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Diabetes mellitus and the risk of bladder cancer

A PRISMA-compliant meta-analysis of cohort studies

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Abstract

Background: Epidemiologic studies have reported inconsistent results regarding the relationship between diabetes mellitus (DM) and the incidence of bladder cancer. This comprehensive systematic review and meta-analysis explored and evaluated this relationship in participants with different characteristics.

Methods: Studies indexed in the PubMed, Embase, and the Cochrane Library databases that compared bladder cancer incidence mortality between DM and non-DM participants were included in the present study. The relative risks (RRs) of a random-effects model were used to assess these associations.

Results: The final analysis included 21 cohort studies, involving a total of 13,505,643 participants. Overall, DM was associated with an increased risk of bladder cancer or cancer mortality when compared with non-DM participants (RR: 1.23; 95% confidence interval [CI]: 1.12–1.35; $P < .001$). Furthermore, DM had a harmful impact on subsequent bladder cancer risk in men compared with those without DM (RR: 1.23; 95% CI: 1.06–1.42; $P = .005$), whereas no significant relationship was observed between DM and bladder cancer in women (RR: 1.24; 95% CI: 0.95–1.61; $P = .119$). There was no significant gender difference for this relationship (ratio of RR: 0.99; 95% CI: 0.73–1.34; $P = .958$). In addition, cancer incidence (RR: 1.21; 95% CI: 1.09–1.35; $P < .001$) and cancer mortality (RR: 1.25; 1.17–1.35; $P < .001$) both increased in DM patients. Finally, smoking status and follow-up duration might also affect this relationship in men and women.

Conclusions: The findings of this study indicated that DM was associated with elevated bladder cancer or cancer mortality risk, especially in men. This relationship in women requires further exploration.

Abbreviations: BMI = body mass index, CI = confidence interval, DM = diabetes mellitus, HR = hazard ratio, NOS = Newcastle–Ottawa Scale, OR = odds ratio, RR = relative risk.

Keywords: bladder cancer, diabetes mellitus, meta-analysis

1. Introduction

Bladder cancer is the 10th most common cancer worldwide and remains a major public health problem, with approximately 73,510 cases and 14,880 deaths in 2012.[1] The established causal risk factors for bladder cancer include gender, age, smoking, early menopause, and occupational exposure.[2–6] Diabetes mellitus (DM) is associated with elevated risks of cancer at different sites, including biliary tract,[7] lung,[8] hepatocellular,[9] colorectal,[10] ovarian,[11] prostate,[12] breast,[13] renal,[14] esophageal,[15] gastric,[16] non-Hodgkin lymphoma, leukemia, and myeloma,[17] pancreatic,[18] and endometrial[19] cancers. Further, although numerous meta-analyses have evaluated the association of DM with the risk of bladder cancer,[20–25] inconsistent results have been reported and require further verification.

Fang et al[20] reported the positive association between DM and risk of bladder cancer, which was significant only in women. The study conducted by Zhu et al[21] indicated that men with DM have a modestly increased risk of bladder cancer, while women with DM did not. Yang et al[22] also reported DM to be a risk factor for bladder cancer, with no gender differences in this relationship. Xu et al[23] performed a meta-analysis of 15 cohort studies and observed a positive association between DM and the risk of bladder cancer but did not report a gender difference. Zhu et al suggested that DM patients have an increased bladder cancer incidence and mortality. Furthermore, the incidence of bladder cancer was significantly increased only in men, while bladder cancer mortality was significantly increased in both men and women.[24] Finally, Larsson et al[25] concluded that DM patients may have a modestly increased risk of bladder cancer in their assessment of case–control or cohort studies. However, whether the association between DM and the risk of bladder cancer differs according to different patient characteristics remains unclear. This meta-analysis further examined whether diabetes is a risk factor for bladder cancer in specific subpopulations.

2. Methods

2.1. Data sources, search strategy, and selection criteria

This review was conducted and reported according to the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement (Checklist S1).[26] Ethics approval was not

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necessary for this study, as only deidentified pooled data from individual studies were analyzed. Cohort studies that explored the relationship between DM and bladder cancer were eligible for inclusion in the present study, with no restrictions on the language and publication status. Electronic databases including PubMed, Embase, and the Cochrane Library were systematically searched using the following text word or Medical Subject Heading terms: ("diabetes mellitus" OR "diabetes" OR "DM" OR "impaired glucose") AND ("bladder" OR "urothelium" OR "transitional cell" OR "urothelial") AND ("neoplasm" OR "tumor" OR "cancer" OR "carcinoma" OR "malignant") AND ("cohort" OR "epidemiologic") through October 10, 2017. The details of search strategies are presented in Supplementary Material 1, http://links.lww.com/MD/B947. In order to identify unpublished studies or updated information that could provide useful data, we contacted corresponding authors to obtain potential relevant data. The reference lists of the included studies or relevant reviews were also manually screened in order to identify additional relevant studies.

