Association between diabetes or antidiabetic therapy and lung cancer: A meta-analysis

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ABSTRACT

Aims/Introduction: Diabetes can increase the risk of cancers at several sites, but the association between diabetes and lung cancer remains unclear. We aimed to provide the quantitative estimates for the association between diabetes or antidiabetic treatment and lung cancer risk in the present meta-analysis.

Materials and Methods: Cohort studies were identified by searching the PubMed database (January 1960 through October 2012) and manually assessing the cited references in the retrieved articles. Study-specific relative risks (RRs) and 95% confidence intervals (CIs) were estimated using a random-effects model. Study quality was assessed using the Newcastle–Ottawa scale.

Results: A total of 19 cohort studies were included in the present meta-analysis. Of these, 14 studies focused on the association between diabetes and lung cancer incidence, and seven studies focused on the association between antidiabetic treatment and lung cancer incidence. Compared with non-diabetic individuals, diabetic patients do not have an increased risk of lung cancer (RR = 1.04, 95% CI 0.87–1.24). The association between diabetes and lung cancer remained not statistically significant in subgroup analysis stratified by study characteristics, study quality, diabetes ascertainment or important confounders. A null association between insulin or biguanides therapy and lung cancer risk was found. However, the diabetic patients receiving thiazolidinedione (TZD) treatment had a 20% reduced risk of lung cancer than those without TZD treatment.

Conclusions: No association between diabetes and lung cancer risk was found. However, TZD treatment might reduce lung cancer risk in diabetic patients. (J Diabetes Invest, doi: 10.1111/jdi.12112, 2013)

KEY WORDS: Diabetes, Lung cancer, Meta-analysis

INTRODUCTION

Cancer is one of the major causes of death worldwide, and an estimated 12.7 million new cancer cases and 7.6 million cancer deaths occur annually. Lung cancer is one of the most common cancers worldwide according to incidence and mortality[1]. However, its etiology remains largely elusive, although research has confirmed that cigarette smoking, low intake of fruits and vegetables, and previous lung diseases are risk factors of lung cancer[2–4]. A number of epidemiological studies also showed that diabetes mellitus (DM) is a strong risk factor of several cancers, such as breast cancer[5], colorectal cancer[6], pancreatic cancer[7] and endometrial cancer[8]. Several hypotheses on biological mechanisms have been proposed to explain the plausible causal association between DM and the risk of these cancers. It is suggested that abnormal metabolism, including hyperglycemia[9] and hyperinsulinemia[10], might promote cancer development. Also, some epidemiological studies investigated the association between diabetes or antidiabetic treatment and lung cancer risk[11,12]. However, the results were inconclusive and conflicting.

The present meta-analysis aimed to quantitatively summarize results from published cohort studies to provide a more precise estimate of the association between diabetes or antidiabetic treatment and lung cancer incidence with study characteristics, diabetes ascertainment, study quality and potential confounders.

MATERIALS AND METHODS

Retrieval of Studies

We carried out a literature search of the PubMed database (from January 1960 through October 2012, published in English) for observational cohort studies that evaluated the effect of diabetes on the risk of lung cancer. We searched the relevant studies with the following text words and/or Medical Subject Heading (MeSH) terms: 'diabetes mellitus or diabetes or diabetic or antidiabetes drugs' and 'lung or trachea or bronchus' and 'cancer or neoplasm or carcinoma or tumor'. No restrictions were imposed. In addition, we reviewed the reference lists of the relevant articles to identify additional studies.

Inclusion and Exclusion Criteria

The inclusion criteria in the meta-analysis are set out as: (i) with original data from cohort studies or prospective nested

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case–control studies; (ii) reporting on the association between DM (mainly type 2 DM) and lung cancer incidence or the association between antidiabetic drugs and lung cancer in diabetic patients; (iii) one of the interested outcomes was lung cancer incidence; and (iv) rate ratio, hazard ratio or standardized incidence ratio (SIR) with their 95% confidence intervals (CIs; or data that can be used to calculate them) were reported. Studies were excluded if they provided only an estimate of the effect without means for calculating its CI. When there were several publications from the same population, only data from the most recent report were included. Studies with the interested exposure of type 1 diabetes only or diabetes diagnosed before 30 years-of-age were also excluded.

Data Extraction

The data extraction was carried out independently by two authors and included the following information from each publication: the first author's last name, publication year, the year the study was carried out, country of the study population, methods of ascertainment of diabetes, the number of participants with the outcome, cohort sample size, the sex of the participants, type of diabetes (type 1 or 2), estimated effects with their 95% CIs and covariates adjusted for in their analysis. We extracted the risk estimates when controlling for the most potential confounders.

Quality Assessment

The quality of each study was assessed independently by two authors according to the Newcastle–Ottawa Scale (NOS)[13]. The NOS for cohort studies or case–control studies consists of three parameters of quality: selection, comparability and exposure/outcome assessment. The NOS measures with a maximum of four stars for selection, two stars for comparability and three stars for exposure or outcome. We defined NOS scores of 1–3, 4–6, and 7–9 for low-, intermediate- and high-quality studies, respectively. Discrepancies between two authors were dealt with by a joint re-evaluation of the original article.

