Diabetes but Not Insulin Increases the Risk of Lung Cancer: A Taiwanese Population-Based Study

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Abstract

Background: The trend of lung cancer incidence in Taiwan is unknown, and the association between type 2 diabetes/insulin use and lung cancer is rarely studied.

Methods: The trends of lung cancer incidence in 1979–2007 in the Taiwanese general population were calculated. A random sample of 1,000,000 subjects covered by the National Health Insurance in 2005 was recruited. A total of 494,002 men and 502,948 women and without lung cancer were followed for the annual cumulative incidence of lung cancer in 2005, with calculation of the risk ratios between diabetic and non-diabetic subjects. Logistic regression estimated the adjusted odds ratios for risk factors.

Results: The trends increased significantly in both sexes (P<0.0001). The sex-specific annual cumulative incidence increased with age in either the diabetic or non-diabetic subjects, but the risk ratios attenuated with age. In logistic regressions, diabetes was associated with a significantly higher risk, with odds ratios (95% confidence interval) for diabetes duration <1, 1–3, 3–5 and ≥5 years versus non-diabetes of 2.189 (1.498-3.200), 1.420 (1.014-1.988), 1.545 (1.132-2.109), and 1.329 (1.063-1.660), respectively. Such an association was not related to a higher detection with chest X-ray examination. Insulin use and medications including oral anti-diabetic drugs, statin, fibrate, and anti-hypertensive agents were not significantly associated with lung cancer. Age, male sex, and chronic obstructive pulmonary disease were positively; but dyslipidemia, stroke and higher socioeconomic status were negatively associated with lung cancer.

Conclusions: Diabetes is significantly associated with a higher risk of lung cancer, but insulin use does not increase the risk.

Introduction

Lung cancer is the most common cancer around the world [1]. In Taiwan, lung cancer is currently the third most common cancer in either sex, but it ranks as the second and first cancerous killer in men and women, respectively [2]. There has been no report on the secular trends of lung cancer incidence in Taiwan over the past decades. Diabetic patients are prone to develop cancer involving pancreas, liver, breast, colorectum, bladder and endometrium [3]. However, the association between diabetes and lung cancer is rarely studied. Studies conducted in western countries showed contradictory results. In earlier studies from UK [4] and the USA [5], diabetes was not associated with the risk of lung cancer. However, two recent studies, from Denmark [6] and Sweden [7], respectively, suggested a significantly higher risk of lung cancer in the diabetic patients.

Insulin use has been implicated as a risk factor for cancer [3]. However, whether insulin use would increase the risk of lung cancer is an issue that has not been extensively investigated. In the UK study, insulin therapy with or without oral anti-diabetic agents was not associated with lung cancer [4], but in the Danish study both insulin users and non-users have significantly higher risk of lung cancer [6]. None of the studies have compared the risk between insulin users and non-users.

Because diabetes affects hundreds of millions of people worldwide and insulin is commonly used for the control of blood glucose in patients with type 2 diabetes mellitus (T2DM), it is important to elucidate the link between T2DM/insulin use and lung cancer. The purpose of the present study was to evaluate 1) the trends of lung cancer incidence in the Taiwanese general population from 1979 to 2007 by using the Taiwan Cancer Registry database; and 2) the association between T2DM/insulin use and lung cancer by analyzing the National Health Insurance (NHI) reimbursement database.

Materials and Methods

Trends of lung cancer incidence in 1979–2007

The study was approved by the National Health Research Institutes of Taiwan (Registered number 99274). The trends of
both crude and age-standardized (to the 2000 World Health Organization population) lung cancer incidence in 1979–2007 in the general population were first calculated from the released database (available online) of the Taiwan Cancer Registry [8]. The population-based registry was established in 1979 and supported by the Department of Health of Taiwan. It is an ongoing registry including all hospitals with more than 50 beds in Taiwan. Newly diagnosed cases of cancer should be reported and the completeness and accuracy are evaluated each year. The proportion of histologically verified cases of lung cancer was 92.7% [2].