The inclusion criteria of this study are as follows: cohort design; comparison of the incidence or mortality of bladder cancer in DM and non-DM individuals; and reported odds ratios (ORs), hazard ratios (HRs), or relative risks (RRs) with corresponding confidence intervals (CIs). The exclusion criteria included case–control, cross-sectional, or cohort studies of diabetic patients that provided data as standard incidence ratios; patients with previous with bladder cancer; and unavailable data, whether through lack of calculations or translation. The search strategies and study selection were conducted independently by 2 authors; any inconsistencies were settled by the corresponding author, who made a final decision by referring to the original articles.

2.2. Data collection and quality assessment

Two authors independently extracted the baseline characteristics and data of the included studies, including the first author or study group name, country, sample size, mean age, number of men and women separately, diabetes assessment, mean body mass index (BMI), percentage of current smokers, percentage of alcohol users, follow-up duration, reported outcomes, adjusted factors, and effect estimate of the relationship between DM and bladder cancer. If direct reports of the effect estimate and corresponding 95% CI were not available, the estimated value was derived indirectly from other data. The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of the included studies based on selection (4 items), comparability (1 item), and outcome (3 items).[27] A "star system" (range, 0–9) was developed for assessment (Table 1).

2.3. Statistical analysis

The RRs with 95% CIs were defined as the effect estimates for the relationship between DM and the risk of bladder cancer. The HR was considered equivalent to the RR in cohort studies and OR was assumed to be an accurate estimate of RR due to the low incidence of bladder cancer in DM patients. The maximum adjusted RR was used to avoid bias caused by adjusted factors. A fixed-effects model was used for pooled RR and 95% CI in single studies if the effect estimates were reported separately according to different characteristics.[28] The pooled RRs and 95% CIs for the DM versus non-DM and the risk of bladder cancer were calculated by using a random-effects model.[29] Heterogeneity was assessed by the I^2 and Q statistics, with $P < .10$ indicative of significant heterogeneity.[30,31] Subgroup analysis was performed to evaluate the effects of country (Western vs. Eastern), mean age (≥60 vs. <60 years), follow-up duration (≥10.0 vs. <10.0 years), reported outcomes (cancer incidence vs. cancer mortality), adjusted BMI (yes vs. no), and adjusted smoking (yes vs. no). Sensitivity analyses were performed by removing each individual study from the overall analysis to assess the influence of a single study in the meta-analysis.[32] We assessed publication bias visually with funnel plots and statistically using Begg and Egger tests.[33,34] All *P* values were 2-sided, with a significant level of .05. Statistical analyses were performed using STATA (version 10.0; Stata Corporation, College Station, TX).

3. Results

3.1. Study selection

We identified 406 records in the initial search; after discarding 325 duplicates and irrelevant studies, 81 full-text records were assessed. We further excluded studies that enrolled single-arm DM patients, patients with a history of bladder cancer, or studies which focused on antidiabetic drugs (n = 22). A total of 59 studies were included in the qualitative analysis. We removed 34 studies with duplicate cohorts and 4 studies that did not report an effect estimate. Finally, 21 studies were included in the meta-analysis.[35–55] A manual search of the reference lists of these studies did not yield any new eligible studies. The study selection process is shown in Fig. 1.

3.2. Characteristics of the included studies

Table 1 summarizes the baseline characteristics of the included studies. The sample size ranged from 28,731 to 4,501,578 individuals, for a total of 13,505,643 participants. Seven studies were conducted in the United States, 7 in Europe, 5 in Asia, and 2 were international multicenter studies. The follow-up duration ranged from 2.0 to 16.0 years. Sixteen studies reported the relationship between DM and the incidence of bladder cancer, while 7 studies reported the relationship between DM and the risk of bladder cancer mortality. Study quality was evaluated by using the NOS and studies with scores ≥7 were considered to be high quality. Three studies had a score of 9, 7 studies had a score of 8, 8 studies had a score of 7, and 3 studies had a score of 6.

