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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-004875
Article Type:	Research
Date Submitted by the Author:	17-Jan-2014
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology, Oncology, Diabetes and endocrinology
Keywords:	EPIDEMIOLOGY, ONCOLOGY, Epidemiology < ONCOLOGY, Adult oncology < ONCOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, PUBLIC HEALTH

Prospective investigation of type 2 diabetes in relation to lung cancer risk among 133,024 Chinese adults

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Word count: Text: 2572 words; Abstract: 244 words

Tables: 3 ; Figures: 0

Keywords: type 2 diabetes; lung cancer; cohort study; Shanghai

List of abbreviations: BMI, body mass index ; CI, confidence interval; MET, metabolic equivalents; HR, hazard ratio; HRT, hormone replacement therapy; IGF, insulin-like growth factor; PA, physical activity; RR, relative risk; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study; T2D, type 2 diabetes; WHR, waist-to-hip ratio

Abstract

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

Setting: We conducted two prospective population-based cohort studies (Shanghai Men's Health Study and Shanghai Women's Health Study) in China. Cox proportional hazards regression models with T2D as a time-varying exposure were modeled to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Participants: The study population included 61,491 male participants aged 40-74y from Shanghai Men's Health Study and 74, 941 female participants aged 40-70y from Shanghai Women's Health Study.

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 review of medical charts by clinical and/or pathological experts.

Results: During follow-up through 2010, 1017 incident lung cancer cases (492 for men and 525 for women) were identified among 59,910 men and 73,114 women. After adjustments for smoking, alcohol drinking, body mass index, physical activity, and other potential confounders, T2D is not associated with the lung cancer risk either in men (HR=0.87, 95%CI: 0.62-1.21) or in women (HR=0.92, 95%CI: 0.69-1.24). Analyses after excluding lung cancer cases occurred within the first 3 years after diabetes onset and among never smokers yielded similar results.

Conclusions: There is little evidence that preexisting 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 large sample size and long term follow-up.
- This null association was remained after excluding lung cancer cases occurred within the first 3 years after diabetes onset and among never smokers.
- However, using self-reported diabetes as exposure, and the lack of pharmacologic data on diabetes treatments including hypoglycemic agents 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-standardized rates from 2.4% in 1994 [2] to 9.7% in 2007 to 2008 [3].

Individuals with preexisting type 2 diabetes (T2D) have been shown to be at risk for a number of cancers, including cancers of the liver [4 5] and pancreas [6]. A link between type 2 diabetes and lung cancer risk has also been suggested, but the evidence is limited and inconsistent. An inverse association was observed in four cohort studies [7-10], whereas an elevated risk of lung cancer was associated with type 2 diabetes in five other cohort studies, particularly among women [11-15]. Other studies, including eight cohort [16-23] and two case-control [24 25] 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). In addition, all previous studies only considered a single measurement of diabetes at baseline survey, and diabetes newly identified over follow-up periods were neglected, which may have resulted in some underestimation of the true associations.

To further clarify whether type 2 diabetes influence the risk of lung cancer, we assessed the association of type 2 diabetes 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 on-going large population-based, prospective cohorts in urban Shanghai, China.

Methods

Study population

The study population included 61,491 male participants of the Shanghai Men's Health Study (SMHS) and 74, 941 female participants of the Shanghai Women's Health Study (SWHS). Consent has been obtained from each subject after full explanation of the purpose and nature of all procedures used. Details of the study design, scientific rationale, and baseline characteristics of the subjects have been published previously [26 27]. Briefly, for the SWHS, female residents of Shanghai aged 40-70 years old were recruited from 1997-2000, with an overall participation rate of 92.7%. For the SMHS, men aged 40-74 years old with no history of cancer were recruited in Shanghai from 2002-2006, with an overall participation rate of 74.1%. 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 previous history of cancer at enrollment (none for men and n=1598 for women), were younger than 20 years old 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 was 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 current analysis.

Diabetes assessment

The procedures for identification of diabetes cases have been described elsewhere [4]. Briefly, a case of type 2 diabetes was considered to be confirmed if a subject reported having been diagnosed with type 2 diabetes by physician(s) and met at least one of the following self-reported items: 1) fasting plasma

glucose concentration ≥7 mmol/L on two separate occasions, 2) plasma glucose concentration ≥ 11.1 mmol/L at 2 hours for a 75 g oral glucose tolerance test, and 3) use of insulin or other hypoglycemic agents.

Follow up and outcome ascertainment

The participants were followed up with home visits every 2 to 3 years to update exposure information and to ascertain new diagnosis of cancers. For the SMHS, the first follow up interview was conducted from 2004-2008 with a response rate of 97.6%. For the 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 tumor 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 further review of medical charts by clinical and/or pathological experts. Outcome data through December 31, 2010 for both men and women was used for the present analysis.

