ORIGINAL ARTICLE

Diabetes Mellitus Increases the Risk of Bladder Cancer: An Updated Meta-Analysis of Observational Studies

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Abstract

Background: Increasing evidence suggests that diabetes mellitus (DM) may be associated with an increased risk of bladder cancer. We performed an updated meta-analysis to examine the association between DM and risk of bladder cancer.

Materials and Methods: We systematically searched the EMBASE and Medline (PubMed) databases (from inception through February 1, 2013) and reviewed the reference lists of relevant publications to search for additional studies. Summary relative risks (RRs) with 95% confidence intervals (CIs) were calculated with random-effects models.

Results: In total, 10 case-control and 14 cohort studies met the inclusion criteria. Analysis of all studies showed that DM was associated with an increased risk of bladder cancer (RR 1.30, 95% CI 1.18–1.43). There was heterogeneity among studies ($P_{\text{heterogeneity}} < 0.001$, $I^2 = 81.5\%$). Cohort studies showed a lower risk (RR 1.23, 95% CI 1.09–1.37) than case-control studies (odds ratio 1.46, 95% CI 1.20–1.78). The positive association was significant only in women (RR 1.23, 95% CI 1.02–1.49), but not in men (RR 1.07, 95% CI 0.97–1.18). The combined RRs remained unchanged before and after the studies on type 1 diabetes were excluded from analysis. The association between DM and bladder cancer risk did not differ significantly by methods of DM ascertainment. The combined RRs were 1.17 (95% CI 1.03–1.34), 1.34 (95% CI 1.19–1.51), and 1.57 (95% CI 0.96–2.55), respectively, when restricting the analysis to the studies accounting for body mass index, cigarette smoking, or glucose-lowering drug use.

Conclusions: This meta-analysis indicates a positive association between DM and risk of bladder cancer. Further studies are warranted to determine whether DM prevention and control can reduce risk of bladder cancer.

Introduction

DIABETES MELLITUS (DM) HAS INCREASED worldwide in recent decades with changes in lifestyle and population aging. It is estimated that around the world more than 366 million people had DM in 2011, and the number is predicted to reach 552 million by 2030.¹ DM is associated with long-term complications that include cardiovascular disease, retinopathy, neuropathy, and nephropathy. Additionally, DM has been implicated as a risk factor for certain malignancies, including cancers of the colon/rectum, breast, and pancreas.^{2–4}

Bladder cancer is the sixth most common cancer in the United States.⁵ Several potential risk factors for bladder cancer have been established, including tobacco smoking, drinking water contaminants such as chlorinated byproducts and arsenic, and use of pioglitazone.^{6–8} A meta-analysis of epidemiologic studies suggested an increased risk of bladder cancer in relation to DM.⁹ Since then, many new epidemiological studies have examined the association of DM with the risk of bladder cancer, but results were inconsistent.^{10,11} Zhu et al.¹² published another relevant study, and this meta-analysis focused on co-

hort studies. Because of a lack of primary studies, there were only a few subgroup analyses. Although prospective cohort studies are expected to have eliminated the selection bias and recall bias that could be of concern in retrospective case-control studies, the consistent results from both cohort and case-control studies should be considered before establishing a causal relationship according to the criteria of Hill.¹³ Considering that long-term randomized trials are impossible to implement on a practical basis, case-control and cohort studies are the best evidence available to assess the association between DM and risk of bladder cancer; thus we included all recently published case-control and cohort studies in this meta-analysis.

Materials and Methods

Searching

We systematically identified studies through searching the EMBASE and Medline (PubMed) databases from their inception to February 1, 2013, for human studies of DM and bladder cancer in any language. The overall search strategy included the search term “diabetes” combined with “bladder cancer” or

“bladder neoplasm.” We also manually reviewed the reference lists of relevant publications to search for additional studies.

Inclusion and exclusion criteria

All studies were included, if they met the following criteria: (1) evaluation of DM and bladder cancer risk; (2) presenting original data from case-control or cohort studies; and (3) providing relative risk (RR) estimates with confidence intervals (CIs) or enough data to calculate them. Major exclusion criteria were (1) studies on mortality rates from bladder cancer or (2) studies that include evaluation of DM and bladder cancer risk with standardized incidence ratios. If the publications were duplicated or shared in more than one study, either the most recent publications or the publications with multivariate-adjusted estimates were included.