3.3. Bladder cancer or cancer mortality in the total cohort

A total of 21 studies reported an association between DM and the risk of bladder cancer or cancer mortality. The pooled RR showed that DM was associated with an increased risk of bladder cancer or cancer mortality when compared with participants without DM (RR: 1.23; 95% CI: 1.12–1.35; $P < .001$; Fig. 2). Furthermore, significant heterogeneity was detected across the included studies ($I^2 = 82.0\%$; $P < .001$). A sensitivity analysis was performed, in which the result was not affected (Table 2).

3.4. Bladder cancer or cancer mortality in men and women

The breakdown of the number of studies available for bladder cancer or cancer mortality included 10 and 6 studies in men and women, respectively. The pooled analysis results for men indicated that the comparison of DM versus non-DM individuals showed a harmful effect (RR: 1.23; 95% CI: 1.06–1.42; $P = .005$;

Table 1

Baseline characteristics of studies included.

Study	Country	Sample size	Mean age, y	Gender, M/F	Diabetes assessment	Mean BMI, kg/m^2	Current smoker, %	Alcohol user, %	Follow-up, y	Antidiabetic agents	Reported outcomes	Adjusted factors	NOS score
NHIC[35]	Korea	1,298,385	47.0	829,770/468,615	Self-report or FPG	23.2	38.9	53.7	10.0	NA	Cancer incidence and cancer mortality	Age, smoking, alcohol	9
BRFSS[36]	The United States	397,783	46.8	151,459/246,324	Self-report	NA	NA	NA	NA	NA	Cancer incidence	Age, race/ethnicity, health insurance coverage, smoking, alcohol, BMI, PI	7
ORLS[37]	The United Kingdom	484,356	>30.0	NA	Medical records	NA	NA	NA	NA	NA	Cancer incidence	Age, sex, time period in single calendar years, district of residence	6
NHI[38]	China	998,947	NA	495,199/503,748	NA	NA	NA	NA	3.0	NA	Cancer incidence	Age, sex, living regions, occupation, systematic disease, oral drugs	6
MEC[39]	The United States	185,816	60.4	83,641/102,175	Self-report	26.5	16.1	NA	10.7	NA	Cancer incidence	Ethnicity, sex, smoking, intensity and duration, employment in a high-risk industry	7
IWHS[40]	The United States	37,459	>55.0	0/37,459	Self-report	NA	NA	NA	13.0	NA	Cancer incidence	Age, smoking, PI, BMI, alcohol, occupation, marital status	8
JPHC[41]	Japan	97,771	51.6	46,548/51,223	Self-report	NA	36.0	48.6	10.7	NA	Cancer incidence	Age, study area, smoking, alcohol, BMI, PI, green vegetable and coffee intake, history of cerebrovascular or IHD	9
HIC[42]	The United Kingdom	28,731	62.0	15,314/13,417	NA	NA	NA	NA	4.0	NA	Cancer incidence	Deprivation decile	7
COSM[43]	Sweden	45,906	60.4	45,906/0	Self-report	25.8	25.0	NA	9.3	NA	Cancer incidence	Age, education, smoking	8
CPS II[44]	The United States	1,056,243	56.7	467,922/588,321	Self-report	NA	20.3	NA	16.0	NA	Cancer incidence and cancer mortality	Age, race, years of education, BMI, smoking, alcohol, total red meat consumption, consumption of citrus fruits, juices and vegetables, PI, HRT	9
JACC[45]	Japan	56,881	40.0–79.0	23,378/33,503	Self-report	NA	23.5	42.4	8.0	NA	Cancer incidence	Age, BMI, smoking, alcohol	8
APCSC[46]	Asia, Australia	367,361	48.0	216,743/150,618	Self-reported or blood glucose	NA	NA	NA	4.0	NA	Cancer mortality	Age	7
ERFC[47]	Europe, North America, Japan, other	820,900	55.0	358,391/462,509	Self-reported, FPG, medication use	26.1	32.8	62.9	13.6	NA	Cancer mortality	Age, smoking, BMI	8
USVA[48]	The United States	4,501,578	52.3	4,501,578/0	Hospital discharge diagnosis	NA	NA	NA	11.7	NA	Cancer incidence	Age, time, latency, race and number of visits, diagnoses of alcohol-related conditions, obesity, COPD	8
Currie[49]	The United Kingdom	112,408	67.8	54,086/58,322	Read code indicative of diabetes	26.2	20.9	NA	2.0	NA	Cancer mortality	Age at baseline, sex, smoking, Charlson comorbidity index, year of diagnosis	7
SHDR[50]	Sweden	1,016,105	67.0	NA	Hospital discharge register	NA	NA	NA	8.0	NA	Cancer mortality	Age at diagnosis, sex, period, obesity, alcohol, smoking, socioeconomic status, diagnosis region	7