Statistical Analysis

Summary relative risks (RRs) and their 95% CIs were calculated using the random effect model (DerSimonian–Laird method), which considers within-study and between-study variation[14]. We used Cochran's Q test and I^2 statistics to assess heterogeneity among the studies. For the Q statistic, a P-value of <0.10 was considered statistically significant for heterogeneity[15]; for I^2, a value of more than 50% was considered as a measure of severe heterogeneity[16]. Sensitivity analysis and subgroup analysis were carried out in order to investigate the sources of heterogeneity in relative risk.

We carried out analysis stratified by: (i) geographic area; (ii) sex; (iii) diabetes ascertainment; (iv) study quality; (v) duration of follow up; (vi) body mass index (BMI) and; (vii) smoking status. Publication bias was evaluated by constructing a funnel plot and by Egger's test[17]. For Egger's test, a P-value of <0.10 was considered to be statistically significant publication bias. All statistical analyses were carried out with Stata SE 12 for Windows (Stata Corp, College Station, TX, USA).

RESULTS

Search Results

From 1,751 initial returns, 720 articles were excluded because they were review articles, case reports or studies in animals. A total of 975 articles were subsequently excluded after title/abstract review. By reviewing the reference list of relevant articles, six articles were added. After detailed evaluation, 41 articles were excluded due to not meeting our inclusion criteria, and two articles were excluded due to overlapping study population. Finally, a total of 19 articles were used in the present meta-analysis (Figure 1).

Characteristics of the Studies

The main characteristics of the 19 studies included in the present analysis are shown in Table 1. Of these studies, 18 studies[18–35] were cohort studies and one study[36] was a prospective nest case–control study. A total of 14 studies[18–30,35] focused on the association between diabetes mellitus and lung cancer incidence, and seven studies[29–34,36] focused on the association between antidiabetes treatment and lung cancer incidence. In terms of the geographical settings of the studies, eight studies were carried out in Europe, six in Asia and five in North America.

Among 14 cohort studies that reported an association between diabetes and the risk of lung cancer, 11 studies[19,20,22–30] used incidence rate ratios as the measure of RR, and three studies[18,21,35] used SIR as the measure of RR. According to the NOS, eight studies were of high quality and six studies were of intermediate quality. Out of the 14 studies, 12 studies included both men and women, and two studies consisted entirely of men[22] and women[29], respectively. The diagnosis of diabetes was self-reported in six studies, and medical reports in eight studies. These 14 cohort studies included a total of 7,736,565 participants (range 5,066–4,501,578), and reported 115,235 incident cases of lung cancer (range 56–102,427). Except for two studies[18,35] only adjusting age, the estimated effects of diabetes on lung cancer in other studies were obtained for adjusting several variables. Six studies controlled for smoking, and only one study controlled for lung disease.

We identified seven studies that reported an association between diabetic treatment and risk of lung cancer. Of these seven studies, one[36] was a prospective nested case–control study, and the others[29–34] were cohort studies. Most studies included both women and men, except for two studies that consisted of only men[34] and women[29], respectively. Among these seven studies, two studies[29,30] reported the relative risk compared with non-diabetics, whereas others reported RR compared with non-antidiabetic treatment in patients with diabetes. Of these seven studies, six studies[29–33,36] focused on the association between biguanide treatment and the risk of lung cancer,