Statistical analysis

Cox proportional hazards regression models with age as time scale were used to calculate age-adjusted and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of type 2 diabetes with the risk of incident lung cancer. type 2 diabetes (yes/no) was modeled as a time-varying exposure in the current study, meaning that information on type 2 diabetes reported in questionnaire *n*, was used to prospectively categorize participants for the periods between completion of questionnaires *n* and *n + 1*, and the risk person-years was allocated to the corresponding groups, the

corresponding method was described elsewhere in detail [4].

Covariates were selected based on their potential to confound or modify the association between type 2 diabetes and lung cancer. All covariates were modeled using baseline values. The covariates included in the multivariate-adjusted models were age (<50y, 50-60y, ≥60y), birth cohort (1920s, 1930s, 1940s, 1950s, 1960s), education (≤elementary school, middle school, high school, >high school), income (low, low to middle, middle to high, high), body mass index (BMI; <18.5, 18.5-24, 24-28, ≥28, according to Chinese standard [28]), 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, ≥20, for men), ever smoking (yes/no, for women), alcohol drinking(0, 0-1.5, ≥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-hr/day in quartiles; 1 MET-hr=15 minutes of moderate intensity activity], history of hepatitis/chronic liver disease (yes/no), hormone replacement therapy (HRT; yes/no for women only), menopausal status (pre-/post-menopausal for women only).

We also tested for potential interactions of diabetes with age, income, education, occupation, family history of lung cancer, alcohol drinking, physical activity, and smoking, by comparing the Cox models with and without the interaction terms using a likelihood ratio test. In testing of the proportional hazard assumption by creating 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 (i.e. the increased detection around the time of type 2 diabetes diagnosis), age-adjusted incidence rates by different time intervals of follow-up

(0–1, 1–3, >3 years) in diabetes cohort and no-diabetes cohort were calculated for lung cancer, which were directly standardized by the entire cohort population.

All data analyses were performed with SAS 9.2 (SAS Institute, Cary, NC), and a two-sided *P* value of 0.05 was considered statistically significant if not specified.

Results

Results from the SMHS and SWHS

The distributions of selected baseline characteristics according to type 2 diabetes are shown in Table 1. In this analysis, 7.7% (4599) of men and 8.6% (6291) of women reported having been diagnosed with type 2 diabetes at baseline or during follow up periods. Compared to men and women without diabetes, patients with type 2 diabetes 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.

After a median follow-up of 6.3 years for SMHS and 12.2 years for SWHS, 1017 incident cases of lung cancer (492 men and 525 women) were identified in the two cohorts. For men, the age-standardized incidence rates (1/100 000 person-years) of lung cancer were 87.48, 20.73, and 161.92 for 0-1, 1-3, ≥3 years following the diabetes index date in diabetes cohort, respectively; 112.97, 119.57, and 141.81 for 0-1, 1-3, ≥3 years since baseline interview for the cohort without diabetes, respectively. For women, the age-standardized incidence rates (1/100 000 person-years) were 80.53, 19.81, 72.85 for 0-1, 1-3, ≥3 years following the diabetes index date in diabetes cohort, respectively; and 29.68, 41.43, 69.46 for 0-1, 1-3, ≥3 years since baseline interview for non-diabetes cohort, respectively.

After adjustments for smoking, BMI, alcohol drinking, and other factors, type 2 diabetes was not associated with the risk of developing lung cancer either in men (HR=0.87, 95%CI: 0.62-1.21) or in women (HR=0.93, 95%CI: 0.69-1.25) (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 subgroup analysis by waist to hip ratio, waist circumference, smoking, and menopausal status (women) did not appreciably alter the main results (Table 3). In addition, we did not observe effect modification by age, income, education, occupation, family history of lung cancer, alcohol drinking, or physical activity (data not shown).

Discussion

No observational study, to our knowledge, has investigated lung cancer risk in relation to type 2 diabetes in mainland China to date. Findings from our population-based cohort study suggested that type 2 diabetes is not associated with the risk of incident lung cancer among Chinese adults, and were further confirmed by a recent meta-analysis [29]. This null association remained regardless of age, income, education, occupation, family history of lung cancer, alcohol drinking, physical activity, smoking status, menopausal status, and WHR in stratified analysis.

Previous epidemiological studies on type 2 diabetes and lung cancer yielded conflicting results, varying from a positive [15 30], null [16 18-21 23 31-33] to an inverse [8-10] association. Differing study design, sample size or follow up time, and covariates adjustments may, in part, explain this inconsistency. A comparative study [7] and 3 cohort studies [8-10] without adjustments for smoking concluded an inverse association; two cohort studies that reported a positive association have not adjusted for BMI [15] or smoking [30]; two studies [24 25] with a null association used case-control design; three studies have a limited follow up periods (<5y) [10 20] or sample size (<10,000) [14]. Consistent with most pertinent

studies [16 18-21 23 31-33] and our meta-analysis, we observed a null association between type 2 diabetes and lung cancer risk overall and among nonsmoking participants.

