

RESEARCH ARTICLE

Diabetes Mellitus Increases the Risk of Bladder Cancer: An Updated Meta-analysis

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Abstract

Purpose: Studies have indicated that diabetes mellitus (DM) is a risk factor for bladder cancer; however, not all evidence supports this conclusion. The aim of this meta-analysis was to collate and evaluate all primary observational studies investigating the risk of bladder cancer associated with DM. **Methods:** The PubMed and Google Scholar databases were searched to identify studies that estimated the association of DM and bladder cancer. Summary effect estimates were derived using a random-effects meta-analysis model. **Results:** A total of 23 studies (8 case-control studies, 15 cohort studies) including 643,683 DM and 4,819,656 non-DM cases were identified. Analysis of all studies showed that DM was associated with an increased risk of bladder cancer compared with non-DM overall (OR=1.68, 95% CI 1.32-2.13). Analysis of subgroups demonstrated this to be the case in both case-control studies (OR=1.59, 95% CI 1.28-1.97, $I^2=58\%$) and cohort studies (RR=1.70, 95% CI 1.23-2.33, $I^2=96\%$). There was no gender difference in DM-associated bladder cancer risk. Bladder cancer risk was increased in Asia and the North America region, but not in Europe. Furthermore, DM-associated bladder cancer risk was obviously higher in Asia than North America and Europe or in those with Caucasian ethnicity. With extension of follow-up time, the bladder cancer risk was not increased for the patients with DM. **Conclusions:** This meta-analysis provided further evidence supporting the DM association with a significantly higher risk of bladder cancer obtained from observational studies.

Keywords: Bladder cancer - diabetes mellitus - meta-analysis - ethnicity

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Introduction

Bladder cancer is one of the most frequent malignant tumors in urinary system and a leading cause of cancer-related death. In the world bladder cancer represents the sixth and tenth most common malignancy in men and women, respectively (Parkin et al., 2005). In the west bladder cancer represents the fourth most common malignancy in men (Jemal et al., 2008). Diabetes mellitus (DM) is also a serious and growing health problem worldwide where it affects about 250 million people and this figure is expected to reach 366 million in 2030 (Wild et al., 2004). Epidemiologic evidence suggests that people with DM are at significantly increased risk for many forms of cancer (Giovannucci et al., 2010; Nicolucci et al., 2010). Notably cancers of the pancreas, breast, endometrium, liver, colon and rectum. But the association between DM and bladder cancer risk has no consistent result.

In recent years, the relationship of DM and the risk of bladder cancer have attracted widespread attention. Several prospective cohort studies with a large number of samples were performed to identify the association between DM and bladder cancer risk (Tripathi et al., 2002;

Coughlin et al., 2004; Jee et al., 2005; Li et al., 2011; Tseng, 2011). And only one meta-analysis has published (Larsson et al., 2006).

However there were still some limitations in this published meta-analysis: (1) The studies and samples were insufficient for which did not contain many new studies with a large number of samples which reported in recent years (Manami et al., 2006; Rousseau, 2006; Susanna et al., 2008; Li et al., 2011; MacKenzie et al., 2011; Tseng, 2011; Attner et al., 2012; Zhang et al., 2012; Newton et al., 2013; Prizment et al., 2013). So the population included in it was too small to reveal the actual relationship between DM and the bladder cancer risk. (2) Two studies about the relationship between DM and the mortality of bladder cancer (Kessler, 1970; Verlato et al., 2003) which could not contain the morbidity of bladder cancer were also included in this meta-analysis. One study did not contain the data of both DM and non-DM, and the data could not be calculated (Kantor et al., 1984). (3) Based on the statistical analysis of WHO, there were gender differences in the incidence of bladder cancer (Parkin et al., 2005; Jemal et al., 2008), but there was no gender subgroup in above meta-analysis. (4) Most of the studies in above

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meta-analysis were from Europe and North America, while only two studies were from Asia. So the data were not comprehensive and representative. To date, many large sample epidemiological studies have investigated the important role of DM in bladder cancer development. The results were inconsistent or even contradictory, some of studies did not support an association of DM with overall bladder cancer incidence (Rousseau et al., 2006; Larssona et al., 2008; Zhang et al., 2012). So after removing the three unqualified literature (Kessler, 1970; Kantor et al., 1984; Verlato et al., 2003), adding the new studies which were not included in above meta-analysis, we performed a meta-analysis of 23 published studies covering 643,683 cases and 4,819,656 controls to get a more precise evaluation of the association between DM and the risk of bladder cancer.