**Annual incidence of lung cancer in 2005 and related risk factors**

According to the Ministry of Interior, Taiwan, in 2005, > 98.0% of the Taiwanese population (22,770,383: 11,562,440 men and 11,207,943 women) was covered by the NHI. A random sample of 1,000,000 people insured by the NHI in 2005 was created by the National Health Research Institutes for academic research. The National Health Research Institutes is the only organization approved, as per local regulations, for conducting sampling of a representative sample of the whole population for the year 2005 with a predetermined sample size of 1,000,000 individuals. The reimbursement databases of these sampled individuals were retrieved and could be provided for academic research after approval. The identification information was scrambled for the protection of the privacy of the sampled individuals. The reimbursement databases from 1996 onward were available. Sex, birth date, medications, and diagnostic codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) were retrieved for analyses in this study. Diabetes was coded 250.1-250.9 and lung cancer, 162. Figure 1 shows a flowchart used for selecting cases in this study. After excluding subjects with type 1 diabetes (in Taiwan, patients with type 1 diabetes were issued a ‘Severe Morbidity Card’ after certified diagnosis), subjects for whom the living region was not known, and subjects diagnosed with lung cancer before 2005, 494,002 men and 502,948 women were recruited for the calculation of the annual incidence of lung cancer in 2005.

**Statistical analyses**

Analyses were conducted using the SAS statistical software, version 9.1 (SAS Institute, Cary, NC). *P* < 0.05 was considered statistically significant.

Linear regression evaluated whether the trends of lung cancer incidence in 1979–2007 in the general population changed significantly, where the incidence was the dependent and the calendar year the independent variable.

The age- and sex-specific annual cumulative incidences of lung cancer in 2005 in diabetic and non-diabetic subjects were calculated for all ages and age $\leq 40$, 40–64, 65–74 and $\geq 75$ years. The numerator was the number of patients with a first diagnosis of lung cancer within 2005; and the denominator was the number of insurants in that specific group. The risk ratio between diabetic and non-diabetic subjects was calculated and the 95% confidence interval (CI) estimated by Taylor series approximation [9]. To minimize the possibility that diabetes might be caused by lung cancer, lag time sensitivity analyses were performed by excluding patients with diabetes duration of $<5$ years.

Logistic regression calculated the adjusted odds ratios. Lung cancer was the dependent variable and the independent variables included age ($<40$, 40–64, 65–74 and $\geq 75$ years), diabetes duration (non-diabetes, $<1$, 1–3, 3–5 and $\geq 5$ years), chest X-ray examination (CXR), comorbidities, medications, living region and occupation. CXR is the most commonly used screening tool for lung cancer [10,11] and was included in the models to control for the potential detection bias through screening. The comorbidities (ICD-9-CM codes) included hypertension (401-405), chronic obstructive pulmonary disease (COPD, 490-496, a surrogate for smoking), stroke (430–438), nephropathy (580–589), ischemic...
heart disease (410–414), peripheral arterial disease (250.7, 785.4, 443.81, 440–448), eye disease (250.5, 362.0, 369, 366.41, 365.44), obesity (278) and dyslipidemia (272.0–272.4). Medications included statin, fibrate, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, calcium channel blocker, sulfonylurea, metformin, insulin, acarbose, pioglitazone and rosiglitazone. Insulin use was categorized as yes versus no (model I), and according to the duration of its use of <5 years and ≥5 years versus non-users (model II). Comorbidities and medications were counted only as they appeared before 2005 to assure temporal correctness of cause and effect (lung cancer). The NHI insurants were classified according to occupation and this served as a surrogate for socioeconomic status. The living region served as a surrogate for geographical distribution of some environmental exposure. Occupation was categorized as I: civil servants, teachers, employees of governmental or private business, professionals and technicians; II: people without particular employers, self-employed or seamen, III: farmers or fishermen; and IV: low-income families supported by social welfare or veterans. Living region was categorized as Taipei, Northern, Central, Southern and Kaoping/Eastern. The regressions were performed for all ages and for age ≥40 years, separately.

Results

Figure 2 shows the crude and age-standardized incidence trends in 1979–2007. Both are increasing significantly in either sex (\(P<0.0001\)).