Although a null association was found between T2D and lung cancer, previous observational studies have inconsistently shown the increased risk of incident several cancers among individuals with type 2 diabetes, including cancers of liver [4 5] and pancreas [6]. The potential biologic links between diabetes and cancer risk included hyperinsulinemia (either endogenous due to insulin resistance or exogenous due to administered insulin or insulin secretogogues), hyperglycemia, or chronic inflammation [34]. The hyperinsulinemia may involve in carcinogenesis by its mitogenic effect via the insulin/ insulin-like growth factor (IGF) axis [34]. On the other hand, hyperglycemia 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 [35], which could favor cancer incidence and progression in diabetic patients. In addition, free fatty acids, interleukin-6, monocyte chemoattractant protein, plasminogen activator inhibitor-1, adiponectin, leptin, and tumor necrosis factor-α, which were produced by adipose tissue among T2D related obesity, may play an etiologic role in regulating malignant transformation or cancer progression [34].

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 diabetes was from self-reported data and a number of patients with diabetes did not know they had the disease [36], the misclassification of type 2 diabetes cannot be ruled out and could be non-differential, thus led to the underestimation of the true association, although previous validation studies [37 38] 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. The validity of the self-reported data for measuring diabetes is also supported by recent meta-analysis showing that summary RR of studies using medical records or diabetes registry as a means of diabetes ascertainment was consistent with the summary RR of studies using self-report data to determine diabetes (data not shown). In addition, the findings from SWHS would have been affected by over-detection bias, given higher incidence rate of lung cancer in the first year following the diabetes index date compared to those without diabetes regardless of different time intervals of follow-up. However, the results were unchanged in the analysis after excluding lung cancer cases occurred within the first 3 years after diabetes onset. Moreover, this potential 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 pharmacologic data on diabetes treatments, including hypoglycemic agents use and degree of glucose control.

In summary, our cohort study indicated that type 2 diabetes is not associated with lung cancer risk. Future research to find other modifiable risk factors for lung cancer should be warranted.

Acknowledgements We would like to thank the participants of the Shanghai Men's Health Study and the Shanghai Women's Health Study for the invaluable contribution to this work.

Contributions YBX contributed to the conception and design of the study; YBX, HLL and YTG acquired data; WSY, YY and YBX performed the statistical analysis and the interpretation of results; WSY wrote the first draft; All authors contributed to the critical review of the manuscript and approved the final manuscript; The corresponding author (YBX) had full access to all of the data and the final responsibility for the decision to submit for publication.

Funding This work was supported by the fund of Key Discipline and Specialty Foundation of Shanghai Municipal Commission of Health and Family Planning, and grants from US National Institutes of Health (R37 CA070867 and R01 CA82729).

Competing interests None. The funding sponsor had no role in the study design, data collection, statistical analysis and result interpretation, as well as in the writing of the report and the decision to submit for publication. The corresponding author had full access to all data in the study and final responsibility for the decision to submit for publication.

Study approval Institutional review board.

Ethics approval IRBs of Vanderbilt University (USA) and Shanghai Cancer Institute (Shanghai, China).

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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)[1]

	Men			Women		
	No type 2 diabetes	Type 2 diabetes	*P* value	No type 2 diabetes	Type 2 diabetes	*P* value
Number of subjects	55311	4599	-	66,823	6291	-
Mean age at baseline (y)	54.89±9.63	60.48±9.61	<0.001	51.94±8.91	58.51±8.34	<0.001
Education level (%)						
≤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	
≥ Prof/Tech/College	23.52	25.57	<0.001	13.92	9.14	<0.001
Income (%)[2]						
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	<0.001	17.87	14.35	<0.001
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	<0.001	49.87	56.26	<0.001
BMI kg/m^2	23.64±3.07	24.61±3.04	<0.001	23.82±3.33	26.00±3.76	<0.001
<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	
>28 (%)	7.71	13.83	<0.001	10.77	27.23	<0.001

Table 1 Continued

	Men			Women		
	No type 2 diabetes	Type 2 diabetes	*P* value	No type 2 diabetes	Type 2 diabetes	*P* value
Smoking status (%)						
Never smokers	29.69	38.16		97.47	95.25	
Former smokers	10.29	17.33				
Current smokers	60.02	44.51	<0.001	2.59 [3]	4.75 [3]	<0.001
Physical activity (MET hours/week)	59.56±34.03	61.04±35.83	<0.001	107.00±45.30	102.50±43.31	<0.001
Ever alcohol intake (%)	34.82	29.03	<0.001	2.29	1.87	0.035
Total energy intake (Kcal/day)	8029.80±2029.10	7481.00±1929.50	<0.001	7033.90±1681.10	6845.10±1842.40	<0.001
Fruit intake (g/day)	155.10±125.00	98.58±110.50	<0.001	271.90±178.30	187.90±175.30	<0.001
Vegetable intake (g/day)	341.20±190.10	373.20±218.40	<0.001	295.70±168.70	305.70±188.70	<0.001
Family history of cancer (%)	28.27	30.03	0.011	26.48	26.61	0.821
Post-menopausal (%)	-	-		46.27	76.58	<0.001
HRT use (%)	-	-		2.07	2.10	0.883

[1] Abbreviations: BMI, body mass index; DM, diabetes mellitus; MET, metabolic equivalents (1 MET-hr=15 minutes of moderate intensity activity); HRT, hormone replacement therapy. Continuous variables are presented as the mean ± the standard deviation.