Materials and Methods

Data Sources and Searches

A comprehensive literature search was conducted using the PubMed and google scholar databases, MEDLINE, EMBASE databases, Web of Science, and the Cochrane Library. The last quest was updated to 30 Jan 2013. Keywords for searching included: diabetes/diabetes mellitus/bladder cancer/bladder neoplasm/bladder tumor/bladder carcinoma/transitional cell carcinoma/urothelial carcinoma. Moreover, references from recent review articles were also checked for additional undetected articles.

Study selection

Two investigators (Sun and Xu) independently reviewed abstracts in duplicate to determine whether they met the general inclusion and exclusion criteria, any discrepancies were resolved by discussion between the investigators.

For the meta-analysis, the following inclusion criteria were considered: (1) case-control studies and cohort studies that had comparative data of the relationship between DM and bladder cancer risk; (2) results expressed as relative risk (RR) or odds ratio (OR) or SIR; (3) studies with a 95 % CI for RR or OR, or sufficient data to deduce these data.

While for the exclusion criteria, we provided as follows: (1) studies without the raw data of the number of DM and events (Kantor et al., 1984); (2) case reports, editorials, and review articles (including meta-analyses); (3) articles about association of diabetic drugs (as TZD, insulin) and bladder cancer were excluded for which DM were included in both case and control groups without non-DM to compare. (4) Article about type 1 diabetes was not excluded (Verlato et al., 2003) Figure 1 depicts the process of study selection.

Data extraction and Quality Assessment

The quality of the individual studies were reviewed and scored by two investigators independently based on the Inclusion and exclusion criteria. These criteria were shown in the Research design and Methods section above. Each article was blinded with respect to authors,

journals, departments, institutions, and countries. Any disagreements were resolved by consensus and reference to the articles. For the individual study, a quality score was calculated as the percentage of applicable criteria that were met in each study. Items estimating both selection bias and misclassification bias (nine points, items A-I) were given twice the weight of items evaluating adjustment or matching for confounders and data analysis (nine points, items J-R). So, each quality score could range from 0% to 100%, while 0% means that none of the quality criterion was met and 100% means that all the quality criteria were met. And the high-quality studies were considered as the ones with more than 60% of the total score. First author's surname, year of publication, age and region of the study population, ethnicity of the study population and follow-up years was reviewed and abstracted for each study.

Titles, abstracts, and articles were reviewed independently. The full text of any article that was deemed potentially eligible was examined for the decision on inclusion or exclusion. Fully adjusted estimates were preferably included and analyzed. The results of the data extraction were summarized in a structured table to explore the variation. There were five cohort studies without original data of control group (used expected events and SIR to estimated the relative risk), we hypothesized that the population of the control was same as the case (Adami et al., 1991; Wideroff et al., 1997; Zendehdel et al., 2003; Swerdlow et al., 2005; Zhang et al., 2012).