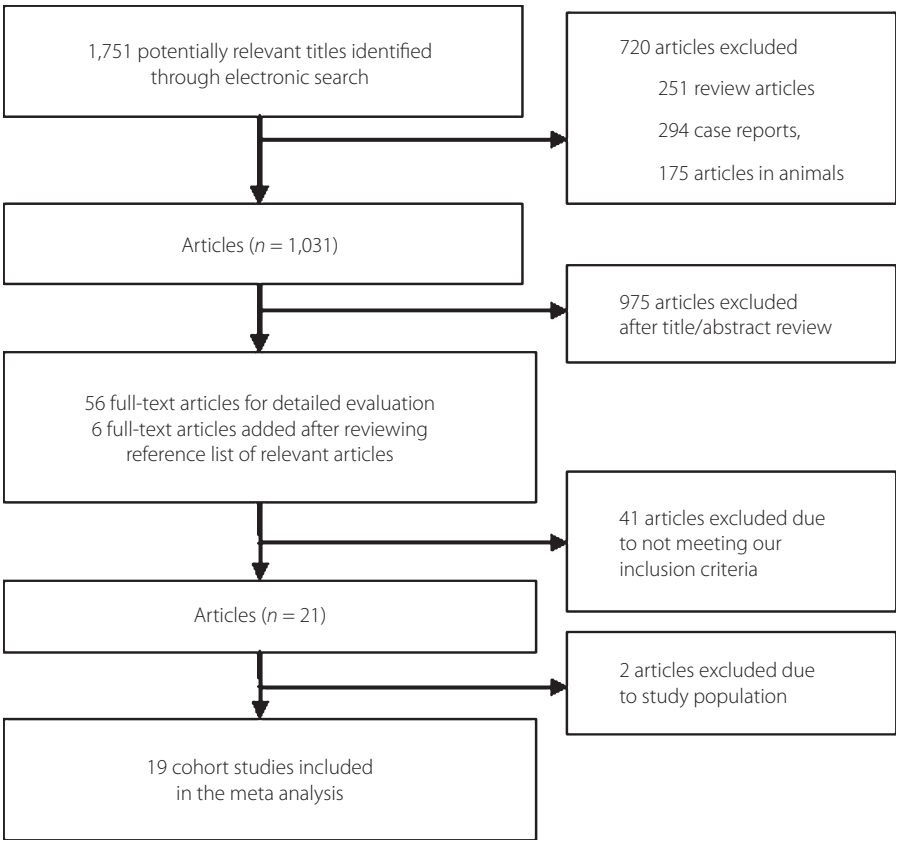

Figure 1 | Flow chart on the articles selection process.

four studies[29–31,33] focused on insulin therapy and the risk of lung cancer, and three studies[31,33,34] reported thiazolidinedione (TZD) treatment and the risk of lung cancer. These seven studies enrolled a total of 934,893 participants.

Analysis

Diabetes and the Risk of Lung Cancer

The pooled RRs from the 14 cohort studies are shown in Figure 2. In analysis of all 14 cohort studies, we obtained a summary relative risk (SRR) of 1.04 (95% CI 0.87–1.24) in a random-effects model for individuals with diabetes compared with individuals without diabetes. There was significant heterogeneity among these studies ($Q = 626.74$, $I^2 = 97.0\%$, $P < 0.001$).

In the sensitivity analysis, the overall heterogeneity and effect size were calculated by removing one study at one time. This analysis confirmed the stability of the null association between DM and lung cancer risk. For example, when we excluded the study of Atchison *et al.*[22] with the largest weight from the analysis, the estimated summary RR remained not significant (SRR = 1.06, 95% CI 0.90–1.25), still with significant heterogeneity ($I^2 = 92.7\%$, $P < 0.001$).

Then we carried out subgroup meta-analysis by various study characteristics (Table 2). In the subgroup analysis by geographic region, a non-significant association between diabetes and lung cancer risk was found for studies carried out in North America (SRR = 1.02, 95% CI 0.74–1.39), Asia (SRR = 1.10, 95% CI 0.94–1.29) and Europe (SRR = 1.00, 95% CI 0.74–1.35). In the analysis stratified by sex, diabetic men and women had a similar risk of lung cancer development compared with non-diabetic participants (men: SRR = 0.94, 95% CI 0.81–1.09; women: SRR = 1.08, 95% CI 0.93–1.26). We also found a null association between diabetes and lung cancer risk both in studies with follow-up duration of ≤20 years (SRR = 1.02, 95% CI 0.93–1.12) and >20 years (SRR = 1.06, 95% CI 0.55–2.03). In the analysis stratified by study quality, the association between diabetes and risk of lung cancer remained non-significant in high-quality studies (SRR = 1.10, 95% CI 0.82–1.46) and in intermediate studies (SRR = 0.97, 95% CI 0.85–1.11). The summary RR was consistent for studies ascertaining diabetes by medical record (SRR = 1.02, 95% CI 0.79–1.33) and by self-report (SRR = 1.07, 95% CI 1.00–1.15).

We also investigated the most important confounders, including BMI or obesity, smoking and lung disease. When the analysis was restricted to studies that controlled for BMI/obesity and smoking, we also found a null association between diabetes and lung cancer risk (SRR = 1.04, 95% CI 0.85–1.28). Only

Table 1 | Characteristics of 19 cohort studies of diabetes or antidiabetic therapy and lung cancer incidence