2 Low: < 10,000 Yuan per family per year for women and <1000 Yuan per person per month for men; Low to middle: 10,000 - 19,999 Yuan per family per year for women and 1000-3000 Yuan per person per month for men; Middle to high: 20,000-29,999 Yuan per family per year for women and 3000-5000 Yuan per person per month for men; High: ≥30,000 Yuan per family per year for women and ≥5000 Yuan per person per month for men.

[3] Due to small number of smokers among women, the number of current and former smokers was combined.

Table 2 Hazard ratios 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		
	No. of cases/person-years	HR (95%CI)	No. of cases/person-years	Age-adjusted HR (95%CI)	Multivariable-adjusted HR (95%CI) [1]
Men					
Entire cohort	450/354,902	1.00(referent)	42/28,825	0.80(0.58-1.10)	0.87(0.62-1.21)
Sensitivity analysis[2]	260/354,604	1.00(referent)	28/28,805	0.94(0.64-1.39)	1.10(0.73-1.64)
Women					
Entire cohort	469/801,158	1.00(referent)	56/72,600	0.88(0.66-1.18)	0.93(0.69-1.25)
Sensitivity analysis[2]	396/801,041	1.00(referent)	52/72,596	0.93(0.69-1.26)	0.99(0.72-1.34)

[1] 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).

[2] Analysis after excluding lung cancer cases occurred within the first 3 years after diabetes onset.

Table 3 Hazard ratios 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) [1]

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

[1] The adjusted covariates are as indicated in Table 1.

[2] 1st tertile: <0.878; 2nd tertile: 0.878-0.924; 3rd tertile: ≥0.924.

[3] A waist circumference≥ 85cm for men was defined as overweight and central adiposity.

[4] 1st tertile: <0.785; 2nd tertile: 0.785-0.831; 3rd tertile: ≥0.831.

[5] A waist circumference ≥80 cm for women was defined as overweight and central adiposity.

[6] Due to limited number of former smokers among women, the former and current smokers were combined.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Page	Recommendation
Title and abstract	1-3	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	3	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	6	Present key elements of study design early in the paper
Setting	6	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	6-7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	6-7	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	8	Describe any efforts to address potential sources of bias
Study size	6	Explain how the study size was arrived at
Quantitative variables	8	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	6-9	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	6-7	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	9	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders

		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	9	Report numbers of outcome events or summary measures over time
Main results	9	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	10	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	10	Summarise key results with reference to study objectives
Limitations	11-12	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	10-12	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	12	Discuss the generalisability (external validity) of the study results
Other information		
Funding	13	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-004875.R1
Article Type:	Research
Date Submitted by the Author:	18-May-2014
Complete List of Authors:	Yang, Wan-Shui; Jiujiang University, Social Science and Public Health Yang, Yang; Shanghai Cancer Institute, Yang, Gong; Vanderbilt School of Medicine, Department of Medicine Chow, Wong-Ho; University of Texas MD Anderson Cancer Center, Li, Honglan; Shanghai Cancer Institute, Department of Epidemiology Gao, Yu-Tang; Shanghai Cancer Institute, Department of Epidemiology Ji, Butian; National Institutes of Health, 3Division of Cancer Epidemiology and Genetics Rothman, Nat; National Cancer Institute, Shu, Xiao-Ou; Vanderbilt School of Medicine, Department of Medicine Zheng, Wei; Vanderbilt School of Medicine, Department of Medicine Xiang, Yong-bing; Shanghai Cancer Institute, Department of Epidemiology
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology, Oncology, Diabetes and endocrinology
Keywords:	EPIDEMIOLOGY, ONCOLOGY, Epidemiology < ONCOLOGY, Adult oncology < ONCOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, PUBLIC HEALTH

Preexisting 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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Word count: Text: 3003 words; Abstract: 242 words

Tables: 3 ; Figures: 0

Keywords: type 2 diabetes; lung cancer; cohort study; Shanghai

List of abbreviations: BMI, body mass index ; CI, confidence interval; MET, metabolic equivalents; HR, hazard ratio; HRT, hormone replacement therapy; IGF, insulin-like growth factor; PA, physical activity; RR, relative risk; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study; T2D, type 2 diabetes; WHR, waist-to-hip ratio

Abstract

Objectives: Observational studies of type 2 diabetes (T2D) and lung cancer risk is 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 modeled to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Participants: The study population included 61,491 male participants aged 40-74y from Shanghai Men's Health Study and 74, 941 female participants aged 40-70y from Shanghai Women's Health Study.