Data Synthesis and Analysis

The OR was used as the common measure for relative risks. In the stratified analysis of cohort study, we used rate ratio(RR) as the measure for relative risk. Forest plots were used to summarize results, and funnel plots were used to assess publication bias. To assess for heterogeneity between studies, we calculated the Cochran Q statistic with significance level of $P < 0.05$. Because the studies and samples were large and there were regional and methodological differences between these studies. The heterogeneity was large or extreme. All analyses and tests were conducted using Review Manager 5.1. To explore the reasons of heterogeneity, subgroup analyses were performed by grouping studies that showed similar characteristics, such as the type of the studies (cohort study and case-control study), gender (male and female), geographical region (North America, Europe and Asia), follow-up time (<10 years, ≥ 10 years and <20 years, ≥ 20 years), ethnicity (Caucasian and Asian), adjustment for smoking (yes and no), adjustment for body mass index

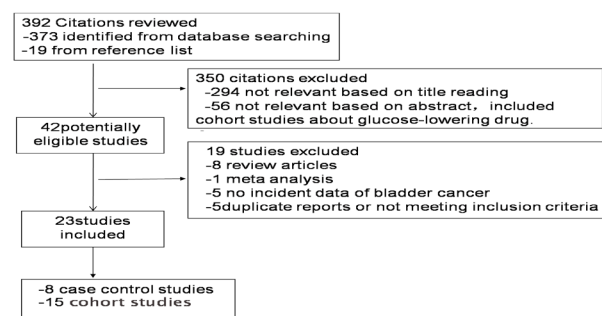


Figure 1. Flowchart of Study Selection Process

Table 1. Main Characters of Studies Included in the Present Meta-analysis

Istauthor, year	Studytype	Region	Ethnicity DM/Total(%)	Patients With	Age, y	Follow-up Time, y	Variables included in adjustment
Ragozzino, 1982	Corhort	USA	Caucasian	1135/2270	NR	25	1, 3
O'Mara, 1985	Case control	USA	Caucasian	164/5147	30-89	8	1, 3
Risch, 1988	Case control	Canada	Caucasian	131/826	35-79	3	1, 3, 5
Adami, 1991	cohort	Sweden	Caucasian	51008	all range	20	1, 3
Vecchia, 1994	Case control	Italy	Caucasian	437/8265	<75years	10	1, 6, 7, 8
Wideroff, 1997	cohort	Denmark	Caucasian	109581/219162	64 (men) 69 (women)	16	1, 3
Kravchick, 2001	Case control	Israel	Caucasian	113/801	71.5 (men) 73 (women)	NR	1, 3, 4
Tripathi, 2002	cohort	USA	Caucasian	25051/443824	55-69	13	3, 4, 6, 9, 10, 11, 12
Ng, 2003	Case control	UK	Caucasian	29/205	NR	2	1, 3, 4
Coughlin, 2004	cohort	USA	Caucasian	52803/1056243	mean 56.7	16	1, 3, 4, 23
Zendehdel, 2003	Cohort	sweden	Caucasian	29187/58374	mean 17.1	14.4	1, 3
Swerdlow, 2005	Cohort	UK	Caucasian	28800/57600	<30 or 30-49	18	1, 3, 13
Jee, 2005	cohort	Korean	Asian	62924/1298385	30-95	10	3, 4, 6, 10
Inoue, 2006	Cohort	Japen	Asian	4668/93103	40-69	10.7	3, 4, 6, 7, 9, 10, 15, 16, 23
Rousseau, 2006	Case control	Canada	Caucasian	78/868	35-70	6	2, 3, 4, 6, 7, 10, 11, 16, 17
Larssona, 2008	cohort	Sweden	Caucasian	2835/459,06	45-79	10	6, 18
MacKenzie, 2011	Case control	USA	Caucasian	91/584	25-74	4	4, 6, 19
Li, 2011	cohort	USA	Caucasian	48388/397753	mean 46.8	NR	2, 3, 4, 6, 9, 10
Tseng, 2011	cohort study	Taiwan	Asian	211,184/137,6315	≥ 40	3	1, 2, 14, 19, 20, 21, 22, 24, 25, 26, 27
Attner, 2012	Case control	Sweden	Caucasian	905/9274	45-84	10	1, 3, 5
Zhang, 2012	cohort study	China	Asian	7950/15900	Mean 61.1	8.5	NR
Newton, 2012	cohort study	USA	Caucasian	12863/172791	NR	11.9	1, 2, 3, 4, 6, 7, 9, 10
Prizment, 2013	cohort study	USA	Caucasian	2274/37327	Mean 61.7	24	2, 4, 6, 7, 9, 10, 12, 29

