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. 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. A number of epidemiological studies also showed that diabetes mellitus (DM) is a strong risk factor of several cancers, such as breast cancer, colorectal cancer, pancreatic cancer and endometrial cancer. 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 and hyperinsulinemia, might promote cancer development. Also, some epidemiological studies investigated the association between diabetes or antidiabetic treatment and lung cancer risk. 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
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)\textsuperscript{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\textsuperscript{14}. We used Cochran’s Q test and I\textsuperscript{2} statistics to assess heterogeneity among the studies. For the Q statistic, a P-value of <0.10 was considered statistically significant for heterogeneity\textsuperscript{15}; for I\textsuperscript{2}, a value of more than 50% was considered as a measure of severe heterogeneity\textsuperscript{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\textsuperscript{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\textsuperscript{18–35} were cohort studies and one study\textsuperscript{36} was a prospective nested case–control study. A total of 14 studies\textsuperscript{18–30,35} focused on the association between diabetes mellitus and lung cancer incidence, and seven studies\textsuperscript{29–34,36} focused on the association between antidiabetic 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\textsuperscript{19,20,22–30} used incidence rate ratios as the measure of RR, and three studies\textsuperscript{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. Of the 14 studies, 12 studies included both men and women, and two studies consisted entirely of men\textsuperscript{22} and women\textsuperscript{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\textsuperscript{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 antidiabetic treatment and risk of lung cancer. Of these seven studies, one\textsuperscript{36} was a prospective nested case–control study, and the others\textsuperscript{29–34} were cohort studies. Most studies included both women and men, except for two studies that consisted of only men\textsuperscript{34} and women\textsuperscript{35}, respectively. Among these seven studies, two studies\textsuperscript{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\textsuperscript{29–33,36} focused on the association between biguanide treatment and the risk of lung cancer,
four studies focused on insulin therapy and the risk of lung cancer, and three studies 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 both in studies with follow-up duration of ≤20 years (SRR = 1.02, 95% CI 0.93–1.26). We also found a null association between diabetes and lung cancer risk in studies with follow-up duration of >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 = 1.04, 95% CI 0.85–1.28). Only 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 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 = 1.04, 95% CI 0.85–1.28).

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).

**Figure 1** | Flow chart on the articles selection process.

720 articles excluded
251 review articles
294 case reports,
175 articles in animals
975 articles excluded after title/abstract review
41 articles excluded due to not meeting our inclusion criteria
2 articles excluded due to study population
19 cohort studies included in the meta analysis

1,751 potentially relevant titles identified through electronic search
Articles (n = 1,031)
56 full-text articles for detailed evaluation
6 full-text articles added after reviewing reference list of relevant articles
Articles (n = 21)

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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† |
|---------------------|-----|------------------|-----------|------|--------|-------------------|-------------|
| 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, Sweden | 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 |
| Wilderoff, 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 |

one study22 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)33 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.33 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 studies22,32,33,36 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 (I² = 65.4%, P = 0.034).
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 (I² = 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 risk38, and insulin can stimulate tumor cell proliferation, metastasis and IGF-1 (which has functions of mediating mitogenic and anti-apoptotic effects) production39-42.
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,46 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 studies19,26,28,29 adjusted for BMI and smoking, but without adjustment for lung diseases. Only one study22 adjusted for lung diseases and obesity, but without adjustment for smoking. Other unmeasured founders, 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

Data from physiological and clinical studies have shown that insulin and IGF-1 increased the risk of colorectal carcinogenesis43. The consequences of hyperglycemia on dysregulation of cholesterol metabolism, the rennin-angiotensin system (RAS) and adenosine monophosphate-activated protein kinase pathways led to carcinogenesis44–48.

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 ascertainment and variable adjustments

| Subgroup | No. of studies | Summary RR (95% CI) | Tests for heterogeneity |
|----------|---------------|---------------------|------------------------|
|          |               | Q   | P   | I²  |
| 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) | 90.00 | <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 ascertainment |               |     |     |     |
| 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 with 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.
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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