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 review of medical charts by clinical and/or pathological experts. Outcome data through December 31, 2010 for both men and women was 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 case was detected in 492 men and 525 women. A null association between T2D and lung cancer risk was observed in both men (HR=0.87, 95%CI: 0.62-1.21) and women (HR=0.92, 95%CI: 0.69-1.24) after adjustments for potential confounders. Similar results were observed among never smokers.

Conclusions: There is little evidence that preexisting 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 large sample size and long term follow-up.
- This null association was remained after excluding lung cancer cases occurred within the first 3 years after diabetes onset and among never smokers.
- However, using self-reported diabetes as exposure, and the lack of pharmacologic data on diabetes treatments including hypoglycemic agents 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-standardized rates from 2.4% in 1994 [2] to 9.7% in 2007 to 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 preexisting 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 type 2 diabetes 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 type 2 diabetes 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 baseline survey, and diabetes newly identified over follow-up periods were neglected, which may have resulted in some underestimation of the true associations. In addition, to our knowledge, no prospective study, to date, has evaluated the effect of diabetes on the lung cancer risk.

To further clarify whether type 2 diabetes influence the risk of lung cancer, we assessed the association of type 2 diabetes 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 on-going large

population-based, prospective cohorts in urban Shanghai, China.

Methods

Study population

The study population included 61491 male participants of the Shanghai Men's Health Study (SMHS) and 74941 female participants of the Shanghai Women's Health Study (SWHS). Consent has been obtained from each subject after full explanation of the purpose and nature of all procedures used. Details of the study design, scientific rationale, and baseline characteristics of the subjects have been published previously [27 28]. Briefly, for the SWHS, the recruitment for female residents of Shanghai aged 40-70 years old started in 1996 and was completed in 2000, with an overall participation rate of 92.7% (75221/81170). For the SMHS, the recruitment for men aged 40-74 years old 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% (61491/83125). 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 previous history of cancer at enrollment (none for men and n=1598 for women), were younger than 20 years old 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 was 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 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 the SMHS and 1996–2000 for the SWHS), and updated in each of the subsequent follow-up questionnaires (2004–2008 for the SMHS, and 2000–2002, 2002–2004 and 2004–2007 for the SWHS). Participants were asked whether they had ever been diagnosed with DM by a physician (yes/no) and if yes, the age at 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 present study, a case of T2D was considered to be confirmed if the participant reported having been diagnosed with type 2 diabetes and met at least one of the following self-reported items: (i) fasting plasma glucose concentration is greater than 7 mmol/l on two separate occasions, (ii) plasma glucose concentration is greater than 11.1 mmol/l at 2 h for a 75 g oral glucose tolerance test and (iii) the use of insulin or other hypoglycemic 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 was not shown).

Follow up and outcome ascertainment

The participants were followed up with home visits every 2 to 3 years to update exposure information and to ascertain new diagnosis of cancers. For the SMHS, the first follow up interview was conducted from 2004-2008 with a response rate of 97.6%. For the 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 tumor 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 further review of medical charts by clinical and/or pathological experts. Outcome data through December 31, 2010 for both men and women was used for the present analysis, with median follow-up periods of 6.3 years and 12.2 years for SMHS and SWHS, respectively.

Statistical analysis

Cox proportional hazards regression models with age as time scale were used to calculate age-adjusted and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of type 2 diabetes with the risk of incident lung cancer. Type 2 diabetes (yes/no) was modeled as a time-varying exposure in the current study, meaning that information on type 2 diabetes reported in questionnaire *n*, was used to prospectively categorize participants for the periods between completion of questionnaires *n* and *n + 1*, and the risk person-years was allocated to the corresponding groups, the corresponding method was described elsewhere in detail [5].

Covariates were selected based on their potential to confound or modify the association between type 2 diabetes and lung cancer. All covariates were modeled using baseline values. The covariates included in the multivariate-adjusted models were age (less than 50y, 50-60y, more than 60y), 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), body mass index (BMI; less than 18.5, 18.5-24, 24-28, more than 28, according to Chinese standard [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-hr/day in quartiles; 1 MET-hr=15 minutes 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 (pre-/post-menopausal for women only).

We also tested for potential interactions of diabetes with age, income, education, occupation, family history of lung cancer, alcohol drinking, physical activity, and smoking, by comparing the Cox models with and without the interaction terms using a likelihood ratio test. In testing of the proportional hazard assumption by creating 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 (i.e. the increased detection around the time of type 2 diabetes diagnosis), age-adjusted incidence rates by different time intervals of follow-up (0–1, 1–3, more than 3 years) in diabetes cohort and no-diabetes cohort were calculated for lung cancer, which were directly standardized 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 9.2 (SAS Institute, Cary, NC), and a two-sided *P* value of 0.05 was considered statistically significant if not specified.