1, sex; 2, race; 3, age; 4, smoking; 5, area of residence; 6, BMI; 7, education; 8, diabetes duration; 9, physical activity; 10, alcohol; 11, occupation; 12, married1; 13, insulin treatment; 14, oral hypoglycemic drugs; 15, green vegetable intake; 16, coffee intake; 17, family income; 18, waist circumference; 19, nephropathy; 20, urinary tract diseases; 21, hypertension; 22, stroke; 23, estrogen replacement therapy; 24, ischaemic heart disease and cerebrovascular disease; 25, peripheral arterial disease; 26, dyslipidaemia and medications; 27, antihypertensive drugs; 28, statin, fibrates; 29, Waist-to-hip; NR, none reported

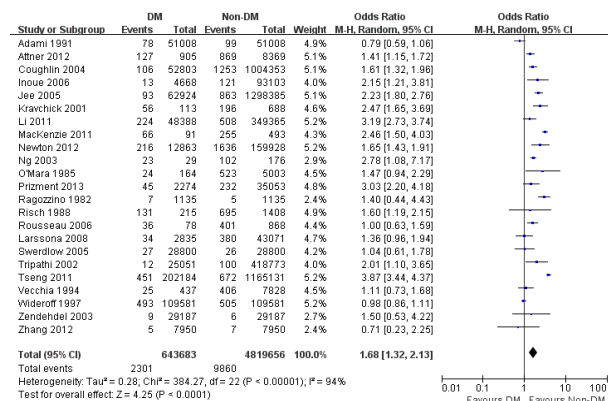


Figure 2. Forest Plot for the Overall Association Between Diabetes and Bladder Cancer Risk Using Random Effects Model

(BMI) (yes and no) and adjustment for physical activity (yes and no).

For publication bias assessing, inverted funnel plot was employed. In the funnel plot, the results of the small studies are shown to be more widely scattered than those of the large studies. Where there is absence of publication bias, the plot resembles a symmetrical inverted funnel.

Results

Description of studies

Twenty three relevant studies were retrieved about incidence, including eight case-control studies (O'Mara et al., 1985; Risch et al., 1988; Vecchia et al., 1994; Kravchick et al., 2001; Ng et al., 2003; Rousseau et al., 2006; MacKenzie et al., 2011; Attner et al., 2012), fifteen cohort studies (Ragozzino et al., 1982; Adami et al., 1991;

Wideroff et al., 1997; Tripathi et al., 2002; Zendehdel et al., 2003; Coughlin et al., 2004; Swerdlow et al., 2005; Jee et al., 2005; Inoue et al., 2006; Larssona et al., 2008; Li et al., 2011; Tseng et al., 2011; Zhang et al., 2012; Newton et al., 2012; Prizment., 2013), comprising a total of 643,683 patients with DM and 4,819,656 patients without DM. The characteristics of selected studies are summarized in Table 1. In some studies, the integral number of male and female were not reported (O'Mara et al., 1985; Risch et al., 1988; Kravchick et al., 2001; Ng et al., 2003; Inoue et al., 2006; Rousseau et al., 2006; Attner et al., 2012; Prizment et al., 2013; Verlato et al., 2013), and two of them were only included with women (Tripathi et al., 2002; Prizment et al., 2013), also another two of them were only included with men (Larssona et al., 2008; Attner et al., 2012), so there were 279,508 male and 291,644 female patients with DM, 2,199,602 male and 1,742,232 female patients without DM, respectively. There were ten studies with North America region, eight for Europe region and five with Asia region, respectively. There were eighteen studies with Caucasian ethnicity, five with Asian ethnicity, respectively. There were eleven, ten and five studies with adjustment for smoking, BMI and physical activity, respectively.

