs I	0.83 (0.65–1.06)	0.13	0.88 (0.69–1.13)	0.31
	IV vs I	0.81 (0.65–1.01)	0.06	0.86 (0.68–1.09)	0.21

Refer to the Methods section for the categories of occupation

All variables were included in the same model, in the model either for all ages or for individuals aged ≥40 years

for, and this was not done in the study conducted in the USA. With increasing diabetes duration, the impact of age and chronic complications (specifically nephropathy and urinary tract diseases) may set in and influence the association. Therefore heterogeneity in the association may be seen during different stages of diabetes.

In a clinical trial, although the incidences of cancers were comparable in patients using pioglitazone and placebo, more cases of bladder cancer (14 vs 5) were observed in pioglitazone users [14]. However, we did not observe any significant association between bladder cancer and the different glucose-lowering therapies (Table 2). No pioglitazone user (total users, 422) developed bladder cancer (data not shown).

It was unlikely that diabetes was caused by bladder cancer, because we believe that diabetes diagnosed >5 years before bladder cancer (Table 1) can hardly be a consequence of the carcinogenic process. Another explanation for the increased incidence of bladder cancer in the diabetic patients is screening bias: they may more frequently undergo urine testing for screening and diagnosis of diabetic nephropathy, which can lead to accidental discovery of haematuria, a clinical feature of bladder cancer. If this is the case, more cancers are expected in the early stages in diabetic patients, which would decrease the mortality rate from bladder cancer in diabetic patients. However, this was contradictory to our previous observation of significantly higher mortality rate ratios for bladder

cancer in diabetic patients compared with the general population [15].

Occupation was not associated with the risk of bladder cancer (Table 2), implying that socioeconomic status or income might not be a significant risk factor. Because cancer is considered a severe morbidity and most medical co-payments can be waived for those insured with NHI, different detection rates among different social classes was unlikely.

The reason for a lower risk of bladder cancer in patients with chronic obstructive pulmonary disease (Table 2) is not clear. One possibility is that they are prone to develop lung cancer and cardiovascular disease and may have a shorter life expectancy [16], rendering a lower chance for the development of bladder cancer.

Although statin use may be associated with a lower risk of bladder cancer [17] or not be associated with bladder cancer [18, 19] in white people, a Japanese study did show a significantly higher risk of bladder cancer in pravastatin users [20]. Whether the higher risk associated with statin use (Table 2) was attributable to the effect of statins per se or to a residual effect of severe dyslipidaemia is not known, because patients requiring statin are always under-treated in Taiwan [21] and those receiving statin may have more severe dyslipidaemia. Further studies are required to clarify the link between different statins and cancer.

This study has several strengths. It is population-based with a large, nationally representative sample. The database included outpatients and inpatients, and we included the diagnoses from both sources. The use of medical records reduced the bias related to self-reporting. We also excluded patients with type 1 diabetes to demonstrate a link with type 2 diabetes.

The study limitations included a lack of actual measurement data for confounders such as obesity, smoking, alcohol drinking, water intake, family history, lifestyle, diet, hair dye use and some occupational exposure and genetic variables. In addition, we did not have any biochemical data for evaluating the impact of these confounders. Because the sampling of the 1,000,000 individuals by the National Health Research Institute was based on all NHI insurants in the year 2005 and the data on the incident bladder cancer cases were retrieved up to 2003, people who died during this period would not be included in the study. However, since the incidence of bladder cancer is low and the 3-year duration used for the evaluation of incident cases is relatively short, we believe that the effect of possible right censoring would be negligible. As a matter of fact, in secondary analyses, the relative risks for the various risk factors in Tables 1 and 2, as estimated from odds ratios in logistic regression analysis (which does not consider a time-to-event and dying individuals as right censored), yielded similar results and conclusions (data not shown).

In summary, this study shows that the risk of bladder cancer is increased in patients with diabetes, nephropathy and urinary tract diseases, including infection and stones, which suggests a more complicated scenario in the link between bladder cancer and diabetes at different disease stages. With an increase in the prevalence of nephropathy and urinary tract diseases, the association with diabetes weakens with the duration of diabetes. Prevention and early treatment of diabetes and diseases involving the urinary system may be important for reducing bladder cancer.