Results

Results from the SMHS and SWHS

The distributions of selected baseline characteristics according to type 2 diabetes are shown in Table 1. In this analysis, 7.7% (4599) of men and 8.6% (6291) of women reported having been diagnosed with type 2 diabetes at baseline or during follow up periods. Compared to men and women without diabetes, patients with type 2 diabetes 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.

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

After adjustments for smoking, BMI, alcohol drinking, and other factors, type 2 diabetes was not associated with the risk of developing lung cancer either in men (HR=0.87, 95%CI: 0.62-1.21) or in women (HR=0.93, 95%CI: 0.69-1.25) (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 subgroup analysis by waist to hip ratio, 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 physical activity. 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 our knowledge, has investigated lung cancer risk in relation to type 2 diabetes in mainland China to date. Findings from our population-based cohort study suggested that type 2 diabetes 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, physical activity, smoking status, menopausal status, and WHR in stratified analysis.

Previous epidemiological studies on type 2 diabetes 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 covariates adjustments may, in part, explain this inconsistency. A comparative study [8] and 3 cohort studies [9-11] without adjustments for smoking concluded an inverse association; two cohort studies that reported a positive 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 periods (<5y) [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 type 2 diabetes and lung cancer risk overall and among nonsmoking participants.

Although a null association was found between T2D and lung cancer, previous observational studies have inconsistently shown the increased risk of incident several cancers among individuals with type 2 diabetes, including cancers of liver [5 6] and pancreas [7]. The potential biologic links between diabetes and cancer risk included hyperinsulinemia (either endogenous due to insulin resistance or exogenous

due to administered insulin or insulin secretogogues), hyperglycemia, and/or chronic inflammation [36]. The hyperinsulinemia may involve in carcinogenesis by its mitogenic effect via the insulin/ insulin-like growth factor (IGF) axis [36]. On the other hand, hyperglycemia 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 favor cancer incidence and progression in diabetic patients. In addition, free fatty acids, interleukin-6, monocyte chemoattractant protein, plasminogen activator inhibitor-1, adiponectin, leptin, and tumor necrosis factor-α, which were produced by adipose tissue among T2D related obesity, may play an etiologic role in regulating malignant transformation or cancer progression [36].

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 diabetes were self-reported and a number of patients with diabetes did not know they had the disease [38], the misclassification of type 2 diabetes cannot be ruled out and could be non-differential, thus led to the underestimation of the true association. Nevertheless, we observed a high agreement between self-report data and data from medical records and laboratory test for T2D in a random sample of subjects 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 over-detection bias, given higher incidence rate of lung cancer in the first year following the diabetes index date compared to those without diabetes regardless of different time intervals of follow-up. However, the results were

unchanged in the analysis after excluding lung cancer cases occurred within the first 3 years after diabetes onset. Moreover, this potential 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 pharmacologic data on diabetes treatments, including hypoglycemic agents 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. Whereas this finding should be interpreted with cautions because the information for the history of hypoglycemic drug use were also on the basis of self-reported data in our study.

In summary, our cohort study indicated that type 2 diabetes is not associated with lung cancer risk. Future research to find other modifiable risk factors for lung cancer should be warranted.

Acknowledgements We would like to thank the participants of the Shanghai Men's Health Study and the Shanghai Women's Health Study for the invaluable contribution to this work.

Contributions YBX contributed to the conception and design of the study; YBX, HLL and YTG acquired data; WSY, YY and YBX performed the statistical analysis and the interpretation of results; WSY wrote the first draft; All authors contributed to the critical review of the manuscript and approved the final manuscript; The corresponding author (YBX) had full access to all of the data and the final responsibility for the decision to submit for publication.

Funding This work was supported by the US National Institutes of Health (grant number R37 CA070867 and R01 CA82729); the fund of Key Discipline and Specialty Foundation of Shanghai Municipal Commission of Health and Family Planning.

Competing interests None. The funding sponsor had no role in the study design, data collection, statistical analysis and result interpretation, as well as in the writing of the report and the decision to submit for publication. The corresponding author had full access to all data in the study and final responsibility for the decision to submit for publication.

Study approval Institutional review board.

Ethics approval IRBs of Vanderbilt University (USA) and Shanghai Cancer Institute (China).

Data sharing No additional unpublished data.

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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)[1]

	Men		Women	
	No type 2 diabetes	Type 2 diabetes	No type 2 diabetes	Type 2 diabetes
Number of subjects	55311	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 (%)[2]				
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
Great 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[3]	4.75[3]
Physical activity (MET hours/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
Post-menopausal (%)	-	-	46.27	76.58
HRT use (%)	-	-	2.07	2.10

[1] Abbreviations: BMI, body mass index; DM, diabetes mellitus; MET, metabolic equivalents (1 MET-hr=15 minutes of moderate intensity activity); HRT, hormone replacement therapy. Continuous variables are presented as the mean (the standard deviation).