Table 1 shows the cumulative incidences and the risk ratios between the diabetic and non-diabetic subjects. The cumulative incidence markedly increased with age in either the diabetic or

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Figure 2. Trends of lung cancer incidence in the general population of Taiwan from 1979 to 2007 (diamonds: crude rates, squares: age-standardized rates using the 2000 World Health Organization population as referent).

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non-diabetic subjects. Risk ratio analysis showed that diabetic patients had a higher risk than non-diabetic subjects in all age groups, though the risk ratios attenuated with increasing age and would not be significant in the older age groups in either sex.

Table 2 shows the results of the logistic regressions for all ages and for age ≥40 years, respectively. The results were similar in models I and II. Only the odds ratios for age, sex, diabetes duration and insulin use are shown for the models conducted for

| Sex/Rate/Risk ratio | Age (years) | All ages | <40 | 40–64 | 65–74 | ≥75 |
|---------------------|-------------|----------|-----|-------|-------|-----|
| **Men**             |             |          |     |       |       |     |
| **Diabetes of any duration** | | | | | | |
| **Diabetic men**    |             |          |     |       |       |     |
| n of lung cancer    | 183         | 2        | 40  | 53    | 88    |     |
| n of diabetic men   | 51934       | 6978     | 26361| 9883  | 8712  |     |
| Rate in diabetic men| 352.37      | 28.66    | 151.74| 536.27| 1010.10|     |
| **Non-diabetic men**|             |          |     |       |       |     |
| n of lung cancer    | 278         | 13       | 92  | 62    | 111   |     |
| n of non-diabetic men| 442080    | 282848   | 128347| 17755 | 13130 |     |
| Rate in non-diabetic men| 62.88      | 4.60     | 71.68| 349.20| 845.39|     |
| Risk ratio (95% CI) | 5.60 (4.65–6.75)| 6.24 (1.41–27.63) | 2.12 (1.46–3.07) | 1.54 (1.07–2.21)| 1.19 (0.90–1.58)|     |
| **Excluding diabetes diagnosed <5 years** | | | | | | |
| **Diabetic men**    |             |          |     |       |       |     |
| n of lung cancer    | 109         | 2        | 24  | 29    | 54    |     |
| n of diabetic men   | 29730       | 3221     | 14029| 6438  | 6042  |     |
| Rate in diabetic men| 366.63      | 62.09    | 171.07| 450.45| 893.74|     |
| **Non-diabetic men**|             |          |     |       |       |     |
| n of lung cancer    | 278         | 13       | 92  | 62    | 111   |     |
| n of non-diabetic men| 442080    | 282848   | 128347| 17755 | 13130 |     |
| Rate in non-diabetic men| 62.88      | 4.60     | 71.68| 349.20| 845.39|     |
| Risk ratio (95% CI) | 5.83 (4.67–7.27)| 13.51 (3.05–59.84) | 2.39 (1.52–3.74) | 1.29 (0.83–2.00) | 1.06 (0.76–1.46) |     |
| **Women**           |             |          |     |       |       |     |
| **Diabetes of any duration** | | | | | | |
| **Diabetic women**  |             |          |     |       |       |     |
| n of lung cancer    | 138         | 3        | 37  | 48    | 50    |     |
| n of diabetic women | 62986       | 10170    | 30488| 13121 | 9207  |     |
| Rate in diabetic women| 219.10     | 29.90    | 121.36| 365.83| 543.07|     |
| **Non-diabetic women**|             |          |     |       |       |     |
| n of lung cancer    | 172         | 19       | 77  | 31    | 45    |     |
| n of non-diabetic women| 439975    | 286159   | 126040| 16660 | 11116 |     |
| Rate in non-diabetic women| 39.09      | 6.64     | 61.09| 186.07| 404.82|     |
| Risk ratio (95% CI) | 5.60 (4.48–7.01)| 4.44 (1.31–15.01) | 1.99 (1.34–2.94) | 1.97 (1.25–3.09) | 1.34 (0.90–2.00) |     |
| **Excluding diabetes diagnosed <5 years** | | | | | | |
| **Diabetic women**  |             |          |     |       |       |     |
| n of lung cancer    | 91          | 1        | 29  | 26    | 35    |     |
| n of diabetic women | 39263       | 5298     | 18081| 9158  | 6726  |     |
| Rate in diabetic women| 231.77     | 18.88    | 160.39| 283.90| 520.37|     |
| **Non-diabetic women**|             |          |     |       |       |     |
| n of lung cancer    | 172         | 19       | 77  | 31    | 45    |     |
| n of non-diabetic women| 439975    | 286159   | 126040| 16660 | 11116 |     |
| Rate in non-diabetic women| 39.09      | 6.64     | 61.09| 186.07| 404.82|     |
| Risk ratio (95% CI) | 5.93 (4.60–7.64)| 2.84 (0.38–21.23) | 2.63 (1.71–4.02) | 1.53 (0.91–2.57) | 1.29 (0.83–2.00) |     |