Study	Country	Sample size	Mean age, y	Gender, M/F	Diabetes assessment	Mean BMI, kg/m^2	Current smoker, %	Alcohol user, %	Follow-up, y	Antidiabetic agents	Reported outcomes	Adjusted factors	NOS score
Marianne[51]	The United States	442,712	54.0	230,210/212,502	Medical records or oral antidiabetic agent	NA	NA	NA	3.5	NA	Cancer incidence	Age, sex, schistosomiasis, pelvic radiation	8
Chung[52]	China	54,751	40.0–80.0	54,751/0	Self-report or FPG	NA	NA	NA	6.8	NA	Cancer mortality	Age	6
NIH-AARP Diet and Health Study[53]	The United States	494,867	50.0–71.0	295,276/199,591	Self-report	NA	NA	NA	11.0	NA	Cancer incidence	Sex, BMI, race/ethnicity, education, marital status, family history of cancer, self-reported health status, intake of red meat, white meat, fruits, vegetables, alcohol, coffee; vigorous PA; PA at work; smoking; multivitamin use; and, for female-specific cancers, postmenopausal HRT use	8
CPRD[54]	The United Kingdom	636,483	58.0	335,009/301,474	Medical records	NA	21.6	NA	5.8	Insulin: 0.6%; and other drugs: 18.0%	Cancer incidence	Age, sex, smoking, BMI	7
BCLHD[55]	The United Kingdom	370,200	60.7	201,188/106,012	Medical records	NA	NA	NA	4.0	NA	Cancer incidence	Sex, year of birth, socioeconomic status, year of cohort entry	7

BMI = body mass index, COPD = chronic obstructive pulmonary disease, FPG = fasting plasma glucose, HRT = hormone replacement therapy, IHD = ischemic heart disease, NA = not available, NOS = Newcastle–Ottawa Scale, PA = physical acitivity, PI = physical inactivity.

Figure 1. Flowchart of the study selection process.

Fig. 3), whereas there was no significant difference in women (RR: 1.24; 95% CI: 0.95–1.61; $P = .119$; Fig. 4). Heterogeneity was observed in the magnitude of the relationship across the included studies for both men ($I^2 = 77.7\%$; $P < .001$) and women ($I^2 = 53.5\%$; $P = .057$). Sensitivity analyses for men and women separately did not alter the conclusions (Table 3). Furthermore, there was no significant gender difference in this relationship (ratio of RR: 0.99; 95% CI: 0.73–1.34; $P = .958$).

3.5. Subgroup analysis of the total cohorts of men and women

Substantial heterogeneity was detected in the total cohort of men and women. Therefore, we performed subgroup analyses of the association between DM with the risk of bladder cancer in the total cohort and men and women in order to minimize heterogeneity and evaluate this relationship in specific subpopulations. The results are presented in Table 4. First, stratified analysis in the total cohort was consistent with the overall analysis except if the study did not adjust for smoking and there were no significant differences between subgroups in total cohorts based on predefined factors; second, DM was not associated with bladder cancer in men if the mean age was ≥60.0 years, the study did not adjust for smoking, and neglected to include the follow-up duration. Furthermore, there was a significant difference between subgroups based on adjusting for smoking (ratio of RR: 1.32; 95% CI: 1.17–1.49; $P < .001$), whereas there were no significant differences based on other factors. Third, DM was associated with increased risk of bladder cancer in women ≥60.0 years, a follow-up duration >10.0 years, and in studies that did not adjust for BMI. Furthermore, there was a significant difference between subgroups based on follow-up duration (ratio of RR: 1.56; 95% CI: 1.09–2.24; $P = .015$). No significant differences were observed in the other stratified analyses.