Name, year	Country	Sex	DM ascertainment	Follow up	Case	Sample	Quality scale (NOS)	Adjustments†
Diabetes and lung cancer incidence								
Steenland, 1995	USA	M/W	SR (type NA)	1971 – 1987	M:151; W:59	13,054	9/9	1, 4,6, 8,9, 10, 11
Lee, 2012	Taiwan, China	M/W	MR (type 2)	1998 – 2009	M:2777; W:1700	985,815	7/9	1, 2, 20, 22,23
Hemminki, 2010	Swedish	M/W	MR (type 2)	1964 – 2007	887	125,126	7/9	1, 2, 4, 5,12
Atchison, 2011	USA	M	MR (type 2)	1969 – 1996	102427	4,501,578	7/9	1, 3, 6, 9, 12, 15, 16, 28
Ogunleye, 2009	Scotland, UK	M/W	MR (type 2)	1993 – 2004	275	28,731	7/9	1, 2, 14
Swerdlow, 2005	UK	M/W	MR (type 2)	1972 – 2003	56	5,066	5/9	1, 2, 5, 13
Wideroff, 1997	Denmark	M/W	MR (type 2 and 1)	1977 – 1989	M:713; W:250	109,581	6/9	1, 2, 13
Inoue, 2006	Japan	M/W	SR (type 1 and 2)	1990 – 2003	M:547; W:198	97,771	8/9	1, 5, 6, 8, 9, 11, 17, 18, 25, 26
Jee, 2005	Koreans	M/W	SR (type 2)	1993 – 2002	NA	1,298,385	6/9	1, 8, 9
Khan, 2006	Japan	M/W	SR (type NA)	1988 – 1997	M:269; W:87	56,881	7/9	1, 6, 8, 9
Luo, 2012	USA	W	SR (type 2)	1998 – 2010	1951	145,765	8/9	1, 3, 4, 6, 7, 8, 9, 11, 17, 19, 37
Hall, 2005	UK	M/W	MR (type NA)	1987 – 2000	2659	334,120	7/9	1, 2, 8
Hense, 2011	Germany	M/W	SR (type 2)	2003 – 2008	M:121; W:42	26,742	5/9	1
Zhang, 2012	China	M/W	MR (type 2)	2002 – 2008	M:41; W:25	7,950	6/9	1
Antidiabetic therapy and lung cancer incidence								
Luo, 2012	USA	W	SR (type 2)	1998 – 2010	NA	145,765	8/9	1, 3, 4, 6, 7, 8, 9, 11, 17, 19, 37
Hall, 2005	UK	M/W	MR (type NA)	1987 – 2000	NA	334,120	7/9	1, 2, 8
Lai, 2012	Taiwan, China	M/W	MR (type 2)	2000 – 2008	629	98,120	7/9	1, 2, 28, 29, 31
Libby, 2009	UK	M/W	MR (type 2)	1993 – 2004	93	8,170	8/9	1,2, 6, 8, 14, 21,33
Ferrara, 2011	USA	M/W	MR (type 2)	1997 – 2005	1637	252,467	7/9	1, 2, 3, 4, 8, 13, 15, 21, 22, 27, 33
Govindarajan, 2007	USA	M	MR (type 2)	1997 – 2004	1110	87,678	5/9	1, 3, 6, 21, 33
Smiechowski, 2012	UK	M/W	MR (type 2)	1988 – 2009	808	8,573	8/9	1, 2, 6, 8, 9, 12, 13, 15, 21, 28, 32, 30, 33, 34, 35, 36

NA, data not applicable; M, man; W, woman; SR, Self-reported; MR, medical records. †1, age; 2, sex; 3, race/ethnicity; 4, education socioeconomic status or income; 5, region; 6, body mass index/obesity; 7, waist-to-hip ratio; 8, smoking; 9, alcohol; 10, recreational; 11, physical activity; 12, period; 13, calendar year, year of cohort entry; 14, deprivation; 15, diabetes duration/latency; 16, number of visits, 17, green vegetable/fruit intake; 18, coffee; 19,energy intake, 20, dyslipidemia; 21, baseline HbA1c; 22, creatinine; 23, history of hypertension; 24, gout; 25, history of cerebrovascular disease; 26, history of ischaemic heart disease; 27, congestive heart failure; 28, chronic obstructive pulmonary disease; 29, pulmonary tuberculosis; 30, asthma; 31, pulmonary propensity score; 32, previous cancer; 33, antidiabetic drugs; 34, nonsteroidal anti-inflammatory drugs; 35, aspirin; 36, statins; 37, history of hormone therapy use.

one study[22] consisted entirely of men controlled for lung disease. In that study, it was found that diabetic men had a reduced risk of lung cancer (RR = 0.79, 95% CI 0.77–0.80) compared with non-diabetic men.

Antidiabetic Treatment and Lung Cancer Incidence

Insulin Therapy and Lung Cancer Incidence

Luo *et al.*[29] reported a significantly increased risk of lung cancer for patients receiving insulin treatment as compared with non-diabetic subjects (RR = 1.71, 95% CI 1.15–2.53). However, Hall *et al.*[30] reported a non-significant association between insulin therapy and lung cancer risk (RR = 0.94, 95% CI 0.66–1.35) as compared with non-diabetic subjects. A null association between insulin therapy and lung cancer risk was reported by Lai *et al.* (RR = 1.00, 95% CI 0.68–1.45)[31] and Ferrara *et al.* (RR = 1.1, 95% CI 0.9–1.3)[33] compared with non-insulin treatment in patients with diabetes.

Biguanides Therapy and Lung Cancer Incidence

No significant association between biguanides therapy and lung cancer risk was found by Luo *et al.*[29] and Hall *et al.*[30] compared with non-diabetic subjects. Lai *et al.*[31] reported a significantly reduced risk of lung cancer for patients receiving biguanides therapy compared with non-biguanides therapy in patients with diabetes. However, another three studies[32,33,36] reported a null association between biguanides therapy and lung cancer risk compared with non-biguanides therapy in patients with diabetes. The pooled risk estimates were 0.91 (95% CI 0.8–1.03) with significant heterogeneity (I^2 = 65.4%, P = 0.034).