Data abstraction

Two investigators independently extracted the data and reached consensus on all items. The following information was sought from each study: the first author’s last name, year of the publication, country of study location, study design, type of DM (DM assessment), numbers of cases and controls (in case-control studies), type of control (in case-control studies), number of exposed and unexposed (in cohort studies), follow-up period (for cohort studies), risk of estimates with their corresponding CIs for bladder cancer associated with DM, and confounders considered. From each study, we extracted the risk estimate that was adjusted for the greatest number of potential confounders.

Statistical analysis

Major outcome variables were quantitative measures of the association between DM and bladder cancer risk. Because bladder cancer is a rare disease, odds ratios (ORs) from case-control studies and RRs from cohort studies produce comparable estimates. Summary RRs and their 95% CIs were calculated with the method of DerSimonian and Laird¹⁴ by the use of the assumptions of a random-effects model that considers both within-study and between-study variation. Separate and combined analyses were carried out for case-control and cohort studies. We examined possible heterogeneity in results across studies using the Q and I^2 statistics.¹⁵ For the Q statistic, a P value of <0.10 was considered representative of statistically significant heterogeneity. I^2 is the proportion of total variation contributed by between-study variation.¹⁵ The “leave one out” sensitive analysis¹⁶ was carried out using $I^2 > 50\%$ as the criterion to evaluate the key studies with substantial impact on between-study heterogeneity. In an attempt to evaluate the possible publication bias, Egger’s test (linear regression method)¹⁷ and Begg’s test (rank correlation method)¹⁸ were used, and a P value of <0.05 was considered representative of significant statistical publication bias. All statistical analyses were performed with STATA version 9.2 software (StataCorp, College Station, TX).

Results

Description of studies

Figure 1 shows a flow diagram of how we selected relevant studies. We identified 26 potentially relevant stud-

FIG. 1. Selection of studies for the meta-analysis.

ies.^{3,4,10,11,19–40} Two studies were excluded because of overlapping publications from the same study population.^{39,40} Thus, a total of 24 case-control and cohort studies met our inclusion criteria (Tables 1 and 2). Among these 24 studies, 10 were case-control studies, and 14 were cohort studies. All included studies were published between 1984 and 2013, of which 71% ($n=17$) were published in 2006 or more recently. Six studies were conducted in Europe, six in Asia, and 12 in North America. The study population in 17 studies consisted of both sexes, six studies included men only, and one study included women only. In total, 9,752,495 participants were included in these 24 studies. Because no detailed number of cases was available in two cohort studies,^{4,10} 40,410 bladder cancer cases were included among the 22 reported studies.

DM and bladder cancer risk

Ten case-control studies^{3,19–27} and 14 cohort studies^{4,10,11,28–38} were included in the meta-analysis. Analysis of all studies showed that, compared with individuals without DM, those with DM had a statistically significant increased risk of bladder cancer (RR 1.30, 95% CI 1.18–1.43) (Fig. 2). There was statistically significant heterogeneity among studies ($Q=129.96$, $P_{\text{heterogeneity}} < 0.001$, $I^2=81.5\%$). The key contributors of the articles to the between-study heterogeneity assessed by the “leave one out” sensitive analysis were three studies.^{23,32,34} After exclusion of the above-mentioned articles that were the key contributors to between-study heterogeneity, the meta-analysis also showed a significant association of DM and the risk of bladder cancer (RR 1.24, 95% CI 1.15–1.34; $P_{\text{heterogeneity}}=0.011$, $I^2=45.7\%$).

In the subgroup analyses (Table 3), a positive association was observed only in women (RR 1.23, 95% CI 1.02–1.49) but not in men (RR 1.07, 95% CI 0.97–1.18). Analyses stratified by study design showed that DM was associated with a greater risk of bladder cancer in case-control studies (RR 1.46, 95% CI