Meta-analyses results

Overall, there was statistically association between DM and bladder cancer risk for DM vs non-DM comparison (OR=1.68, 95% CI 1.32-2.13, I²=94%, P heterogeneity < 0.00001; Figure 2). In the stratified analysis by study type, among a total of 4,794,823 patients without DM, 6,413 bladder cancer events were documented over follow-up, meanwhile, among a total of 641,651 patients

Table 2. Main Results of Pooled Odds Ratios (ORs)/Rate Ratio (RR) with Confidence Interval (CI) in the Meta-analysis

Variables	No. of studies	No. of DM	No. of Non-DM	Random-effects model; OR/RR(95% CI)	Heterogeneity between studies, I^2	Test for overall effect, P value	Test for subgroup differences, P value
Overall	23	643,683	4,819,656	1.68 (1.32-2.13)	$P < 0.00001, I^2 = 94\%$	$P < 0.0001$	
Study type							
Cohort	15	641,651	4,794,823	1.70 (1.23-2.34)	$P < 0.00001, I^2 = 96\%$	$P = 0.001$	
Case-control	8	2032	24,833	1.59 (1.28-1.97)	$P = 0.02, I^2 = 58\%$	$P < 0.0001$	
Gender							$P = 0.68$
Male	13	279,508	2,199,602	1.49 (1.05-2.09)	$P < 0.00001, I^2 = 96\%$	$P = 0.02$	
Female	12	291,644	1,742,232	1.65 (1.12-2.44)	$P < 0.00001, I^2 = 91\%$	$P = 0.01$	
Geographical region							$P = 0.0004$
North America	10	143,062	1,976,379	1.89 (1.46-2.43)	$P < 0.0001, I^2 = 86\%$	$P < 0.00001$	
Europe	8	222,782	278,020	1.14 (0.94-1.40)	$P = 0.007, I^2 = 64\%$	$P = 0.19$	
Asia	5	277,839	2,565,257	2.39 (1.62-3.54)	$P < 0.00001, I^2 = 87\%$	$P < 0.0001$	
Follow-up time							$P = 0.71$
<10 years	8	233,574	1,340,957	1.79 (1.17-2.74)	$P < 0.00001, I^2 = 94\%$	$P = 0.007$	
≥10, <20 years	10	317,191	3,041,450	1.46 (1.15-1.84)	$P < 0.00001, I^2 = 84\%$	$P = 0.002$	
≥20 years	3	54,417	87,196	1.50 (0.51-4.45)	$P < 0.00001, I^2 = 95\%$	$P = 0.46$	
Ethnicity							$P = 0.04$
Caucasian	18	365,844	2,254,399	1.54 (1.22-1.93)	$P < 0.00001, I^2 = 91\%$	$P = 0.0002$	
Asian	5	277,839	2,565,257	2.44 (1.66-3.59)	$P < 0.00001, I^2 = 86\%$	$P < 0.00001$	
Adjustment for smoking							$P = 0.05$
Yes	11	209,282	3,361,185	2.12 (1.70-2.64)	$P < 0.00001, I^2 = 84\%$	$P < 0.00001$	
No	12	434,401	1,458,471	1.33 (0.87-2.03)	$P < 0.00001, I^2 = 96\%$	$P < 0.00001$	
Adjustment for BMI							$P = 0.31$
Yes	10	159,609	2,406,867	1.91 (1.48-2.47)	$P < 0.00001, I^2 = 87\%$	$P < 0.00001$	
No	13	484,074	2,412,789	1.51 (1.02-2.22)	$P < 0.00001, I^2 = 94\%$	$P = 0.04$	
Adjustment for physical activity							$P = 0.07$
Yes	5	93,244	1,056,222	2.36 (1.62-3.43)	$P < 0.00001, I^2 = 90\%$	$P < 0.00001$	
No	18	550,439	3,763,434	1.52 (1.13-2.04)	$P < 0.00001, I^2 = 95\%$	$P = 0.006$	