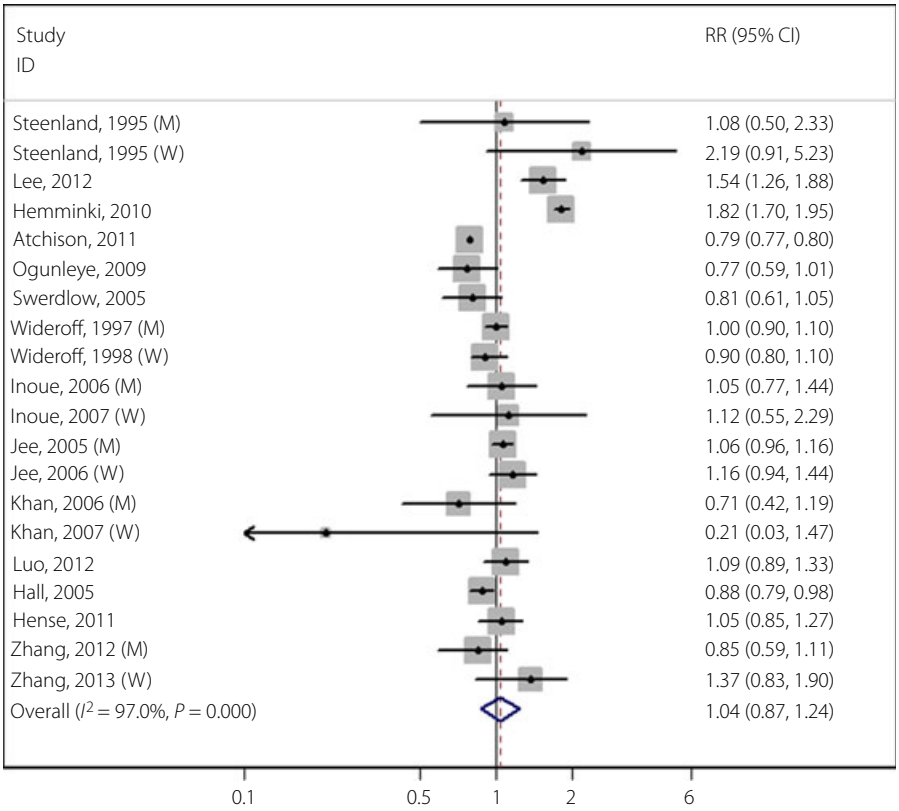

Figure 2 | Association between diabetes and lung cancer incidence. All statistical tests were two-sided. Statistical heterogeneity between studies was assessed with Cochran's *Q* test. Squares, study-specific relative risk (RR) estimate (size of the square reflects the study-specific statistical weight; i.e., the inverse of the variance); horizontal lines, 95% confidence interval (CI); diamond, summary relative risk estimate and corresponding 95% CI.

TZD Therapy and Lung Cancer Incidence

Govindarajan *et al.*[34] and Lai *et al.*[31] found a lower risk of lung cancer among diabetic patients with TZD treatment compared with non-TZD treatment. However, Ferrara *et al.*[33] reported a null association. The pooled risk estimates were 0.8 (95% CI 0.67–0.95) with significant heterogeneity (I^2 = 70.6%, P = 0.033).

Publication Bias

The Begg's funnel plot for the association between diabetes and lung cancer showed an apparent asymmetry, and the *P*-value for Egger's regression asymmetry test was 0.086 (Figure 3). These results suggested the presence of a potential publication bias, a language bias, inflated estimates by a flawed methodological design in smaller studies and/or a lack of publication of small trials with opposite results. For the small number of antidiabetic treatment studies, we could not evaluate the publication bias in the analysis.

DISCUSSION

To our knowledge, this is the first meta-analysis evaluating the relationship between diabetes including antidiabetic treatment and the incidence of lung cancer. Findings from this meta-analysis show that patients with diabetes do not have an increased risk of lung cancer compared with their non-diabetic counterparts. There were also no significant associations when evaluating the studies stratified by geographic region, sex, duration of follow up, study quality, diabetes ascertainment or most important confounders (BMI or obesity and smoking). The different subgroup analysis showed the same results. It indicates the validity of the conclusion.

A null association was also found between biguanides therapy, and insulin therapy and lung cancer risk. However, TZD therapy was associated with an estimated reduction of 20% in the risk of lung cancer among patients with type 2 diabetes compared with non-TZD treatment.