TABLE 1. MAIN CHARACTERISTICS OF COHORT STUDIES INCLUDED IN THE META-ANALYSIS, ARRANGED BY YEAR OF PUBLICATION

Reference (year)	Country (study period)	Sex	Age (years)	Cases	Years of follow-up	Cohort size	DM assessment	Adjustments
Jee et al. ⁴ (2005)	Korea (1992–2002)	M	30–95	NA	10	829,770	Blood glucose level or medication use (type 2)	Age, smoking, and alcohol
Inoue et al. ²⁸ (2006)	Japan (1990–2003)	M/F	40–79	105 M/30 F	10.7 (mean)	46,548 M/51,223 F	Self-report (type 1 and 2)	Age, study area, history of cerebrovascular disease, history of ischemic heart disease, smoking, ethanol intake, BMI, leisure-time physical activity, green vegetable intake, and coffee intake
Rapp et al. ²⁹ (2006)	Austria (1988–2001)	M	35–54	11 (ICD-9)	8.4 (mean)	63,585	Glucose levels (NA)	Age, smoking, occupational group, and BMI
Khan et al. ³⁰ (2006)	Japan (1988–1999)	M	40–79	60 (ICD-10)	11	23,378	Self-report (NA)	Age, smoking, BMI, and alcohol
Larsson et al. ¹¹ (2008)	Sweden (1998–2007)	M	45–79	414 (ICD-O-2)	9.3 (mean)	45,906	Self-report (NA)	Age, education, smoking status, and pack-years of smoking
Ogunleye et al. ³¹ (2009)	Scotland, United Kingdom (1993–2004)	M/F	All ages	68 (ICD-10)	1,417 days (mean)	28,731	Diagnosis of type 2 DM	Age, sex, and deprivation
Yood et al. ³² (2009)	United States (2000–2004)	M/F	18 years or older	243 (ICD-9; procedure codes; treatment codes)	4	442,512	Diagnosis of type 2 DM medication use	Age, gender, schistosomiasis, and pelvic radiation
Tseng ¹⁰ (2011)	Taiwan (2003–2005)	M/F	All ages	NA (ICD-9: 188)	3	998,947	Medical records (type 2)	Age, sex, nephropathy, urinary tract diseases, comorbidities, glucose-lowering drugs, living region, and occupation
Woolcott et al. ³³ (2011)	United States (1993–2004)	M/F	45–75	818 (ICD-O-2: C-67)	10.7 (mean)	185,816	Self-report (NA)	Age, ethnicity, sex, smoking, and employment
Atchison et al. ³⁴ (2011)	United States (1969–1996)	M	18–100	19,300 (ICD A-8 and ICD 9-CM:188)	10.5 vs. 11.9 (mean; men with vs. without diabetes)	4,501,578	Diagnosis of DM (NA)	Age, time, latency, race and number of visits, diagnoses of alcohol-related conditions, obesity and chronic obstructive pulmonary disease
Lo et al. ³⁵ (2012)	Taiwan (1996–2009)	M/F	NA	4311 (ICD-9-CM: 188.0)	14	1,790,868	Medical records (type 2)	Sex, age, urbanization, hypertension, and hyperlipidemia
Newton et al. ³⁶ (2012)	United States (1992–2007)	M/F	NA	1,852 (NA)	15	172,791	Self-report (exclusion if diagnosis < 30 years)	Age, sex, race, BMI, smoking status, education, and alcohol intake
Prizment et al. ³⁷ (2013)	United States (1986–2010)	F	55–69	277 (ICD-O-3: C670–679, 8120, 8122, 8123, or 8130)	24	37,327	Self-report (exclusion if diagnosis < 30 years)	Age, BMI, WHR, education, smoking status, pack-years of smoking, occupation, marital status, physical activity, and alcohol use
Lai et al. ³⁸ (2013)	United States (1995–2006)	M/F	50–71	4,331 (NA)	11	494,867	Self-report (type 1 and 2)	Age, sex, BMI, race/ethnicity, education, marital status, family history of cancer, self-reported health status, intake of red meat, white meat, fruits, vegetables, alcohol, and coffee, vigorous physical activity, physical activity at work, cigarette smoking, multivitamin use, and, for female-specific cancers, postmenopausal hormone therapy use

BMI, body mass index; F, female; M, male; NA, not available; WHR, waist-to-hip ratio.