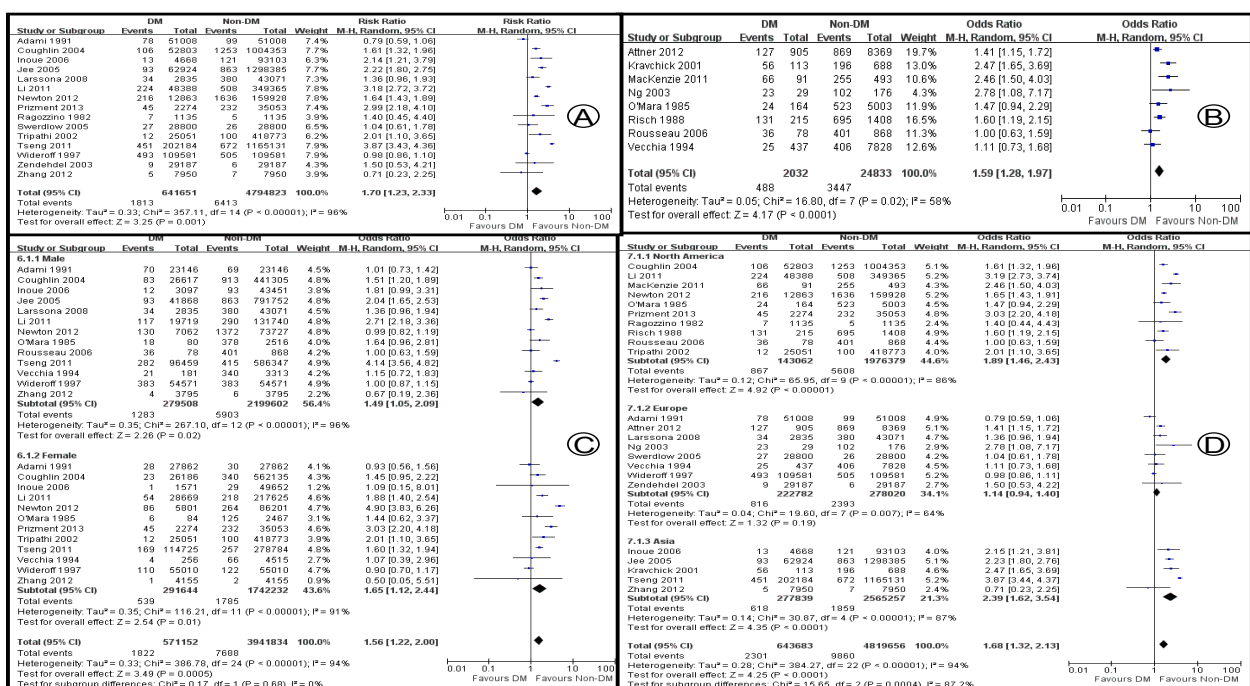


Figure 3. Subgroup Analysis by Study Type, Gender and Geographical Region. Forest plot for the association between diabetes and bladder cancer risk in cohort studies(A), case control studies(B) using random effects model; Forest plot for the association between diabetes and bladder cancer risk by gender(C) and geographical region(D) using random effects model

with DM, 1813 bladder cancer events were documented over follow-up in cohort studies. Compared with non-DM individuals, individuals with DM was associated with a significantly higher risk of bladder cancer (pooled $RR = 1.70, 95\% \text{ CI } 1.23-2.33, I^2 = 96\%, P_{\text{heterogeneity}} < 0.00001$; Figure 3A). There were 488 events among 2032 patients

with DM, meanwhile, 3447 events among 24,833 patients without DM in case-control studies, the same results were also found in case-control studies (OR 1.59, 95% CI 1.28-1.97, $I^2 = 58\%, P_{\text{heterogeneity}} = 0.02$; Figure 3B). In the stratified analysis by gender, the risk of bladder cancer was increased in male (OR=1.49, 95% CI 1.05-