CI = confidence interval

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Table 2. Mutually-adjusted odds ratios for lung cancer derived from incident cases in 2005 for all ages and age ≥40 years.

| Variables                  | Interpretation                          | Model I       |          |          |          | Model II      |          |          |          |
|---------------------------|-----------------------------------------|---------------|----------|----------|----------|---------------|----------|----------|----------|
|                           |                                         | OR            | 95% CI   | *P* value| OR       | 95% CI       | *P* value| OR       | 95% CI   |
| All ages                  |                                         |               |          |          |          |               |          |          |          |
| Age                       | 40–64 years vs. <40 years                | 9.548         | (6.718–13.571) | <0.0001 | 9.548    | (6.718–13.572) | <0.0001 |          |          |
|                           | 65–74 years vs. <40 years                | 29.089        | (19.941–42.433) | <0.0001 | 29.089   | (19.942–42.434) | <0.0001 |          |          |
|                           | ≥75 years vs. <40 years                  | 51.981        | (35.581–75.923) | <0.0001 | 51.985   | (35.591–75.929) | <0.0001 |          |          |
| Sex                       | Men vs. Women                            | 1.452         | (1.254–1.661) | <0.0001 | 1.452    | (1.254–1.661) | <0.0001 |          |          |
| Diabetes duration         | <1 year vs. Non-diabetes                 | 2.189         | (1.498–3.200) | <0.0001 | 2.189    | (1.498–3.200) | <0.0001 |          |          |
|                           | 1–3 years vs. Non-diabetes               | 1.420         | (1.014–1.988) | 0.0414  | 1.420    | (1.014–1.989) | 0.0413  |          |          |
|                           | 3–5 years vs. Non-diabetes               | 1.545         | (1.132–2.110) | 0.0061  | 1.545    | (1.132–2.110) | 0.0061  |          |          |
|                           | ≥5 years vs. Non-diabetes                | 1.329         | (1.063–1.660) | 0.0124  | 1.329    | (1.063–1.660) | 0.0125  |          |          |
| Insulin                   | Yes vs. No                               | 0.808         | (0.492–1.327) | 0.3992  | -        | -            |          |          |          |
|                           | <5 years vs. Non-user                    | -             | -         |          | 0.882    | (0.216–3.606) | 0.8609  |          |          |
|                           | ≥5 years vs. Non-user                    | -             | -         |          | 0.800    | (0.476–1.345) | 0.3999  |          |          |
| Chest X-ray               | Yes vs. No                               | 3.355         | (2.717–4.143) | <0.0001 | 3.355    | (2.717–4.143) | <0.0001 |          |          |
| Hypertension              | Yes vs. No                               | 0.991         | (0.818–1.202) | 0.9302  | 0.991    | (0.817–1.202) | 0.9297  |          |          |
| COPD                      | Yes vs. No                               | 1.204         | (1.032–1.404) | 0.0182  | 1.204    | (1.032–1.404) | 0.0183  |          |          |
| Stroke                    | Yes vs. No                               | 0.774         | (0.639–0.936) | 0.0083  | 0.774    | (0.639–0.936) | 0.0083  |          |          |
| Nephropathy               | Yes vs. No                               | 0.859         | (0.693–1.064) | 0.1632  | 0.859    | (0.693–1.064) | 0.1632  |          |          |
| IHD                       | Yes vs. No                               | 1.120         | (0.944–1.328) | 0.1943  | 1.120    | (0.944–1.328) | 0.1943  |          |          |
| PAD                       | Yes vs. No                               | 1.003         | (0.800–1.258) | 0.9795  | 1.003    | (0.800–1.258) | 0.9799  |          |          |
| Eye disease               | Yes vs. No                               | 0.965         | (0.663–1.407) | 0.8517  | 0.965    | (0.662–1.406) | 0.8517  |          |          |