The lack of a positive association between a history of diabetes and lung cancer risk is particularly surprising, because several hypotheses have been suggested on the adverse biological interaction between diabetes and cancer risk. Patients with type 2 diabetes often have insulin resistance, compensatory hyperinsulinemia and elevated levels of insulin-like growth factor-1 (IGF-1)[37]. Insulin and IGF have been associated with increased cancer risk[38], and insulin can stimulate tumor cell proliferation, metastasis and IGF-1 (which has functions of mediating mitogenic and anti-apoptotic effects) production[39–42].

Table 2 | Summary relative risk (RR) estimates and 95% confidence intervals (CIs) for cohort studies of the association between diabetes and lung cancer incidence by study quality, geographical area, sex, duration of follow up, DM ascertainments and variable adjustments

Subgroup	No. of studies	Summary RR (95% CI)	Tests for heterogeneity		
			Q	*P*	I^2 statistics, %
Study quality					
High quality	8	1.10 (0.82 – 1.46)	168.53	<0.001	94.1
Intermediate quality	6	0.97 (0.85 – 1.11)	90.0	<0.001	79.73
Geographical area					
Europe	6	1.00 (0.74 – 1.35)	216.46	<0.001	97.2
North America	3	1.02 (0.74 – 1.39)	15.59	<0.001	80.8
Asia	5	1.10 (0.94 – 1.29)	20.91	0.007	61.7
Sex					
Man	8	0.94 (0.81 – 1.09)	62.09	<0.001	88.7
Woman	8	1.08 (0.93 – 1.26)	11.48	0.119	39.0
Duration of follow up					
≤20 years	11	1.02 (0.93 – 1.12)	41.26	<0.001	63.6
>20 years	3	1.06 (0.55 – 2.03)	527.65	<0.001	99.6
DM ascertainments					
MR	8	1.02 (0.79 – 1.33)	580.08	<0.001	98.4
SR	6	1.07 (1.00 – 1.15)	8.33	0.501	0.0
Adjustment for BMI and smoking	4	1.04 (0.85 – 1.28)	7.68	0.263	21.9

RR, relative risk; CI, confidence interval; DM, diabetes mellitus; MR, medical record; SR, self reported; BMI, body mass index.

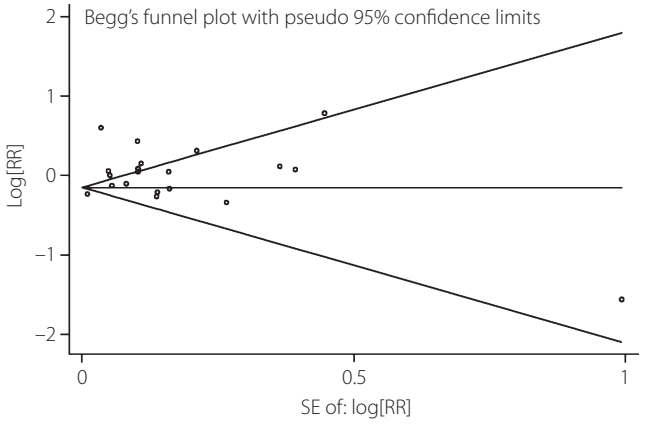

Figure 3 | Begg's funnel plot wit pseudo 95% confidence limits of cohort studies evaluating the association between diabetes and lung cancer risk. Egger's regression asymmetry test ($P = 0.086$). RR, relative risk; SE, standard error.

Data from physiological and clinical studies have shown that insulin and IGF-1 increased the risk of colorectal carcinogenesis[43]. The consequences of hyperglycemia on dysregulation of cholesterol metabolism, the rennin–angiotensin system (RAS) and adenosine monophosphate-activated protein kinase pathways led to carcinogenesis[44–48].

The present study showed that TZD treatment could reduce the risk of lung cancer by 20%, so this could be the reason for the null association between DM and lung cancer risk. Therefore, a possible association between diabetes and lung cancer risk cannot be precluded.

The present study had several strengths. First, the number of cases included was large and the studies included were all cohort studies or prospective nested case–control studies, suggesting that the present study showed solid evidence in evaluating the epidemiological association between DM and lung cancer risk. Second, the included studies originated from different countries, making the present results more generalized. Third, based on the NOS, all of the studies included in the present meta-analysis were of high quality or intermediate quality.