[2] Low: less than 10,000 Yuan per family per year for women and less than 1000 Yuan per person per month for men; Low to middle: 10,000 - 19,999 Yuan per family per year for women and 1000-3000 Yuan per person per month for men; Middle to high: 20,000-29,999 Yuan per family per year for women and 3000-5000 Yuan per person per month for men; High: greater

than 30,000 Yuan per family per year for women and more than 5000 Yuan per person per month for men.

[3] Due to small number of smokers among women, the number of current and former smokers was combined.

Table 2 Hazard ratios 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		
	No. of cases/person-years	HR (95%CI)	No. of cases/person-years	Age-adjusted HR (95%CI)	Multivariable-adjusted HR (95%CI) [1]
Men					
Entire cohort	450/354,902	1.00(referent)	42/28,825	0.80(0.58-1.10)	0.87(0.62-1.21)
Sensitivity analysis[2]	260/354,604	1.00(referent)	28/28,805	0.94(0.64-1.39)	1.10(0.73-1.64)
Women					
Entire cohort	469/801,158	1.00(referent)	56/72,600	0.88(0.66-1.18)	0.93(0.69-1.25)
Sensitivity analysis[2]	396/801,041	1.00(referent)	52/72,596	0.93(0.69-1.26)	0.99(0.72-1.34)

[1] 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).

[2] Analysis after excluding lung cancer cases occurred within the first 3 years after diabetes onset.

Table 3 Hazard ratios 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) [1]

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

[1] The adjusted covariates are as indicated in Table 1.

[2] 1st tertile: <0.878; 2nd tertile: 0.878-0.924; 3rd tertile: ≥0.924.

[3] A waist circumference≥ 85cm for men was defined as overweight and central adiposity.

[4] 1st tertile: <0.785; 2nd tertile: 0.785-0.831; 3rd tertile: ≥0.831.

[5] A waist circumference ≥80 cm for women was defined as overweight and central adiposity.

[6] Due to limited number of former smokers among women, the former and current smokers were combined.

Preexisting 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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Word count: Text: 3003 words; Abstract: 242 words

Tables: 3 ; Figures: 0

Keywords: type 2 diabetes; lung cancer; cohort study; Shanghai

List of abbreviations: BMI, body mass index ; CI, confidence interval; MET, metabolic equivalents; HR, hazard ratio; HRT, hormone replacement therapy; IGF, insulin-like growth factor; PA, physical activity; RR, relative risk; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study; T2D, type 2 diabetes; WHR, waist-to-hip ratio

Abstract

Objectives: Observational studies of type 2 diabetes (T2D) and lung cancer risk is 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 modeled to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Participants: The study population included 61,491 male participants aged 40-74y from Shanghai Men's Health Study and 74, 941 female participants aged 40-70y from Shanghai Women's Health Study.

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 review of medical charts by clinical and/or pathological experts. Outcome data through December 31, 2010 for both men and women was 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 case was detected in 492 men and 525 women. A null association between T2D and lung cancer risk was observed in both men (HR=0.87, 95%CI: 0.62-1.21) and women (HR=0.92, 95%CI: 0.69-1.24) after adjustments for potential confounders. Similar results were observed among never smokers.

Conclusions: There is little evidence that preexisting 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 large sample size and long term follow-up.
- This null association was remained after excluding lung cancer cases occurred within the first 3 years after diabetes onset and among never smokers.
- However, using self-reported diabetes as exposure, and the lack of pharmacologic data on diabetes treatments including hypoglycemic agents 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-standardized rates from 2.4% in 1994 [2] to 9.7% in 2007 to 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 preexisting 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 type 2 diabetes 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 type 2 diabetes 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 baseline survey, and diabetes newly identified over follow-up periods were neglected, which may have resulted in some underestimation of the true associations. In addition, to our knowledge, no prospective study, to date, has evaluated the effect of diabetes on the lung cancer risk.

To further clarify whether type 2 diabetes influence the risk of lung cancer, we assessed the association of type 2 diabetes 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 on-going large

population-based, prospective cohorts in urban Shanghai, China.