3.6. Publication bias

Review of the funnel plot could not rule out potential publication bias for the relationship between DM and bladder cancer risk in

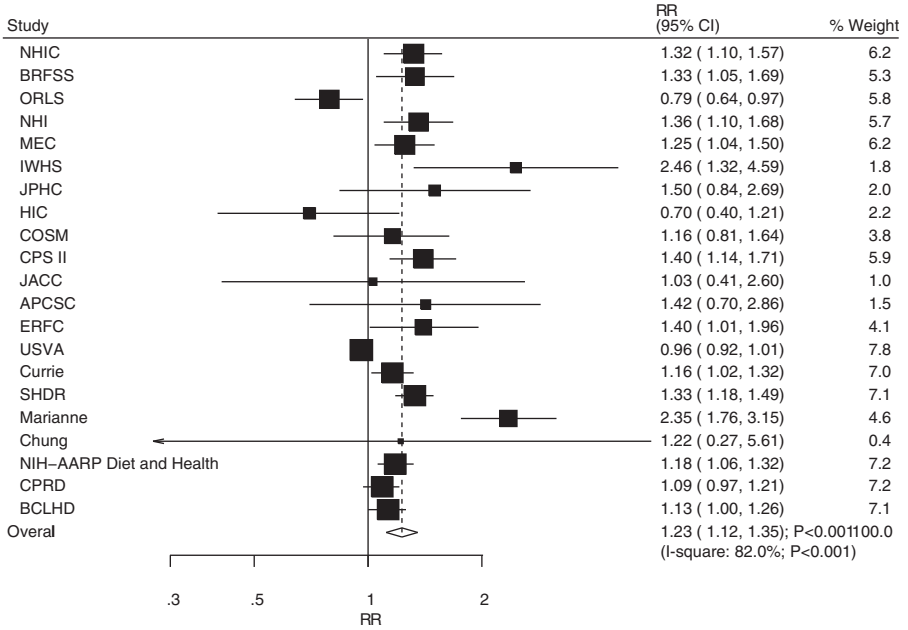

Figure 2. Association between diabetes mellitus and the risk of bladder cancer or cancer mortality.

the total cohort (Fig. 5). Furthermore, although the Begg test results showed no evidence of publication bias ($P = .928$), and the Egger test showed significant publication bias ($P = .009$). After adjusting for publication bias using the trim and fill method, we noted that DM was associated with greater risk of bladder cancer or cancer mortality (RR: 1.16; 95% CI: 1.06–1.28; $P = .002$).[56]

4. Discussion

This meta-analysis used data from cohort studies to explore the correlations between DM and the risk of bladder cancer. This large quantitative study included 13,505,643 individuals from 21 cohort studies with a broad range of baseline characteristics. The findings from this study indicated that DM patients had an increased risk of bladder cancer or cancer mortality. Although DM play a harmful effect on bladder cancer in men but not in women, but the gender difference for the relationship between DM and bladder cancer was not associated with statistically significant. Subgroup analysis revealed a positive relationship in both cancer incidence and cancer mortality. Furthermore, adjustment for smoking status played an important role in this relationship in men, whereas follow-up duration may affect this relationship in women.

Table 2

Sensitivity analysis for total cohort.

Excluding study	RR and 95% CI	*P*	Heterogeneity, %	*P* value for heterogeneity
NHIC	1.22 (1.11–1.35)	<.001	82.2	<.001
BRFSS	1.22 (1.11–1.35)	<.001	82.5	<.001
ORLS	1.26 (1.15–1.39)	<.001	81.3	<.001
NHI	1.22 (1.11–1.35)	<.001	82.2	<.001
MEC	1.23 (1.11–1.36)	<.001	82.6	<.001
IWHS	1.21 (1.10–1.33)	<.001	81.9	<.001
JPHC	1.22 (1.11–1.35)	<.001	82.7	<.001
HIC	1.24 (1.13–1.37)	<.001	82.5	<.001
COSM	1.23 (1.12–1.36)	<.001	82.9	<.001
CPS II	1.22 (1.10–1.35)	<.001	82.0	<.001
JACC	1.23 (1.12–1.36)	<.001	82.9	<.001
APCSC	1.22 (1.11–1.35)	<.001	82.8	<.001
ERFC	1.22 (1.11–1.35)	<.001	82.6	<.001
USVA	1.25 (1.14–1.36)	<.001	67.9	<.001
Currie	1.24 (1.12–1.37)	<.001	82.8	<.001
SHDR	1.22 (1.11–1.35)	<.001	80.9	<.001
Marianne	1.19 (1.09–1.30)	<.001	77.4	<.001
Chung	1.23 (1.12–1.35)	<.001	82.9	<.001
NIH-AARP Diet and Health	1.24 (1.11–1.37)	<.001	82.6	<.001
CPRD	1.24 (1.12–1.38)	<.001	82.9	<.001
BCLHD	1.24 (1.12–1.38)	<.001	82.9	<.001

CI = confidence interval, RR = relative risk.