Nevertheless, several limitations of the present meta-analysis deserve mentioning. First, the majority of the included studies did not distinguish between type 1 and type 2 diabetes. Type 1 diabetes, which accounts for approximately 5–10% of all diagnosed cases of diabetes[47], could have a different association with the risk of lung cancer. Therefore, the risk estimates between type 2 diabetes and lung cancer could be slightly affected. Furthermore, because diabetes is an underdiagnosed disease, misclassification of exposure to diabetes is likely to influence the actual association between diabetes and lung cancer. Second, as the studies included in the present meta-analysis are all observational studies, the observed null association between diabetes and risk of lung cancer is inevitably impacted by confounding bias. Inadequate adjustments for some important confounders in the studies might result in a spurious association between diabetes and lung cancer risk. Obesity has been proved to reduce the risk of lung cancer[48]. Previous lung diseases and smoking were strongly associated with a diagnosis of lung cancer[2,3]. However, none of the included studies adjusted simultaneously for these factors. Four studies[19,26,28,29] adjusted for BMI and smoking, but without adjustment for lung diseases. Only one study[22] adjusted for lung diseases and obesity, but without adjustment for smoking. Other unmeasured confounders, such as physical activity, fruit and vegetable intake, and drinking, might also exert some effects on the results. Third, further studies on the association between antidiabetic treatment and the risk of lung cancer are required due to the small number of studies in the present meta-analysis. Some other antidiabetic treatments might also affect the association. Fourth, despite the use of a random-effects model and subgroup analysis, significant heterogeneity still existed. Fifth, hyperglycemic severity or glycated hemoglobin levels were not included in those original articles used in the present meta-analysis, so we could not further analyze the association between cancer prevalence and hyperglycemic severity. In addition, the types of lung cancer are not provided either, so we

could not compare the risk of cancer with DM or antidiabetic medications in each type of lung cancer. Finally, the possibility of publication bias might exist, because related studies were identified from limited databases, and studies with null results tend to be unpublished.

In conclusion, the present meta-analysis found no evidence to support a hypothesis that diabetes could increase the risk of lung cancer, which is further supported by consistent results from various subgroup analyses. A null association between biguanides therapy or insulin therapy and lung cancer risk was also found. However, TZD therapy was associated with an estimated 20% reduction of the risk of lung cancer among patients with type 2 diabetes.

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REFERENCES

1. Jemal A, Bray F, Center MM, *et al*. Global cancer statistics. *CA Cancer J Clin* 2011; 61: 69–90.
2. Brenner DR, Boffetta P, Duell EJ, *et al*. Previous lung diseases and lung cancer risk: a pooled analysis from the International Lung Cancer Consortium. *Am J Epidemiol* 2012; 176: 573–585.
3. Powell HA, Iyen-Omofoman B, Baldwin DR, *et al*. Chronic obstructive pulmonary disease and risk of lung cancer: the importance of smoking and timing of diagnosis. *J Thorac Oncol* 2013; 8: e34–e35.
4. Biesalski HK, Bueno de Mesquita B, Chesson A, *et al*. European Consensus Statement on Lung Cancer: risk factors and prevention. Lung cancer panel. *CA Cancer J Clin* 1998; 48: 167–176; discussion 4–6.
5. Hardefeldt PJ, Edirimanne S, Eslick GD. Diabetes increases the risk of breast cancer: a meta-analysis. *Endocr Relat Cancer* 2012; 19: 793–803.
6. Jiang Y, Ben Q, Shen H, *et al*. Diabetes mellitus and incidence and mortality of colorectal cancer: a systematic review and meta-analysis of cohort studies. *Eur J Epidemiol* 2011; 26: 863–876.
7. Ben Q, Xu M, Ning X, *et al*. Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. *Eur J Cancer* 2011; 47: 1928–1937.
8. Friberg E, Orsini N, Mantzoros CS, *et al*. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia* 2007; 50: 1365–1374.
9. Yang XL, Chan JC. Diabetes, insulin and cancer risk. *World J Diabetes* 2012; 3: 60–64.
10. Rosta A. Diabetes and cancer risk: oncologic considerations. *Orv Hetil* 2011; 152: 1144–1155.
11. Currie CJ, Poole CD, Jenkins-Jones S, *et al*. Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. *Diabetes Care* 2012; 35: 299–304.
12. Chang CH, Lin JW, Wu LC, *et al*. Association of thiazolidinediones with liver cancer and colorectal cancer in type 2 diabetes mellitus. *Hepatology* 2012; 55: 1462–1472.
13. Nos. The Newcastle-Ottawa Scale (Nos) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. Available from: http://wwwohrica/programs/clinical_epidemiology/oxfordasp.
14. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177–188.
15. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med* 1997; 127: 820–826.
16. Higgins JP, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557–560.
17. Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.
18. Hense HW, Kajuter H, Wellmann J, *et al*. Cancer incidence in type 2 diabetes patients – first results from a feasibility study of the D2C cohort. *Diabetol Metab Syndr* 2011; 3: 15.
19. Steenland K, Nowlin S, Palu S. Cancer incidence in the National Health and Nutrition Survey I. Follow-up data: diabetes, cholesterol, pulse and physical activity. *Cancer Epidemiol Biomarkers Prev* 1995; 4: 807–811.
20. Lee MY, Lin KD, Hsiao PJ, *et al*. The association of diabetes mellitus with liver, colon, lung, and prostate cancer is independent of hypertension, hyperlipidemia, and gout in Taiwanese patients. *Metabolism* 2012; 61: 242–249.
21. Hemminki K, Li X, Sundquist J, *et al*. Risk of cancer following hospitalization for type 2 diabetes. *Oncologist* 2010; 15: 548–555.
22. Atchison EA, Gridley G, Carreon JD, *et al*. Risk of cancer in a large cohort of U.S. veterans with diabetes. *Int J Cancer* 2011; 128: 635–643.
23. Ogunleye AA, Ogston SA, Morris AD, *et al*. A cohort study of the risk of cancer associated with type 2 diabetes. *Br J Cancer* 2009; 101: 1199–1201.
24. Swerdlow AJ, Laing SP, Qiao Z, *et al*. Cancer incidence and mortality in patients with insulin-treated diabetes: a UK cohort study. *Br J Cancer* 2005; 92: 2070–2075.
25. Wideroff L, Gridley G, Mellemkjaer L, *et al*. Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. *J Natl Cancer Inst* 1997; 89: 1360–1365.
26. Inoue M, Iwasaki M, Otani T, *et al*. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. *Arch Intern Med* 2006; 166: 1871–1877.
27. Jee SH, Ohrr H, Sull JW, *et al*. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* 2005; 293: 194–202.
28. Khan M, Mori M, Fujino Y, *et al*. Site-specific cancer risk due to diabetes mellitus history: evidence from the Japan