| Obesity                   | Yes vs. No                               | 1.113         | (0.526–2.353) | 0.7030  | 1.113    | (0.526–2.354) | 0.7799  |          |          |
| Dyslipidemia              | Yes vs. No                               | 0.813         | (0.667–0.991) | 0.0404  | 0.813    | (0.667–0.991) | 0.0404  |          |          |
| Statin                    | Yes vs. No                               | 1.018         | (0.792–1.307) | 0.8923  | 1.017    | (0.792–1.307) | 0.8923  |          |          |
| Fibrate                   | Yes vs. No                               | 0.853         | (0.655–1.110) | 0.2362  | 0.853    | (0.656–1.110) | 0.2362  |          |          |
| ACE/ARB                   | Yes vs. No                               | 1.064         | (0.847–1.337) | 0.5949  | 1.064    | (0.847–1.337) | 0.5943  |          |          |
| CCB                       | Yes vs. No                               | 0.989         | (0.786–1.244) | 0.9246  | 0.989    | (0.786–1.244) | 0.9243  |          |          |
| Sulfonylurea              | Yes vs. No                               | 1.097         | (0.799–1.506) | 0.5677  | 1.097    | (0.799–1.506) | 0.5677  |          |          |
| Metformin                 | Yes vs. No                               | 1.020         | (0.731–1.423) | 0.9064  | 1.020    | (0.731–1.423) | 0.9064  |          |          |
| Acrabose                  | Yes vs. No                               | 1.016         | (0.628–1.646) | 0.9460  | 1.017    | (0.628–1.646) | 0.9460  |          |          |
| Pioglitazone              | Yes vs. No                               | 1.602         | (0.794–3.224) | 0.1882  | 1.603    | (0.794–3.235) | 0.1882  |          |          |
| Rosiglitazone             | Yes vs. No                               | 0.927         | (0.559–1.538) | 0.7372  | 0.928    | (0.559–1.539) | 0.7372  |          |          |
| Living region             | Northern vs. Taipei                      | 0.899         | (0.703–1.150) | 0.3984  | 0.899    | (0.703–1.150) | 0.3984  |          |          |
|                           | Central vs. Taipei                       | 1.040         | (0.838–1.292) | 0.7198  | 1.040    | (0.838–1.292) | 0.7198  |          |          |
|                           | Southern vs. Taipei                      | 1.150         | (0.918–1.442) | 0.2254  | 1.150    | (0.917–1.441) | 0.2254  |          |          |
| Variables | Interpretation | Model I |       | Model II |       |
|-----------|----------------|---------|-------|----------|-------|
|           |                 | OR      | 95% CI | P value  | OR    | 95% CI | P value  |
|           | Kao-Ping/Eastern vs. Taipei | 1.213  | (0.990–1.486) | 0.0625 | 1.213 | (0.990–1.485) | 0.0628 |
| Occupation| II vs. I        | 1.299  | (1.026–1.644) | 0.0297 | 1.299 | (1.026–1.644) | 0.0297 |
| Occupation| III vs. I       | 1.280  | (1.037–1.580) | 0.0213 | 1.280 | (1.037–1.580) | 0.0213 |
| Occupation| IV vs. I        | 1.424  | (1.166–1.739) | 0.0005 | 1.424 | (1.166–1.739) | 0.0005 |
| Age ≥40 years* |                 |         |       |          |       |
| Age       | 65–74 years vs. 40–64 years | 3.071  | (2.488–3.789) | <0.0001 | 3.071 | (2.488–3.789) | <0.0001 |
| Age       | ≥75 years vs. 40–64 years | 5.514  | (4.467–6.806) | <0.0001 | 5.514 | (4.467–6.806) | <0.0001 |
| Sex       | Men vs. Women   | 1.512  | (1.300–1.759) | <0.0001 | 1.512 | (1.300–1.759) | <0.0001 |
| Diabetes duration | <1 year vs. Non-diabetes | 2.131  | (1.448–3.135) | 0.001  | 2.131 | (1.448–3.135) | 0.001  |
| Diabetes duration | 1–3 years vs. Non-diabetes | 1.421  | (1.014–1.991) | 0.0414 | 1.421 | (1.014–1.992) | 0.0412 |
| Diabetes duration | 3–5 years vs. Non-diabetes | 1.513  | (1.105–2.073) | 0.0099 | 1.513 | (1.105–2.073) | 0.0099 |
| Diabetes duration | ≥5 years vs. Non-diabetes | 1.300  | (1.038–1.628) | 0.0225 | 1.300 | (1.037–1.628) | 0.0226 |
| Insulin   | Yes vs. No      | 0.815  | (0.496–1.339) | 0.4192 | -     | -     | -     |
| Insulin   | <5 years vs. Non-user | -     | -     | -     | 0.893 | (0.218–3.652) | 0.8743 |
| Insulin   | ≥5 years vs. Non-user | -     | -     | -     | 0.807 | (0.480–1.336) | 0.4182 |