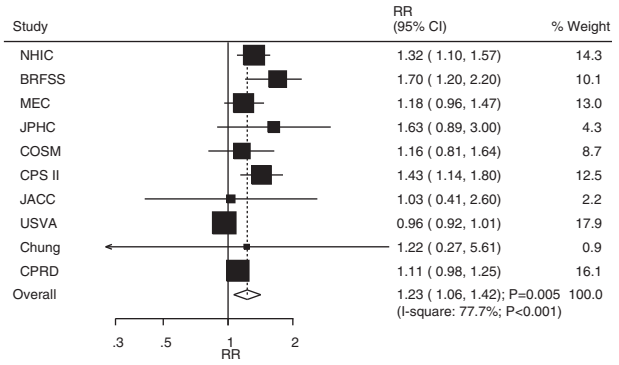

Figure 3. Association between diabetes mellitus and the risk of bladder cancer or cancer mortality in men.

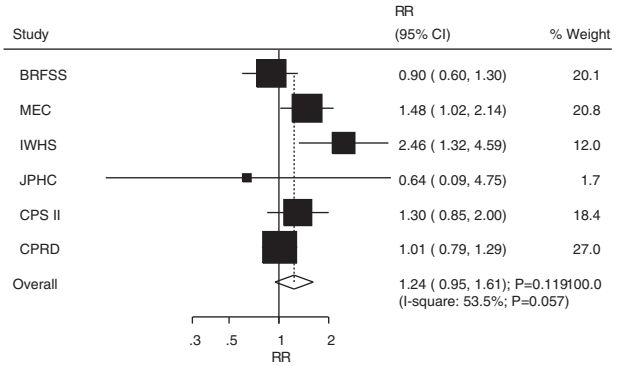

Figure 4. Association between diabetes mellitus and the risk of bladder cancer or cancer mortality in women.

The methodological assessment of the included studies was based on the representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, demonstration that the outcomes were not present at the start of the study, comparability on the basis of the design or analysis, assessment of outcome, adequate follow-up duration, and adequate follow-up rate. Although most of the studies included in this meta-analysis provided clear information on these items, ascertainment of exposure, follow-up duration, and different adjusted factors might have contributed to the heterogeneity among the included studies. Furthermore, the number of studies on this relationship in specific populations might have affected the pooled outcomes. Therefore, the relationship between DM and bladder cancer in specific subpopulations should be interpreted with caution.

Previous meta-analyses combined case–control and cohort studies in order to evaluate the association of DM and the risk of bladder cancer[20–22,25]; although stratified analyses were conducted based on several important confounders, the results of the subgroup analyses might unreliable due to different study designs across the stratified analysis. Furthermore, the included cohort studies of diabetic patients used the total population as the control, which might have affected the accuracy of the selection of the nonexposed cohort.[21,23–25] In addition, the relationship in men and women was not performed, and the ratio of RR between subgroups remains unknown. Finally, the effect estimates of bladder cancer and cancer mortality were summarized separately due to the lower number of cases of cancer mortality, which might have biased the final conclusion. The important strengths of our study include the comprehensive inclusion of cohort studies with large sample sizes; most of the cohorts were prospective designs, population-based, and with long follow-up durations. In addition, the heterogeneity was evaluated in multiple ways and detailed stratified analyses were also conducted.

Previous studies have illustrated the burden of DM as an important cause of premature illness and death due to cancer.[7–25] This study showed that DM was associated with an increased risk of bladder cancer or cancer mortality. However, significant heterogeneity was detected across the included studies; to minimize the consequences of heterogeneity, we conducted a sequential exclusion of each study from the pooled analysis. The findings remained stable after each individual study was sequentially excluded, which supported the relationship between DM and bladder cancer.

Table 3

Sensitivity analysis for men and women.

