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Pre-existing type 2 diabetes and risk of lung cancer: a report from two prospective cohort studies of 133 024 Chinese adults in urban Shanghai

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ABSTRACT

Objectives: Observational studies of type 2 diabetes (T2D) and lung cancer risk are limited and controversial. We thus examined the association between T2D and risk of incident lung cancer using a cohort design.

Setting: Data from two ongoing population-based cohorts (the Shanghai Men's Health Study, SMHS, 2002–2006 and the Shanghai Women's Health Study, SWHS, 1996–2000) were used. Cox proportional-hazards regression models with T2D as a time-varying exposure were modelled to estimate HRs and 95% CIs.

Participants: The study population included 61 491 male participants aged 40–74 years from SMHS and 74 941 female participants aged 40–70 years from SWHS.

Outcome measure: Lung cancer cases were identified through annual record linkage to the Shanghai Cancer Registry and Shanghai Municipal Registry of Vital Statistics, and were further verified through home visits and a review of medical charts by clinical and/or pathological experts. Outcome data until 31 December 2010 for men and women were used for the present analysis.

Results: After a median follow-up of 6.3 years for SMHS and 12.2 years for SWHS, incident lung cancer cases were detected in 492 men and 525 women. A null association between T2D and lung cancer risk was observed in men (HR=0.87, 95% CI 0.62 to 1.21) and women (HR=0.92, 95% CI 0.69 to 1.24) after adjustments for potential confounders. Similar results were observed among never smokers.

Conclusions: There is little evidence that pre-existing T2D may influence the incidence of lung cancer.

Strengths and limitations of this study

- We showed a null association between type 2 diabetes and risk of lung cancer in two population-based prospective cohorts with a large sample size and long-term follow-up.
- This null association remained after excluding lung cancer cases occurring within the first 3 years after diabetes onset and among never smokers.
- However, using self-reported diabetes as exposure, and the lack of pharmacological data on diabetes treatments including hypoglycaemic agent use and degree of glucose control do not allow firm conclusions.

INTRODUCTION

Lung cancer is the most commonly diagnosed cancer as well as the leading cause of cancer-related death globally and in China.[1] The prevalence of diabetes has increased substantially in China, with the age-standardised rates from 2.4% in 1994[2] to 9.7% in 2007–2008,[3] which may parallel a marked lifestyle transition.[4] Unlike the stable transition in most Western developed countries, these changes have occurred within a very short time in China.

Individuals with pre-existing type 2 diabetes (T2D) have been shown to be at risk for a number of cancers, including cancers of the liver[5 6] and pancreas.[7] A link between T2D and lung cancer risk has also been suggested, but the evidence is limited and inconsistent. An inverse association was observed in four cohort studies,[8–11] whereas an elevated risk of lung cancer was associated with T2D in five other cohort studies, particularly among women.[12–16] Other studies, including eight cohort[17–24] and two case–control[25 26] studies, have reported a null association. These discrepancies could be due to a number of factors including insufficient statistical power (small sample size), different study designs and exposure ascertainments, and the lack of adjustments for important covariates such as smoking

and body mass index (BMI). On the other hand, all previous studies only considered a single measurement of diabetes at the baseline survey, and cases of diabetes newly identified over follow-up periods were neglected, which may have resulted in some underestimation of the true associations. In addition, to the best of our knowledge, no prospective study until now has evaluated the effect of diabetes on lung cancer risk in mainland China.

To further clarify whether T2D influences the risk of lung cancer, we assessed the association of T2D with the risk of lung cancer by using data from the Shanghai Men's Health Study (SMHS) and the Shanghai Women's Health Study (SWHS), two ongoing large, population-based prospective cohorts in urban Shanghai, China.