Acknowledgements The author thanks the following institutes in Taiwan for their continuous support for the epidemiologic studies on diabetes and arsenic-related health hazards: the National Genotyping Centre of National Research Program for Genomic Medicine, National Science Council; the Department of Health (DOH89-TD-1035; DOH97-TD-D-113-97009); and the National Science Council (NSC-86-2314-B-002-326, NSC-87-2314-B-002-245, NSC88-2621-B-002-030, NSC89-2320-B002-125, NSC-90-2320-B-002-197, NSC-92-2320-B-002-156, NSC-93-2320-B-002-071, NSC-94-2314-B-002-142, NSC-95-2314-B-002-311, and NSC-96-2314-B-002-061-MY2).

Duality of interest statement The author declares that there is no duality of interest associated with this manuscript.

References

1. Larsson SC, Orsini N, Brismar K, Wolk A (2006) Diabetes mellitus and risk of bladder cancer: a meta-analysis. Diabetologia 49:2819–2823
2. Larsson SC, Andersson SO, Johansson JE, Wolk A (2008) Diabetes mellitus, body size and bladder cancer risk in a prospective study of Swedish men. Eur J Cancer 44:2655–2660
3. Mackenzie T, Zens MS, Ferrara A, Schned A, Karagas MR (2011) Diabetes and risk of bladder cancer: evidence from a case–control study in New England. Cancer 117:1552–1556
4. Tripathi A, Folsom AR, Anderson KE, Iowa Women's Health Study (2002) Risk factors for urinary bladder carcinoma in postmenopausal women. The Iowa Women's Health Study. Cancer 95:2316–2323
5. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM (2005) Fasting serum glucose level and cancer risk in Korean men and women. JAMA 293:194–202
6. Kuriki K, Hirose K, Tajima K (2007) Diabetes and cancer risk for all and specific sites among Japanese men and women. Eur J Cancer Prev 16:83–89
7. Kakehi Y, Hirao Y, Kim WJ et al (2010) Bladder cancer working group report. Jpn J Clin Oncol 40(Suppl 1):i57–i64
8. Scosyrev E, Trivedi D, Messing E (2010) Female bladder cancer: incidence, treatment, and outcome. Curr Opin Urol 20:404–408
9. Jacobs BL, Lee CT, Montie JE (2010) Bladder cancer in 2010: how far have we come? CA Cancer J Clin 60:244–272
10. Volanis D, Kadiyska T, Galanis A, Delakas D, Logotheti S, Zoumpourlis V (2010) Environmental factors and genetic susceptibility promote urinary bladder cancer. Toxicol Lett 193:131–137

11. Jørgensen L, Heuch I, Jenssen T, Jacobsen BK (2008) Association of albuminuria and cancer incidence. J Am Soc Nephrol 19:992–998
12. Pelucchi C, Bosetti C, Negri E, Malvezzi M, La Vecchia C (2006) Mechanisms of disease: the epidemiology of bladder cancer. Nat Clin Pract Urol 3:327–340
13. Jiang X, Castelao JE, Groshen S et al (2009) Urinary tract infections and reduced risk of bladder cancer in Los Angeles. Br J Cancer 100:834–839
14. Dormandy J, Bhattacharya M, van Troostenburg de Bruyn AR, PROactive investigators (2009) Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: an overview of data from PROactive. Drug Saf 32:187–202
15. Tseng CH, Chong CK, Tseng CP, Chan TT (2009) Age-related risk of mortality from bladder cancer in diabetic patients: a 12-year follow-up of a national cohort in Taiwan. Ann Med 41:371–379
16. Berry CE, Wise RA (2010) Mortality in COPD: causes, risk factors, and prevention. COPD 7:375–382
17. Karp I, Behlouli H, Lelorier J, Pilote L (2008) Statins and cancer risk. Am J Med 121:302–309
18. Farwell WR, Scranton RE, Lawler EV et al (2008) The association between statins and cancer incidence in a veterans population. J Natl Cancer Inst 100:134–139
19. Kaye JA, Jick H (2004) Statin use and cancer risk in the general practice research database. Br J Cancer 90:635–637
20. Sato S, Ajiki W, Kobayashi T, Awata N, PCS Study Group (2006) Pravastatin use and the five-year incidence of cancer in coronary heart disease patients: from the prevention of coronary sclerosis study. J Epidemiol 16:201–206
21. Chiang CW, Chiu HF, Chen CY, Wu HL, Yang CY (2008) Trends in the use of lipid-lowering drugs by outpatients with diabetes in Taiwan, 1997–2003. Pharmacoepidemiol Drug Saf 17:62–69