Population	Excluding study	RR and 95% CI	*P*	Heterogeneity, %	*P* value for heterogeneity
Men	NHIC	1.21 (1.04–1.41)	.014	75.1	<.001
	BRFSS	1.18 (1.03–1.35)	.019	72.8	<.001
	MEC	1.24 (1.05–1.46)	.009	79.3	<.001
	JPHC	1.21 (1.05–1.40)	.010	79.0	<.001
	COSM	1.24 (1.06–1.44)	.007	79.9	<.001
	CPS II	1.20 (1.03–1.39)	.016	74.9	<.001
	JACC	1.23 (1.06–1.43)	.005	80.1	<.001
	USVA	1.27 (1.14–1.40)	<.001	24.5	.226
	Chung	1.23 (1.06–1.42)	.006	80.1	<.001
	CPRD	1.26 (1.05–1.52)	.013	79.2	<.001
Women	BRFSS	1.34 (0.99–1.83)	.060	53.9	.070
	MEC	1.18 (0.87–1.62)	.291	54.4	.067
	IWHS	1.11 (0.92–1.35)	.268	17.2	.305
	JPHC	1.25 (0.95–1.66)	.110	61.5	.034
	CPS II	1.23 (0.89–1.72)	.213	61.7	.033
	CPRD	1.34 (0.95–1.88)	.093	52.7	.076

CI = confidence interval, RR = relative risk.

Table 4

Subgroup analysis of relative risk for bladder cancer in men, women, and total cohort.

Factors	Subsets	Group	RR and 95% CI	*P*	I^2, %	*P* value for heterogeneity	Ratio of RR in total cohorts	Ratio of RR in men	Ratio of RR in women
Country	Western countries	Men	1.20 (1.02–1.41)	.029	83.2	<.001	0.90 (0.77–1.07); *P*=.228	0.90 (0.71–1.14); *P*=.389	1.95 (0.27–14.32); *P*=.510
		Women	1.25 (0.95–1.66)	.110	61.5	.034			
		Total cohort	1.21 (1.09–1.35)	.001	86.0	<.001			
	Eastern countries	Men	1.33 (1.12–1.57)	.001	0.0	.863			
		Women	0.64 (0.09–4.65)	.659	—	—			
		Total cohort	1.34 (1.18–1.52)	<.001	0.0	.990			
Mean age	≥60	Men	1.17 (0.98–1.41)	.084	0.0	.935	0.89 (0.74–1.09); *P*=.266	0.93 (0.72–1.20); *P*=.576	1.44 (0.95–2.18); *P*=.088
		Women	1.48 (1.02–2.14)	.038	—	—			
		Total cohort	1.19 (1.09–1.30)	<.001	38.7	.148			
	<60	Men	1.26 (1.05–1.52)	.013	86.8	<.001			
		Women	1.03 (0.85–1.24)	.777	0.0	.604			
		Total cohort	1.33 (1.12–1.59)	.001	88.0	<.001			
Follow-up duration, y	≥10	Men	1.22 (0.99–1.51)	.061	84.9	<.001	1.02 (0.84–1.25); *P*=.816	1.10 (0.86–1.40); *P*=.442	1.56 (1.09–2.24); *P*=.015
		Women	1.53 (1.14–2.05)	.004	15.7	.313			
		Total cohort	1.28 (1.09–1.49)	.003	85.2	<.001			
	<10	Men	1.11 (0.99–1.25)	.062	0.0	.992			
		Women	0.98 (0.79–1.20)	.827	0.0	.622			
		Total cohort	1.25 (1.10–1.41)	<.001	69.7	<.001			
Reported outcomes	Cancer incidence	Men	1.23 (1.06–1.42)	.006	80.1	<.001	0.97 (0.85–1.10); *P*=.620	0.98 (0.78–1.22); *P*=.833	1.10 (0.72–1.68); *P*=.669
		Women	1.24 (0.95–1.61)	.119	53.5	.057			
		Total cohort	1.21 (1.09–1.35)	<.001	81.3	<.001			
	Cancer mortality	Men	1.26 (1.06–1.49)	.008	0.0	.756			
		Women	1.13 (0.81–1.58)	.478	—	—			
		Total cohort	1.25 (1.17–1.35)	<.001	0.0	.797			
Adjusted BMI	Yes	Men	1.24 (1.02–1.50)	.033	83.0	<.001	1.02 (0.84–1.25); *P*=.812	0.99 (0.79–1.25); *P*=.946	0.80 (0.49–1.29); *P*=.359
		Women	1.18 (0.87–1.62)	.291	54.4	.067			
		Total cohort	1.24 (1.09–1.42)	.001	84.4	<.001			
	No	Men	1.25 (1.10–1.42)	.001	0.0	.846			
		Women	1.48 (1.02–2.14)	.038	—	—			
		Total cohort	1.21 (1.04–1.41)	.011	77.1	<.001			
Adjusted smoking	Yes	Men	1.27 (1.14–1.42)	<.001	33.9	.157	1.08 (0.87–1.33); *P*=.485	1.32 (1.17–1.49); *P* < .001	—
		Women	1.24 (0.95–1.61)	.119	53.5	.057			
		Total cohort	1.24 (1.17–1.32)	<.001	26.4	.178			
	No	Men	0.96 (0.92–1.01)	.088	0.0	.757			
		Women	—	—	—	—			
		Total cohort	1.15 (0.94–1.41)	.174	87.5	<.001			