METHODS

Study population

The study population included 61 491 male participants of SMHS and 74 941 female participants of SWHS. Consent has been obtained from each participant after full explanation of the purpose and nature of all procedures used. Details of the study design, scientific rationale and baseline characteristics of the participants have been published previously.[27 28] Briefly, for SWHS, the recruitment for female residents of Shanghai aged 40–70 years started in 1996 and was completed in 2000, with an overall participation rate of 92.7% (75 221/81 170). For SMHS, the recruitment for men aged 40–74 years with no history of cancer in Shanghai started in April 2002 and was completed in June 2006, with an overall participation rate of 74.1% (61 491/83 125). Participants were interviewed in person using a structured questionnaire to obtain information on demographic characteristics, lifestyle and dietary habits, medical history, family history of cancer and other exposures. Anthropometric measurements, including current weight, height and circumferences of the waist and hip, were also taken at baseline.

In this analysis, we excluded participants who had a history of cancer at enrolment (none for men and n=1598 for women), were younger than 20 years on the day of diabetes diagnosis to reduce potential bias from including patients with type 1 diabetes (n=3 for men and 3 for women), died of cancers of unknown origin or without diagnosis date (n=126 for men and n=114 for women), had missing values for any of the covariates of interest (n=1458 for men and n=109 for women), and were diagnosed with lung cancer before the diagnosis of diabetes (n=1 for men and n=3 for women). After exclusion, a total of 59 910 men and 73 114 women remained in the current analysis.

Diabetes assessment

In our analysis, diabetes cases were identified based completely on the self-reported data. Self-reported diabetes was recorded on the baseline questionnaires (2002–2006 for SMHS and 1996–2000 for SWHS), and updated in each of the subsequent follow-up questionnaires (2004–2008 for SMHS, and 2000–2002, 2002–2004 and 2004–2007 for SWHS). Participants were asked whether they had ever been diagnosed with diabetes mellitus by a physician (yes/no) and if yes, the age at which diagnosis was recorded. From the beginning with the 2004–2008 follow-up questionnaires for men and 2000–2002 follow-up questionnaires for women, and for all subsequent surveys, the question was modified and participants were additionally asked in what year and month and in which hospital their diabetes had been diagnosed since the most recent survey.

In the present study, a case of T2D was considered to be confirmed if the participant reported having been diagnosed with T2D and met at least one of the following self-reported items: (1) fasting plasma glucose concentration is greater than 7 mmol/L on two separate occasions, (2) plasma glucose concentration is greater than 11.1 mmol/L at 2 h for a 75 g oral glucose tolerance test and (3) the use of insulin or other hypoglycaemic agents. A validation study showed that the self-reported diabetes was in good agreement with the measurement of fasting plasma glucose concentration and medical treatment records in our cohorts (data were not shown).

Follow-up and outcome ascertainment

The participants were followed up with home visits every 2–3 years to update exposure information and to ascertain new diagnosis of cancers. For SMHS, the first follow-up interview was conducted from 2004 to 2008 with a response rate of 97.6%. For SWHS, the first, second and third follow-ups were conducted from 2000–2002, 2002–2004 and 2004–2007 with corresponding response rates of 99.8%, 98.7% and 96.7%, respectively.

The incident lung cancer cases were defined as a primary tumour with an International Classification of Diseases (ICD)-9 code 162, and were identified through annual record linkage to the Shanghai Cancer Registry and Shanghai Municipal Registry of Vital Statistics. All possible cancer cases were verified through home visits and a further review of medical charts by clinical and/or pathological experts. Outcome data until 31 December 2010 for men and women were used for the present analysis, with median follow-up periods of 6.3 and 12.2 years for SMHS and SWHS, respectively.