Insulin use is categorized as yes versus no (Model I), and according to the duration of its use (Model II).

OR: odds ratio, CI: confidence interval, COPD: chronic obstructive pulmonary disease, IHD: ischemic heart disease, PAD: peripheral arterial disease, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, CCB: calcium channel blocker.

Refer to Materials and Methods for the categories of occupation.

*For age ≥40 years, only the odds ratios for age, sex, diabetes duration and insulin are shown. The odds ratios for other variables are not remarkably different from those seen in the analyses for all ages.

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Discussion

The trends of lung cancer were increasing significantly in 1979–2007 (Figure 2) and diabetes was associated with an increased risk at any duration (Table 2), with the highest risk ratio observed in the youngest age of <40 years (Table 1). However, insulin use was not associated with a significant change in the risk of lung cancer (Table 2).

Recently two retrospective cohort analyses using the NHI database to evaluate the association between diabetes and lung cancer in Taiwan have been reported [12,13]. The study by Lai et al. selected a group of new-onset diabetic patients aged ≥20 years (n = 19,624) from 2000–2005 and a group of non-diabetic patients matched on age and sex at baseline (n = 78,496) and traced the incidence of lung cancer for a period of up to 9 years in these two groups [12]. They concluded that there was no association between diabetes and lung cancer. However, this study could possibly be under-powered without sufficient case numbers. Furthermore, they have neglected the high incidence of diabetes and the duration of follow-up in the baseline non-diabetic group with a mean age of 56.5 years. Another study by Lee et al. followed 985,815 insurants with and without diabetes in 1997 and followed them from 1998 to 2009 [13]. They found that diabetes at baseline was associated with a significantly higher risk of lung cancer, with risk ratio (95% CI) of 1.54 (1.26–1.88) after adjustment for age, sex, hypertension, dyslipidemia and gout. This study also neglected the possible incidence of diabetes among the baseline non-diabetic group during the long duration of follow-up. Therefore, this study could have possibly underestimated the risk of lung cancer associated with diabetes.

The present study strengthened the link between diabetes and lung cancer, and supported a lack of association with insulin use. Diabetes was unlikely caused by lung cancer because diabetes diagnosed 5 years before lung cancer (Tables 1 and 2) can hardly be a consequence of the carcinogenic process. Detection bias was also unlikely because CXR had been adjusted in the analyses (Table 2).