TABLE 2. MAIN CHARACTERISTICS OF CASE-CONTROL STUDIES INCLUDED IN THE META-ANALYSIS, ARRANGED BY YEAR OF PUBLICATION

Reference (year)	Country	Sex	Age (years)	Cases	Controls (selection method)	DM assessment	Adjustments
Kantor et al. ¹⁹ (1984)	United States	M/F	21–84	2,982	5,782 (P)	Self-report (type 1 and 2)	Age, sex, race, and smoking
O'Mara et al. ²⁰ (1985)	United States	M/F	30–89	527	4,620 (H) ^a	Self-report (type 1 and 2)	Age
Risch et al. ²¹ (1988)	Canada	M/F	35–79	826	792 (P)	Self-report (type 2) ^b	Age, sex, place of residence, and smoking
La Vecchia et al. ²² (1994)	Italy	M/F	<75	431	7,834 (H)	Self-report (type 1 and 2)	Age and sex
Kravchick et al. ²³ (2001)	Israel	M/F	41–90	252	549 (H)	Self-report (type 1 and 2)	Age, sex, and smoking
Ng et al. ²⁴ (2003)	United Kingdom	M/F	>60	125	80 (H)	Medical records (types 1 and 2)	Age and smoking
Rousseau et al. ²⁵ (2006)	Canada	M	35–70	437	509 (P)	Self-report (type 1 and 2)	Age, family income, years of schooling, ethnicity, smoking, proxy status, BMI, β -carotene consumption, coffee consumption, and occupational exposure to aromatic amines
Jiang et al. ²⁶ (2009)	United States	M/F	25–64	1,586	1,586 (P)	Self-report (type 1 and 2)	Age, sex, smoking, education, NSAID pills, intake of carotenoids, and duration of employment as a hairdresser/barber
MacKenzie et al. ²⁷ (2011)	United States	M/F	25–74	331	263 (P)	Self-report (type 1 and 2)	Age, gender, smoking, BMI, and UTI
Attner et al. ³ (2012) ^c	Sweden	M/F	NA	1,093	8,043 (P)	Medical records (types 1 and 2)	Age, gender, obesity, and abnormal blood lipids

^aThe relative risk (and its 95% confidence interval) was derived by pooling the sex-specific relative risks, weighted by the inverse of their variance. The confidence interval was estimated from data provided in the article.

^bOnset of diabetes after age 20 years.

^cMultivariate analysis for the time interval 90–1,460 days prior to the diagnosis of cancer.

BMI, body mass index; F, female; H, hospital-based; M, male; NA, not available; NSAID, nonsteroidal anti-inflammatory drug; P, population-based; UTI, urinary tract infections.

1.20–1.78) than in cohort studies (RR 1.23, 95% CI 1.09–1.37; $n = 14$). In cohort studies, DM was not associated with the risk of bladder cancer in studies with follow-up time of below 10 years (RR 1.30, 95% CI 0.91–1.47),^{10,11,29,31,32} whereas a positive association was observed in the studies with follow-up time of 10 years or above (RR 1.17, 95% CI 1.04–1.31).^{4,28,30,33–38} A significant positive association was consistently observed in studies conducted in North America^{19–21,25–27,32–34,36–38} and Asia,^{4,10,23,28,30,35} but a null association was obtained from the studies conducted in Europe (RR 1.11, 95% CI 0.84–1.48).^{3,11,22,24,29,31} The summary estimate was slightly higher for studies published before 2005 (RR 1.39, 95% CI 1.12–1.73)^{4,19–24} than those after 2005 (RR 1.27, 95% CI 1.13–1.42).^{3,10,11,25–38} No difference was observed between the studies with self-reported DM and those with DM identified by medical records or medication use. The summary estimate was also similar for studies that included type 2 DM only (RR 1.34, 95% CI 1.14–1.58)^{4,10,21,31,32,35–37} and for those including both type 1 and type 2 DM (RR 1.37, 95% CI 1.16–1.63),^{3,19,20,22–28,38} but no association was found for studies in which the type of DM was not available (RR 1.10, 95% CI 0.91–1.33).^{11,29,30,33,34}

Obesity, cigarette smoking, and glucose-lowering drugs or insulin use are potential confounders for the association between DM and bladder cancer. When we restricted the analysis to the studies that had adjusted for body mass index (BMI) or obesity,^{3,25,27–30,34,36–38} the RR was 1.17 (95% CI 1.03–1.34). Among the 16 studies that controlled for cigarette smoking,^{4,11,19,21,23–30,33,36–38} the combined RR was 1.34 (95% CI 1.19–1.51). There were three studies^{10,21,27} that had adjusted for glucose-lowering drugs, and the combined RR was 1.57 (95% CI 0.96–2.55). Three studies^{10,27,36} comparing those with DM who used insulin with those without DM yielded a combined RR of 1.52 (95% CI 1.00–2.32).