Statistical analysis

Cox proportional hazards regression models with age as a time scale were used to calculate age-adjusted and multivariate-adjusted HRs and 95% CIs for the associations of T2D with the risk of incident lung cancer. T2D (yes/no) was modelled as a time-varying exposure in the current study, meaning that information on T2D reported in questionnaire n was used to prospectively categorise participants for the periods between completion of questionnaires n and n+1, and that the risk person-years were allocated to the corresponding

groups; the corresponding method has been described elsewhere in detail.[5]

Covariates were selected based on their potential to confound or modify the association between T2D and lung cancer. All covariates were modelled using baseline values. The covariates included in the multivariate-adjusted models were age (less than 50, 50–60, more than 60 years), birth cohort (1920s, 1930s, 1940s, 1950s, 1960s), education (illiteracy or elementary school, middle school, high school, graduate school), income (low, low to middle, middle to high, high; see table 1), BMI (less than 18.5, 18.5–24, 24–28, more than 28, according to Chinese standards[29]), occupation (housewife (women only), manual, clerical and professional), smoking status (never smoking, ever smoking, current smoking, for men), smoking pack-years (0–10, 10–20, more than 20, for men), ever smoking (yes/no, for women), alcohol drinking (0, 0–1.5, more than 1.5, drink/day, for men), ever alcohol drinking (yes/no, for women), family history of cancer (yes/no), total energy intake (kcal/day, quartiles), fruit intake (g/day, quartiles), vegetable intake (g/day, quartiles), total physical activity (PA; standard metabolic equivalents (METs) as MET-h/day in quartiles; 1 MET-h=15 min of moderate intensity activity),[30 31] history of hepatitis/chronic liver disease (yes/no), hormone replacement therapy (HRT; yes/no for women only), menopausal status (premenopausal/postmenopausal for women only).

We also tested for potential interactions of diabetes with age, income, education, occupation, family history of lung cancer, alcohol drinking, PA and smoking, by comparing the Cox models with and without the interaction terms using a likelihood ratio test. In the testing of the proportional hazard assumption by creating an interaction of diabetes and a logarithm of time in the model, we found no violation of proportionality.

To investigate the potential effect for over-detection bias (ie, the increased detection around the time of T2D diagnosis), age-adjusted incidence rates by different time intervals of follow-up (0–1, 1–3, more than 3 years) in the diabetes cohort and no diabetes cohort were calculated for lung cancer, which were directly standardised by the entire cohort population. To examine whether diabetes treatments affect the risk of lung cancer associated with T2D, a separate analysis that excluded treated diabetes was conducted.

All data analyses were performed with SAS V.9.2 (SAS Institute, Cary, North Carolina USA), and a two-sided p value of 0.05 was considered statistically significant if not specified.

RESULTS

Results from SMHS and SWHS

The distributions of selected baseline characteristics according to T2D are shown in table 1. In this analysis, 7.7% (4599) of men and 8.6% (6291) of women reported having been diagnosed with T2D at baseline or during follow-up periods. Compared with men and women without diabetes, patients with T2D were older and had higher BMI, greater intake of total energy and vegetable, but less fruit consumption and alcohol drinking at baseline. In SWHS, less than 2.8% of the women reported ever smoking.

Until 31 December 2010, incident lung cancer cases weres detected in 492 men and 525 women. For men, the age-standardised incidence rates (1/100 000 person-years) of lung cancer were 87.48, 20.73 and 161.92 for 0–1, 1–3 and more than 3 years, respectively, following the diabetes index date in the diabetes cohort; 112.97, 119.57 and 141.81 for 0–1, 1–3 and more than 3 years, respectively, since the baseline interview for the cohort without diabetes. For women, the age-standardised incidence rates (1/100 000 person-years) were 80.53, 19.81 and 72.85 for 0–1, 1–3 and more than 3 years, respectively, following the diabetes index date in the diabetes cohort; and 29.68, 41.43 and 69.46 for 0–1, 1–3 and more than 3 years, respectively, since the baseline interview for the non-diabetes cohort.

After adjustments for smoking, BMI, alcohol drinking and other factors, T2D was not associated with the risk of developing lung cancer either in men (HR=0.87, 95% CI 0.62 to 1.21) or in women (HR=0.93, 95% CI 0.69 to 1.25; table 2). This null association remained when the analysis was restricted to never smokers (table 3) or after excluding lung cancer cases diagnosed within the first 3 years after diabetes diagnosis (table 2). Results from the subgroup analysis by waist-to-hip ratio (WHR), waist circumference, smoking and menopausal status (women) did not appreciably alter the main results (table 3). We did not observe effect modification by age, income, education, occupation, family history of lung cancer, alcohol drinking or PA. In addition, an additional analysis that excluded treated diabetes also showed a null association between untreated diabetes and lung cancer (data not shown).