Diabetes has been on the rise worldwide [14], especially in Asian countries [15]. In Taiwan diabetes prevalence increased from 5.0% in 1970 to 12.8% in 1996 in those aged ≥40 years [16]. The incidence of T2DM in Taiwan showed a significant increase from 5.0% in 1970 to 12.8% in 1996 in those aged ≥40 years [16]. The incidence of lung cancer has also been increasing significantly in Taiwan. The percentage of the population with diabetes in Taiwan is expected to increase of 1.8-fold from 1992 to 1996 [17]. If diabetes increases from 5.0% in 1970 to 12.8% in 1996 in those aged ≥40 years [16]. The incidence of T2DM in Taiwan showed a significant increase from 5.0% in 1970 to 12.8% in 1996 in those aged ≥40 years [16]. The incidence of T2DM in Taiwan showed a significant increase from 5.0% in 1970 to 12.8% in 1996 in those aged ≥40 years [16]. The incidence of T2DM in Taiwan showed a significant increase from 5.0% in 1970 to 12.8% in 1996 in those aged ≥40 years [16]. The incidence of T2DM in Taiwan showed a significant increase from 5.0% in 1970 to 12.8% in 1996 in those aged ≥40 years [16]. The incidence of T2DM in Taiwan showed a significant increase from 5.0% in 1970 to 12.8% in 1996 in those aged ≥40 years [16]. The incidence of T2DM in Taiwan showed a significant increase from 5.0% in 1970 to 12.8% in 1996 in those aged ≥40 years [16]. The incidence of T2DM in Taiwan showed a significant increase from 5.0% in 1970 to 12.8% in 1996 in those aged ≥40 years [16]. The incidence of T2DM in Taiwan showed a significant increase from 5.0% in 1970 to 12.8% in 1996 in those aged ≥40 years [16]. The incidence of T2DM in Taiwan showed a significant increase from 5.0% in 1970 to 12.8% in 1996 in those aged ≥40 years [16]. The incidence of T2DM in Taiwan showed a significant increase from 5.0% in 1970 to 12.8% in 1996 in those aged ≥40 years [16].

In summary, this study shows an increasing trend of lung cancer in Taiwan and a link between diabetes and lung cancer, which is more remarkable in the age of <40 years. Insulin or other medications are not, but COPD and lower socioeconomic status are significantly associated with lung cancer. The lower risk in patients with dyslipidemia and stroke awaits further investigation. Given that the population is aging, the incidence of lung cancer is increased.
increasing, and the incidence of T2DM is also increasing [17], the impact of diabetes-related lung cancer on the population should warrant public health attention.