In total, four studies^{10,27,36,37} examined the association of bladder cancer risk with the duration of DM. The combined RRs appeared higher among patients with a shorter duration of DM. Compared with subjects without DM, the combined RR was 1.25 (95% CI 0.93–1.68; $P_{\text{heterogeneity}} = 0.118$, $I^2 = 49.0\%$) for patients diagnosed with DM more than 10 years, 1.38 (95% CI 0.74–2.59; $P_{\text{heterogeneity}} = 0.048$, $I^2 = 74.4\%$) for those with DM duration of 5–10 years, and 1.52 (95% CI 1.09–2.12; $P_{\text{heterogeneity}} = 0.004$, $I^2 = 71.3\%$) for those with DM duration of 5 years or less. The combined RR of three studies evaluating

FIG. 2. Relative risks (RRs) for the association between diabetes mellitus and bladder cancer in case-control and cohort studies. The diamond denotes the pooled RR. Shaded rectangles indicate the RR in each study, with sizes inversely proportional to the SE of the RR. Horizontal lines indicate the 95% confidence interval (CI). M, men; W, women.

the association between DM and the risk of invasive bladder cancer was 1.13 (95% CI 0.93–1.39).^{11,27,36}

Publication bias

The funnel plot (Fig. 3) showed some asymmetry reflecting the relative absence of studies with small sample sizes and inverse associations. Egger's test for publication bias was statistically significant ($P=0.008$). However, Begg's test for publication bias was not statistically significant ($P=0.498$).

Discussion

The findings of this meta-analysis of 10 case-control studies and 14 cohort studies indicate that DM is associated with a moderate increased risk of bladder cancer. This association remained unchanged when subjects with confirmed type 2 DM included. Our meta-analysis showed significant between-

study heterogeneity, and then we carried out the "leave one out" sensitive analysis using $I^2 > 50\%$ as the criterion. After exclusion of three articles^{23,32,34} that were key contributors to the between-study heterogeneity, we found no significantly different RR. The summary RR was slightly higher for case-control studies than that for cohort studies, as well as for North American and Asian studies compared with that for European studies.

We included several newly published case-control and cohort studies in this updated meta-analysis, which allowed for a more detailed and accurate risk estimation than that of prior meta-analyses. The association between blood glucose levels and bladder cancer was stronger in women than in men in a very large cohort.⁴¹ Likewise, the positive association was only observed in women in our analysis, and that was different from results of the previous meta-analysis.¹² The subgroup analysis of women was based on only five studies. Therefore, it is premature to conclude that the positive

TABLE 3. META-ANALYSIS FOR DIABETES MELLITUS AND RISK OF BLADDER CANCER

Analysis	Number of studies	Summary estimate (95% CI)	Heterogeneity	
			I ² (%)	P value
All studies	24	1.30 (1.18–1.43)	81.5	<0.001
Gender				
Male	10	1.07 (0.97–1.18)	53.6	0.022
Female	5	1.23 (1.02–1.49)	28.1	0.234
Study design				
Cohort studies	14	1.23 (1.09–1.37)	84.3	<0.001
Case-control studies	10	1.46 (1.20–1.78)	61.7	<0.001
Duration of follow-up ^a				
<10 years	5	1.30 (0.91–1.47)	79.7	0.001
≥10 years	9	1.17 (1.04–1.31)	83.4	<0.001
Study areas				
Asia	6	1.37 (1.17–1.60)	56.8	0.031
Europe	6	1.11 (0.84–1.48)	54.5	0.052
North America	12	1.33 (1.15–1.54)	86.0	<0.001
Year of publication				
≤2005	7	1.39 (1.12–1.73)	65.5	0.008
>2006	17	1.27 (1.13–1.42)	83.1	<0.001
DM ascertainment				
MR, MU, or blood level	9	1.29 (1.09–1.52)	90.4	<0.001
Self-report	15	1.30 (1.15–1.48)	62.1	0.001
Type of DM				
Only type 2	8	1.34 (1.14–1.58)	81.1	<0.001
Type 1 and type 2	11	1.37 (1.16–1.63)	65.4	0.001
Type not reported	5	1.10 (0.91–1.33)	60.5	0.038
Adjustment for BMI or obesity				
Yes	10	1.17 (1.03–1.34)	69.4	<0.001
No	14	1.37 (1.21–1.56)	71.9	<0.001
Adjustment for cigarette smoking				
Yes	16	1.34 (1.19–1.51)	59.9	0.001
No	8	1.22 (1.03–1.45)	91.0	<0.001

^aIn cohort studies.

BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; MR, medical records; MU, medication use.

association only existed in women. We recommend further studies of high quality be undertaken in this area.