BMI = body mass index, CI = confidence interval, RR = relative risk.

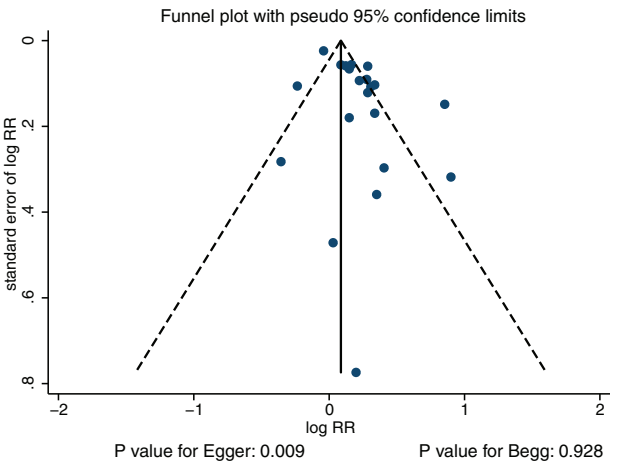

Figure 5. Funnel plot.

Several potential mechanisms may explain the increased bladder cancer burden in DM patients. First, hyperglycemia in these patients might lead to the dysregulation of energy balance, which affects intracellular metabolism and impair the immune system. These phenomena are associated with increased risks of cancer at different sites.[57] Second, insulin in commonly used by DM patients, which results in increased levels of insulin-like growth factor. These increased levels might stimulate cell proliferation and inhibit apoptosis.[57–60] Finally, DM is associated with a higher incidence of urinary tract infections,[61] which might affect the risk of bladder cancer.[38,62]

In the present study, DM was associated with the increased risk of bladder cancer only in men. One possible reason for this observation could be that the number of studies that included women was smaller than expected. Furthermore, the incidence of bladder cancer in women was lower than that in men,[1] which led to lower statistical power and broad CIs. In addition, adjustment for smoking status played an important role in this relationship in men but not in women. The reason could be the higher proportion of male smokers in which smoking had a significant effect on the risk of bladder cancer,[3] whereas this impact in women was small due to the relatively lower proportion of smokers in this population. Finally, follow-up duration affected the association of DM with bladder cancer in women. Most of the included studies that reported on women were conducted in the United States; the criteria for DM in the United States became more sensitive at a later period, which led to the increased inclusion of the earlier stages of DM. Finally, the symptoms of bladder cancer may be hidden and diagnosis might be delayed in women due to other gynecological diseases.

This meta-analysis has several limitations: different DM assessment approaches to indicate the severity of DM might bias this relationship; antihyperglycemic drugs may be associated with the risk of bladder cancer, but mostly were not adjusted for in most of the included studies;[63,64] the inherent bias included recall and selection in retrospective cohort studies, which could affect the incidence of bladder cancer; the ascertainment of the incidence of bladder cancer in different countries may be liable to bias; different adjusted factors across the included studies might affect the progression of bladder cancer; and the publication bias could be due to our searching strategy, missing the studies with negative results. As a result, the risk of bladder cancer in diabetes could be overestimated in our study.

In conclusion, our study indicated that DM has a harmful effect on the risk of bladder cancer or cancer mortality. The composite outcomes of bladder cancer incidence and cancer mortality were significantly increased in men but not in women. Smoking and follow-up duration might affect this relationship. Future large-scale cohort studies should explore this relationship in women.

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