Collaborative Cohort (JACC) Study. *Asian Pac J Cancer Prev* 2006; 7: 253–259.
29. Luo J, Chlebowski R, Wactawski-Wende J, *et al.* Diabetes and lung cancer among postmenopausal women. *Diabetes Care* 2012; 35: 1485–1491.
30. Hall GC, Roberts CM, Boulis M, *et al.* Diabetes and the risk of lung cancer. *Diabetes Care* 2005; 28: 590–594.
31. Lai SW, Liao KF, Chen PC, *et al.* Antidiabetes drugs correlate with decreased risk of lung cancer: a population-based observation in Taiwan. *Clin Lung Cancer* 2012; 13: 143–148.
32. Libby G, Donnelly LA, Donnan PT, *et al.* New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes Care* 2009; 32: 1620–1625.
33. Ferrara A, Lewis JD, Quesenberry CP Jr, *et al.* Cohort study of pioglitazone and cancer incidence in patients with diabetes. *Diabetes Care* 2011; 34: 923–929.
34. Govindarajan R, Ratnasinghe L, Simmons DL, *et al.* Thiazolidinediones and the risk of lung, prostate, and colon cancer in patients with diabetes. *J Clin Oncol* 2007; 25: 1476–1481.
35. Zhang PH, Chen ZW, Lv D, *et al.* Increased risk of cancer in patients with type 2 diabetes mellitus: a retrospective cohort study in China. *BMC public health* 2012; 12: 567.
36. Smiechowski BB, Azoulay L, Yin H, *et al.* The use of metformin and the incidence of lung cancer in patients with Type 2 diabetes. *Diabetes Care* 2013; 36: 124–129.
37. Bach LA, Rechler MM. Insulin-like growth factors and diabetes. *Diabetes Metab Rev* 1992; 8: 229–257.
38. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer* 2008; 8: 915–928.
39. Ulanet DB, Ludwig DL, Kahn CR, *et al.* Insulin receptor functionally enhances multistage tumor progression and conveys intrinsic resistance to IGF-1R targeted therapy. *Proc Natl Acad Sci USA* 2010; 107: 10791–10798.
40. Douglas JB, Silverman DT, Pollak MN, *et al.* Serum IGF-I, IGF-II, IGFBP-3, and IGF-I/IGFBP-3 molar ratio and risk of pancreatic cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev* 2010; 19: 2298–2306.
41. Colao A, Pivonello R, Auriemma RS, *et al.* The association of fasting insulin concentrations and colonic neoplasms in acromegaly: a colonoscopy-based study in 210 patients. *J Clin Endocrinol Metab* 2007; 92: 3854–3860.
42. LeRoith D, Roberts CT Jr. The insulin-like growth factor system and cancer. *Cancer Lett* 2003; 195: 127–137.
43. Sandhu MS, Dunger DB, Giovannucci EL. Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. *J Natl Cancer Inst* 2002; 94: 972–980.
44. Yang X, Ko GT, So WY, *et al.* Associations of hyperglycemia and insulin usage with the risk of cancer in type 2 diabetes: the Hong Kong diabetes registry. *Diabetes* 2010; 59: 1254–1260.
45. Yang X, So WY, Ma RC, *et al.* Diabetes and cancer: the mechanistic implications of epidemiological analyses from the Hong Kong Diabetes Registry. *Diabetes Metab Res Rev* 2012; 28: 379–387.
46. Morss AS, Edelman ER. Glucose modulates basement membrane fibroblast growth factor-2 via alterations in endothelial cell permeability. *J Biol Chem* 2007; 282: 14635–14644.
47. Engelgau MM, Geiss LS, Saaddine JB, *et al.* The evolving diabetes burden in the United States. *Ann Intern Med* 2004; 140: 945–950.
48. Yang Y, Dong J, Sun K, *et al.* Obesity and incidence of lung cancer: a meta- analysis. *Int J Cancer* 2013; 132: 1162–1169.