The association between the duration of DM and bladder cancer risk has been assessed in a few studies, and inconsistent results were found. The risk of bladder cancer increased with longer DM duration in one study,²⁷ whereas the risk was significant for DM diagnosed >1 year previously and decreased with increasing DM duration in a study from Taiwan.¹⁰ Our meta-analysis only found the positive association between those with DM duration of 5 years or less and bladder cancer risk. The mechanism behind these results has been proposed. Insulin has been hypothesized to be a cancer growth promoter, which could explain an increased cancer risk in adults with type 2 DM.^{42,43} As well, hyperinsulinemia has been proposed to be etiologically involved in cancer carcinogenesis. β -Cells in the pancreas may produce lower levels of endogenous insulin compared with the prediabetes state with long-term DM.⁴⁴ Then the risk of bladder cancer may be expected to diminished with the duration of DM. However, it is notable that only four studies were included in the subgroup analysis. Further studies are needed to identify this association between the duration of DM and risk of bladder cancer.

Only three studies assessed the association between insulin therapy for DM and bladder cancer risk. The relation between

DM using insulin and bladder cancer was stronger when we restricted the analysis to those studies. Type-specific bladder cancer risks among patients with DM have been described in three studies,^{11,27,36} and our meta-analysis found association between DM and the risks of invasive bladder cancer. However, maybe there were too few studies, and this could have been due to chance.²⁷

Our study has several potential limitations of the available data. First, DM status in most of the studies was based on self-report, which may lead to some misclassification. However, earlier studies have shown that self-reported responses for many common chronic diseases such as DM are reliable compared with medical records.⁴⁵ In the current analysis, we did not find significant different RRs between studies using medical records, medication use, or blood level as a means of DM ascertainment and using self-report data to determine DM status. Second, many studies did not distinguish between type 1 and type 2 DM. When we restricted the meta-analysis to those studies that consisted of patients with type 2 DM only, the relationship between DM and bladder cancer risk did not significantly alter. Third, some subgroup analyses were based on only a few studies. The subgroup analyses of Asia and Europe were based on only five studies, and the results need to be interpreted with caution. Moreover, as in any other meta-analysis, there is the possibility of publication

FIG. 3. Funnel plot analysis of the publication bias of the articles included about diabetes mellitus and bladder cancer. RR, relative risk.

bias because small studies with null results tend not to be published. The funnel plot showed some asymmetry, as studies with small sample sizes and low RR were missing. The presence of possible publication bias may have resulted in an overestimate of the relationship between DM and bladder cancer risk. Fourth, a limitation is methodological issue related to study design. In most cohort studies, bladder cancer ascertainment was based on cancer registry and medical records. Although nearly all the cases were histologically confirmed, reporting may be not completed, and occult cancers may not be recorded. Some misclassification of outcome is likely. Many cases in case-control studies were from hospitals or medical institutes, and these studies are susceptible to admission rate bias and prevalence-incidence bias, which could inflate the RRs. Finally, DM and bladder cancer share several risk factors that may confound the relationship. However, confounding cannot be fully excluded because our analyses were based on observational studies.

The possible mechanisms underlying the association of DM with bladder cancer risk have been inconclusive. Several possible mechanisms have been proposed, including the effects of hyperglycemia, insulin resistance, or hyperinsulinemia.^{46,47} However, the accumulation of experimental and epidemiological evidence is more consistent with the hyperinsulinemia hypothesis. Type 2 DM is associated with insulin resistance and compensatory hyperinsulinemia.⁴⁸ Most cancer cells express insulin receptors⁴⁹; thus hyperinsulinemia could promote carcinogenesis by directly stimulating the proliferating pathway after insulin receptors.⁵⁰ This hypothesis is supported by evidence that treatment with metformin, which increases insulin sensitivity and decreases hyperinsulinemia, is associated with a lower incidence of cancer in diabetes patients than in those being treated with insulin or sulfonylurea.^{51,52} Apart from the direct effects of

insulin on cancer cells, the effects of promoting tumor cell growth may also be mediated indirectly via insulin-like growth factor (IGF)-1 receptors. Elevated insulin concentrations reduce the level of IGF-binding protein 1,^{53,54} which in turn increases the amount of bioactive IGF-1.^{55,56} IGF-1 has mitogenic and anti-apoptotic activities and could act as a stimulus for growing preneoplastic and neoplastic cells.⁵⁷ It was suggested that patients with bladder cancer have higher plasma levels of IGF-1.⁵⁸

In summary, our analysis further suggests that DM is associated with an increased risk of bladder cancer. With a worldwide increasing prevalence of DM, the incidence of bladder cancer may increase. Our findings furthermore underline the importance of preventing the emerging worldwide epidemic of DM.

Author Disclosure Statement

No competing financial interests exist.

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