DISCUSSION

No observational study, to the best of our knowledge, has investigated lung cancer risk in relation to T2D in mainland China until now. Findings from our population-based cohort study suggested that T2D is not associated with the risk of incident lung cancer among Chinese adults. This null association remained regardless of age, income, education, occupation, family history of lung cancer, alcohol drinking, PA, smoking status, menopausal status and WHR in stratified analysis.

Previous epidemiological studies on T2D and lung cancer yielded conflicting results, varying from a positive,[16 32] null[17 19–22 24 33–35] to an inverse[9–11] association. Differing study design, sample size or follow-up time and covariate adjustments may, in part, explain this inconsistency. A comparative study[8] and three cohort studies[9–11] without adjustments for smoking concluded an inverse association; two cohort studies that reported a positive

Table 1 Characteristics of study participants according to type 2 diabetes status in the Shanghai Men's Health Study (2002–2010) and the Shanghai Women's Health Study (1997–2010)*

	Men		Women	
	No type 2 diabetes	Type 2 diabetes	No type 2 diabetes	Type 2 diabetes
Number of participants	55 311	4599	66 823	6291
Age at baseline (y)	54.89 (9.63)	60.48 (9.61)	51.94 (8.91)	58.51 (8.34)
Education level (%)				
Illiteracy or elementary school	6.27	11.33	19.28	43.18
Middle school	33.51	33.57	37.95	29.27
High school	36.69	29.53	28.85	18.41
Graduate school/college	23.52	25.57	13.92	9.14
Income (%)†				
Low	12.86	9.24	15.58	21.43
Low-middle	77.45	80.82	38.08	39.88
Middle-high	8.93	9.26	28.47	24.34
High	0.76	0.68	17.87	14.35
Occupation (%)				
Housewife	–	–	0.34	0.64
Professional	25.79	31.92	29.98	22.78
Clerical	21.92	22.53	20.81	20.32
Manual worker	52.29	45.55	49.87	56.26
BMI (kg/m^2)	23.64 (3.07)	24.61 (3.04)	23.82 (3.33)	26.00 (3.76)
BMI (%)				
Less than 18.5	4.49	1.48	3.58	1.30
18.5–24.0	50.79	43.23	51.82	29.08
24.0–28.0	37.01	41.47	33.83	42.39
Greater than 28	7.71	13.83	10.77	27.23
Smoking status (%)				
Never smokers	29.69	38.16	97.47	95.25
Former smokers	10.29	17.33		
Current smokers	60.02	44.51	2.59‡	4.75‡
Physical activity (MET h/week)	59.56 (34.03)	61.04 (35.83)	107.00 (45.30)	102.50 (43.31)
Ever alcohol intake (%)	34.82	29.03	2.29	1.87
Total energy intake (kcal/day)	8029.80 (2029.10)	7481.00 (1929.50)	7033.90 (1681.10)	6845.10 (1842.40)
Fruit intake (g/day)	155.10 (125.00)	98.58 (110.50)	271.90 (178.30)	187.90 (175.30)
Vegetable intake (g/day)	341.20 (190.10)	373.20 (218.40)	295.70 (168.70)	305.70 (188.70)
Family history of cancer (%)	28.27	30.03	26.48	26.61
Postmenopausal (%)	–	–	46.27	76.58
HRT use (%)	–	–	2.07	2.10

*Continuous variables are presented as the mean (the SD).
†Low: less than ¥10 000 per family per year for women and less than ¥1000 per person per month for men; low to middle: ¥10 000–19 999 per family per year for women and ¥1000–3000 per person per month for men; middle to high: ¥20 000–29 999 per family per year for women and ¥3000–5000 per person per month for men; high: greater than ¥30 000 per family per year for women and more than ¥5000 per person per month for men.
‡Owing to the small number of smokers among women, the number of current and former smokers was combined.
BMI, body mass index; DM, diabetes mellitus; HRT, hormone replacement therapy; MET, metabolic equivalents (1 MET h=15 min of moderate intensity activity).

association have not adjusted for BMI[16] or smoking;[32] two studies[25 26] with a null association used case–control design; three studies have a limited follow-up period (<5 years)[11 21] or sample size (<10 000).[15] Consistent with most pertinent studies,[17 19–22 24 33–35] we observed a null association between T2D and lung cancer risk overall and among non-smoking participants.