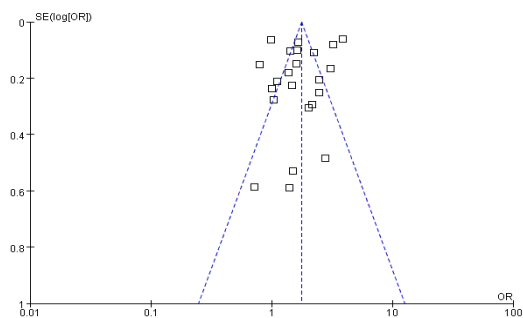


Figure 4. Funnel Plot for Publication Bias Amongst the Overall Studies Included in the Meta-analysis

2.09, $I^2=96\%$), and female (OR =1.65, 95% CI 1.12-2.44, $I^2=91\%$), with DM vs non DM, The difference was not statistically significant among male and female group (test for subgroup differences, $p=0.68$) (Figure 3C). For different geographical region, the risk of bladder cancer was increased in Asia group (OR=2.39, 95% CI 1.62-3.54, $I^2=87\%$), and North America group (OR=1.89, 95% CI 1.46-2.43, $I^2=86\%$), but not increased in Europe group (OR=1.14, 95% CI 0.94-1.40, $I^2=64\%$). The association between DM and bladder cancer risk was obviously higher in Asia group than North America group and Europe group (test for subgroup differences, $p=0.0004$) (Figure 3D). For Caucasian population, there was significant association between diabetes and increased bladder cancer risk (OR=1.54, 95% CI 1.22-1.93, $I^2=91\%$), the association between DM and bladder cancer risk was obviously higher among Asian (OR=2.44, 95% CI 1.66-3.59, $I^2=86\%$) than the risk among Caucasian (test for subgroup differences, $p<0.00001$). In the stratified analysis by adjustment for smoking, the risk of bladder cancer was increased in adjustment for smoking group (OR=2.12, 95% CI 1.70-2.64, $I^2=84\%$), and non-adjustment for smoking group (OR =1.33, 95% CI 0.87-2.03, $I^2=96\%$). The difference was not statistically significant among adjustment for smoking group and non-adjustment for smoking group (test for subgroup differences, $p=0.05$). In the stratified analysis by adjustment for BMI, the risk of bladder cancer was increased in adjustment for BMI group (OR=1.91, 95% CI 1.48-2.47, $I^2=87\%$), and non-adjustment for BMI group (OR =1.51, 95% CI 1.02-2.22, $I^2=96\%$) The difference was not statistically significant among adjustment for BMI group and non-adjustment for BMI group (test for subgroup differences, $p=0.31$). In the stratified analysis by adjustment for physical activity, the risk of bladder cancer was increased in adjustment for physical activity group (OR=2.36, 95% CI 1.62-3.43, $I^2=90\%$), and non-adjustment for physical activity group (OR =1.52, 95% CI 1.13-2.04, $I^2=95\%$) The difference was not statistically significant among adjustment for physical activity group and non-adjustment for physical activity group (test for subgroup differences, $p=0.07$). The main results of pooled odds ratios (ORs)/relative risk (RR) with confidence interval (CI) in the meta-analysis were presented in Table 2.

Publication bias

The shapes of the funnel plots seemed symmetrical for all analyses. No evidence of publication bias was found

in any subgroup analyses under different ethnic decent models. We showed the funnel plots of all studies (Figure 4), the funnel plots of other subgroups were not showed.

Discussion

It was estimated that 366 million people will have type 2 DM to 2030 (Wild et al., 2004) and it will become an increasingly grave public health problem all over the world. Other factors, environmental, demographic or clinical, may have an impact on the association between DM and the risk of bladder cancer. In this meta-analysis, we not only evaluate the potential differential effects on the association between DM and the risk of bladder cancer, but also analysis heterogeneity in the observed OR based on study type, gender, geographical region, adjustment for smoking, adjustment for BMI.