References

1. Dela Cruz CS, Tanoue LT, Matthay RA (2011) Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med 32:659–644.
2. Bureau of Health Promotion. (2010) Cancer Registry Annual Report 2007. Taiwan: Department of Health, Executive Yuan.
3. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gaptur SM, et al. (2010) Diabetes and cancer: a consensus report. Diabetes Care 33:1674–1685.
4. Hall GC, Roberts CM, Boult M, Mo J, MacRae KD (2005) Diabetes and the risk of lung cancer. Diabetes Care 28:590–594.
5. Ehrlich SF, Quesenberry CP Jr, Van Den Eeden SK, Shan J, Ferrara A (2010) Patients diagnosed with diabetes mellitus are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. Diabetes Care 33:55–60.
6. Carstensen B, Witte DR, Friis S (2012) Cancer occurrence in Danish diabetic patients: duration and insulin effects. Diabetologia 55:948–958.
7. Hemminki K, Li X, Sundquist J, Sundquist K (2010) Risk of cancer following diabetes mellitus: a national cohort. JAMA Intern Med 170:120–128.
8. Lee MY, Lin KD, Hsiao PJ, Shin SJ (2012) The association of diabetes mellitus with liver, colon, lung, and prostate cancer is independent of hypertension, hyperlipidemia, and gout in Taiwanese patients. Metabolism 61:242–249.
9. Kleinbaum DG, Kupper LL, Morgenstern H (1982) Epidemiologic Research: Principles and Quantitative Methods, p298–299, John Wiley and Sons.
10. Reddy C, Chilla D, Boltax J (2011) Lung cancer screening: a review of available data and current guidelines. Hosp Pract (Minneap) 39:107–112.
11. Klabunde CN, Marcus PM, Han PK, Richards TB, Vernon SW, et al. (2012) Lung cancer screening practices of primary care physicians: results from a national survey. Ann Fam Med 10:102–110.
12. Lai SW, Liao KF, Chen PC, Tsai PY, Hsieh DP, et al. (2012) Antidiabetes drugs correlate with decreased risk of lung cancer: a population-based observation in Taiwan. Clin Lung Cancer 13:143–148.
13. Lee MY, Lin KD, Hsiao PJ, Shin SJ (2012) The association of diabetes mellitus with liver, colon, lung, and prostate cancer is independent of hypertension, hyperlipidemia, and gout in Taiwanese patients. Metabolism 61:242–249.
14. Wild S, Roglic G, Green A, Sicree R, King H (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27:1047–1053.
15. Chan JC, Malik V, Jia W, Kasowski T, Yajnik CS, et al. (2009) Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA 301:2129–2140.
16. Tseng CH (2009) The epidemiologic transition of diabetes mellitus in Taiwan: Implications for reversal of female preponderance from a national cohort. Open Diabetes Journal 2:18–23.
17. Tseng CH, Tseng CP, Chong CK, Huang TP, Song YM, et al. (2006) Increasing incidence of diagnosed type 2 diabetes in Taiwan: analysis of data from a national cohort. Diabetesologia 49:1753–1760.
18. Tseng CH (2012) Diabetes and non-Hodgkin's lymphoma: Analyses of prevalence and annual incidence in 2005 using the National Health Insurance database in Taiwan. Ann Oncol 23:153–158.
19. Tseng CH (2012) Diabetes, insulin use, and non-Hodgkin's lymphoma mortality in Taiwan. Metabolism 61:1003–1009.
20. Tseng CH (2013) Insulin use and smoking jointly increase the risk of bladder cancer mortality in patients with type 2 diabetes. Clin Genitourin Cancer 11:508–514.
21. Tseng CH (2014) Human insulin does not increase bladder cancer risk. PLoS ONE 9:e86517.
22. Tseng CH (2013) Type 2 diabetes, smoking, insulin use and mortality from hepatocellular carcinoma: a 12-year follow-up of a national cohort in Taiwan. Hepatol Int 7:493–702.
23. Tseng CH (2013) Diabetes is not an independent risk factor for hepatocellular carcinoma. Diabetes Metab Res Rev 29:515–524.
24. Tseng CH (2013) Diabetes, insulin use, smoking, and pancreatic cancer mortality in Taiwan. Acta Diabetol 50:879–886.
25. Tseng CH (2013) New-onset diabetes with a history of dyslipidemia predicts pancreatic cancer. Pancreas 42:42–48.
26. Tseng CH (2011) Diabetes and risk of prostate cancer: A study using the National Health Insurance. Diabetes Care 34:616–621.
27. Tseng CH (2014) Human insulin does not increase prostate cancer risk in Taiwanese. Clin Genitourin Cancer 12:e1–7–12.
28. Tseng CH (2011) Prostate cancer mortality in Taiwanese men: Increasing age-standardized trend in general population and increased risk in diabetic men. Ann Med 43:142–150.
29. Tseng CH (2012) Diabetes, insulin use, and gastric cancer: a population-based analysis of the Taiwanese. J Clin Gastroenterol 47:60–64.
30. Tseng CH (2011) Diabetes conveys a higher risk of gastric cancer mortality despite an age-standardised decreasing trend in the general population in Taiwan. Gut 60:774–779.
31. Tseng CH (2013) Higher risk of mortality from lung cancer in Taiwanese patients with diabetes. Diabetes Res Clin Pract 102:193–201.

Author Contributions
Conceived and designed the experiments: CHT. Performed the experiments: CHT. Analyzed the data: CHT. Contributed reagents/materials/analysis tools: CHT. Wrote the paper: CHT.