Although a null association was found between T2D and lung cancer, previous observational studies have consistently shown the increased risk of several incident cancers among individuals with T2D, including cancers of the liver[5 6] and pancreas.[7] The potential biological links between diabetes and cancer risk included hyperinsulinaemia (either endogenous due to insulin resistance or exogenous due to administered insulin or insulin secretogogues), hyperglycaemia and/or chronic inflammation.[36] The hyperinsulinaemia may involve in carcinogenesis by its mitogenic effect via the insulin/insulin-like growth factor axis.[36] On the other hand, hyperglycaemia may cause an abnormal energy balance and impair the effect of ascorbic acid on the intracellular metabolism and reduce the effectiveness of the immune system,[37] which could favour cancer incidence and progression in diabetic patients. In addition, free fatty acids, interleukin

Table 2 HRs for the association between type 2 diabetes and lung cancer risk in the Shanghai Men's Health Study (2002–2010) and the Shanghai Women's Health Study (1997–2010)

	No type 2 diabetes		Type 2 diabetes		
	Number of cases/ person-years	HR (95% CI)	Number of cases/ person-years	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)*
Men					
Entire cohort	450/354 902	1.00 (referent)	42/28 825	0.80 (0.58 to 1.10)	0.87 (0.62 to 1.21)
Sensitivity analysis†	260/354 604	1.00 (referent)	28/28 805	0.94 (0.64 to 1.39)	1.10 (0.73 to 1.64)
Women					
Entire cohort	469/801 158	1.00 (referent)	56/72 600	0.88 (0.66 to 1.18)	0.93 (0.69 to 1.25)
Sensitivity analysis†	396/801 041	1.00 (referent)	52/72 596	0.93 (0.69 to 1.26)	0.99 (0.72 to 1.34)

*Adjusted for age, birth cohort, education, income, body mass index, occupation, smoking status, smoking pack years (men only), alcohol drinking, family history of lung cancer, total energy intake, fruit intake, vegetable intake, total physical activity, hormone replacement therapy (women only), menopausal status (women only).
†Analysis after excluding lung cancer cases occurred within the first 3 years after diabetes onset.

Table 3 HRs for the association between type 2 diabetes and lung cancer risk, stratified by waist-to-hip ratio, waist circumference, smoking and menopausal status (women) in the Shanghai Men's Health Study (2002–2010) and the Shanghai Women's Health Study (1997–2010)*