To date, associations between DM and bladder cancer risk have been evaluated in 39 studies and the reported risk estimates are inconsistent, with OR ranging from 0.71 to 3.87 and SIR/SMR ranging from 0.67 to 1.60. This time our meta-analysis focused on all these 23 included studies to evaluate one more precise result of the associations between DM and bladder cancer risk. Finally our meta-analysis provides strong evidence for the hypothesis that DM is a risk factor for bladder cancer (OR=1.68, 95% CI 1.32-2.13, $I^2=94\%$, $P_{\text{heterogeneity}} < 0.00001$). Sources of heterogeneity across studies and the possibility of publication bias were systematically explored by using subgroup analysis.

One study (Li et al., 2011) found that diabetic men had higher adjusted prevalence ratios for cancers of the urinary bladder than non-diabetic men ($P<0.05$), while diabetic women did not. Also in a study using the National Health Insurance in Taiwan (Tseng et al., 2011), male sex was a significant risk factor for the patients with diabetes have a higher risk of bladder cancer. On the contrary, the Iowa women's healthy study (Prizment et al., 2013) confirmed a positive association between diabetes and bladder cancer risk among white postmenopausal women. In our meta-analysis DM was associated with an increased risk of bladder cancer in both male and female group. But it did not make any difference between these two groups while the morbidity of bladder cancer is higher in men than women in the normal population (Parkin et al., 2005; Jemal et al., 2008).

An epidemiological study from England (Ng et al., 2003) found that diabetic patients had an increased, significant odds ratio for bladder cancer compared with non diabetics even after adjustment for smoking and age. But after analysis of all the eight studies from Europe, the risk of bladder cancer was not increased in Europe region (OR=1.14, 95% CI 0.94-1.40, $I^2=64\%$, $p=0.19$). On the contrary, most of studies from Asia and North America region confirmed that DM-associated bladder cancer was increased. Based on data from the studies in our meta-analysis, geographical region-related differences in DM-associated bladder cancer risks are different, the association between DM and bladder cancer risk was obviously higher among Asia than North America and Europe. Similarly, the association between DM and

bladder cancer risk was obviously higher among Asian than Caucasian. The reason of the geographical region and ethnicity difference need further study to review.

In a large cohort study (Newton et al., 2013), the risk of bladder cancer among patients with DM was higher in the first half of follow-up time (1992-1999), but not in the follow-up time from 2000 to 2007. Interestingly, for different follow-time group, the risk of bladder cancer was increased in first 20 years, but not increased in next 20 years in our meta-analysis. Maybe one of the reasons is apparent improvement in glucose control among patients with DM due to the well medical education and medicare coverage during the past decades in these studies (Ragozzino et al., 1982; Adami et al., 1991; Prizment et al., 2013;).

To our knowledge, this is an update meta-analysis to assess the the risk of bladder cancer associated with DM. The search work was thorough, systematic and authentic. Many new studies with a large number of samples which reported in recent years have been included in this meta-analysis. More subgroup analyses have been applied in our research than before. So our results indicate an authentic assessment of the etiological association. Nonetheless, several limitations of our meta-analysis demand comment. Firstly, the heterogeneity of authenticate of DM (such as by self-reported DM) may lead to attenuated risk estimates. Secondly, the incidence of DM and bladder cancer was observed in different nations worldwide and ecological fallacy may exist in our meta-analysis. Finally, the lack of a definite mechanism linking DM to bladder cancer is a major limitation for the interpretation of our findings.

In conclusion, there were significant associations existed between DM and increased bladder cancer risk. The increased risk was higher in Asia than North America and Europe region. Also, the increased risk was higher in Asian than Caucasian ethnicity. There was not gender difference in DM-associated bladder cancer risk. With the extension of follow-up time, the bladder cancer risk was not increased for the patients with DM. However, the presence of possible bias and confounding may have resulted in an overestimate of the relationship between DM and bladder cancer risk. So, more epidemiological and experimental research is needed to further explore the association between DM and bladder cancer risk.

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