	No type 2 diabetes		Type 2 diabetes	
	Number of cases/ person-years	HR (95% CI)	Number of cases/ person-years	HR (95% CI)*
Men				
Waist-to-hip ratio†				
1st tertile	187/122 101	1.00 (referent)	7/5808	0.59 (0.27 to 1.28)
2nd tertile	129/121 267	1.00 (referent)	10/9063	0.67 (0.35 to 1.30)
3rd tertile	134/111 533	1.00 (referent)	25/13 954	1.13 (0.71 to 1.78)
Waist circumference (cm)‡				
Less than 85	163/93 856	1.00 (referent)	4/4254	0.38 (0.14 to 1.04)
Greater than 85	287/261 046	1.00 (referent)	38/24 571	1.02 (0.71 to 1.46)
Smoking status				
Never smoker	53/106 860	1.00 (referent)	10/11 199	1.46 (0.71 to 3.02)
Former smoker	76/36 466	1.00 (referent)	13/4811	0.97 (0.52 to 1.80)
Current smoker	321/211 575	1.00 (referent)	19/12 815	0.67 (0.41 to 1.10)
Smoking (pack-years)				
0–10	80/147 829	1.00 (referent)	11/14 143	1.06 (0.54 to 2.06)
10–20	55/70 068	1.00 (referent)	5/4313	0.93 (0.36 to 2.42)
Greater than 20	315/137 004	1.00 (referent)	26/10 369	0.78 (0.51 to 1.19)
Women				
Waist-to-hip ratio¶				
1st tertile	133/282 622	1.00 (referent)	2/8367	0.44 (0.11 to 1.80)
2nd tertile	139/277 675	1.00 (referent)	24/20 108	1.37 (0.80 to 2.34)
3rd tertile	197/240 861	1.00 (referent)	30/44 126	0.63 (0.40 to 1.01)
Waist circumference (cm)§				
Less than 80	245/502 838	1.00 (referent)	15/20 482	1.01 (0.56 to 1.82)
More than 80	224/298 320	1.00 (referent)	41/52 119	0.74 (0.49 to 1.13)
Smoking status**				
Never smoker	428/781 407	1.00 (referent)	50/69 261	0.98 (0.72 to 1.34)
Former and current smoker	41/19 751	1.00 (referent)	6/3339	0.53 (0.21 to 1.39)
Menopausal status				
Yes	365/365 579	1.00 (referent)	49/54 772	0.84 (0.61 to 1.50)
No	104/435 575	1.00 (referent)	7/17 828	2.12 (0.96 to 4.67)

*The adjusted covariates are as indicated in table 1.
†1st tertile: <0.878; 2nd tertile: 0.878–0.924; 3rd tertile: ≥0.924.
‡A waist circumference≥85 cm for men was defined as overweight and central adiposity.
¶1st tertile: <0.785; 2nd tertile: 0.785–0.831; 3rd tertile: ≥0.831.
§A waist circumference ≥80 cm for women was defined as overweight and central adiposity.
**Owing to the limited number of former smokers among women, the former and current smokers were combined.

6, monocyte chemoattractant protein, plasminogen activator inhibitor 1, adiponectin, leptin and tumour necrosis factor α, which were produced by adipose tissue among T2D-related obesity, may play an aetiological role in regulating malignant transformation or cancer progression.[36]

The strengths of our study include the population-based cohort design, large sample size, high response rates of follow-ups (over 96% for in-person home visits) and the use of repeated measures of diabetes status. However, several limitations to this study should be noted. As cases of diabetes were self-reported and a number of patients with diabetes did not know they had the disease,[38] the misclassification of T2D cannot be ruled out and could be non-differential, thus leading to the underestimation of the true association. Nevertheless, we observed a high agreement between self-reported data and data from medical records and laboratory tests for T2D in a random sample of participants from our cohorts. Also, previous validation studies[39 40] indicated that a self-reported history of diabetes could be reasonably accurate and could provide a useful assessment for broad measures of diabetes in the large-scale observational study.

In addition, the findings from SWHS would have been affected by the over-detection bias, given the higher incidence rate of lung cancer in the first year following the diabetes index date compared with those without diabetes, regardless of the different time intervals of follow-up. However, the results were unchanged in the analysis after excluding lung cancer cases occurring within the first 3 years after diabetes onset. Moreover, this potentially increased ascertainment in diabetics is unlikely to occur in SMHS because of the lower incidence rate of lung cancer in the diabetic cohort within the first year after the diabetes diagnosis.

Other limitations to the study include the lack of pharmacological data on diabetes treatments, including hypoglycaemic agent use and degree of glucose control. However, sensitivity analysis showed a similarly null association between untreated diabetes and risk of lung cancer, indicating that the diabetes treatments may not affect our main results. This finding should be interpreted with caution because information for the history of hypoglycaemic drug use was based on self-reported data in our study.

In summary, our cohort study indicated that T2D is not associated with lung cancer risk. Future research to find other modifiable risk factors for lung cancer should be warranted.

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