Methods

Study population

The study population included 61491 male participants of the Shanghai Men's Health Study (SMHS) and 74941 female participants of the Shanghai Women's Health Study (SWHS). Consent has been obtained from each subject after full explanation of the purpose and nature of all procedures used. Details of the study design, scientific rationale, and baseline characteristics of the subjects have been published previously [27 28]. Briefly, for the SWHS, the recruitment for female residents of Shanghai aged 40-70 years old started in 1996 and was completed in 2000, with an overall participation rate of 92.7% (75221/81170). For the SMHS, the recruitment for men aged 40-74 years old 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% (61491/83125). 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 previous history of cancer at enrollment (none for men and n=1598 for women), were younger than 20 years old 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 was 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 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 the SMHS and 1996–2000 for the SWHS), and updated in each of the subsequent follow-up questionnaires (2004–2008 for the SMHS, and 2000–2002, 2002–2004 and 2004–2007 for the SWHS). Participants were asked whether they had ever been diagnosed with DM by a physician (yes/no) and if yes, the age at 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 present study, a case of T2D was considered to be confirmed if the participant reported having been diagnosed with type 2 diabetes and met at least one of the following self-reported items: (i) fasting plasma glucose concentration is greater than 7 mmol/l on two separate occasions, (ii) plasma glucose concentration is greater than 11.1 mmol/l at 2 h for a 75 g oral glucose tolerance test and (iii) the use of insulin or other hypoglycemic 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 was not shown).

Follow up and outcome ascertainment

The participants were followed up with home visits every 2 to 3 years to update exposure information and to ascertain new diagnosis of cancers. For the SMHS, the first follow up interview was conducted from 2004-2008 with a response rate of 97.6%. For the 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 tumor 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 further review of medical charts by clinical and/or pathological experts. Outcome data through December 31, 2010 for both men and women was used for the present analysis, with median follow-up periods of 6.3 years and 12.2 years for SMHS and SWHS, respectively.

Statistical analysis

Cox proportional hazards regression models with age as time scale were used to calculate age-adjusted and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of type 2 diabetes with the risk of incident lung cancer. Type 2 diabetes (yes/no) was modeled as a time-varying exposure in the current study, meaning that information on type 2 diabetes reported in questionnaire *n*, was used to prospectively categorize participants for the periods between completion of questionnaires *n* and *n + 1*, and the risk person-years was allocated to the corresponding groups, the corresponding method was described elsewhere in detail [5].

Covariates were selected based on their potential to confound or modify the association between type 2 diabetes and lung cancer. All covariates were modeled using baseline values. The covariates included in the multivariate-adjusted models were age (less than 50y, 50-60y, more than 60y), 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), body mass index (BMI; less than 18.5, 18.5-24, 24-28, more than 28, according to Chinese standard [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-hr/day in quartiles; 1 MET-hr=15 minutes 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 (pre-/post-menopausal for women only).

We also tested for potential interactions of diabetes with age, income, education, occupation, family history of lung cancer, alcohol drinking, physical activity, and smoking, by comparing the Cox models with and without the interaction terms using a likelihood ratio test. In testing of the proportional hazard assumption by creating 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 (i.e. the increased detection around the time of type 2 diabetes diagnosis), age-adjusted incidence rates by different time intervals of follow-up (0–1, 1–3, more than 3 years) in diabetes cohort and no-diabetes cohort were calculated for lung cancer, which were directly standardized 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 9.2 (SAS Institute, Cary, NC), and a two-sided *P* value of 0.05 was considered statistically significant if not specified.

Results

Results from the SMHS and SWHS

The distributions of selected baseline characteristics according to type 2 diabetes are shown in Table 1. In this analysis, 7.7% (4599) of men and 8.6% (6291) of women reported having been diagnosed with type 2 diabetes at baseline or during follow up periods. Compared to men and women without diabetes, patients with type 2 diabetes 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.

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

After adjustments for smoking, BMI, alcohol drinking, and other factors, type 2 diabetes was not associated with the risk of developing lung cancer either in men (HR=0.87, 95%CI: 0.62-1.21) or in women (HR=0.93, 95%CI: 0.69-1.25) (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 subgroup analysis by waist to hip ratio, 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 physical activity. 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 our knowledge, has investigated lung cancer risk in relation to type 2 diabetes in mainland China to date. Findings from our population-based cohort study suggested that type 2 diabetes 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, physical activity, smoking status, menopausal status, and WHR in stratified analysis.

Previous epidemiological studies on type 2 diabetes 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 covariates adjustments may, in part, explain this inconsistency. A comparative study [8] and 3 cohort studies [9-11] without adjustments for smoking concluded an inverse association; two cohort studies that reported a positive 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 periods (<5y) [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 type 2 diabetes and lung cancer risk overall and among nonsmoking participants.

Although a null association was found between T2D and lung cancer, previous observational studies have inconsistently shown the increased risk of incident several cancers among individuals with type 2 diabetes, including cancers of liver [5 6] and pancreas [7]. The potential biologic links between diabetes and cancer risk included hyperinsulinemia (either endogenous due to insulin resistance or exogenous

due to administered insulin or insulin secretogogues), hyperglycemia, and/or chronic inflammation [36]. The hyperinsulinemia may involve in carcinogenesis by its mitogenic effect via the insulin/ insulin-like growth factor (IGF) axis [36]. On the other hand, hyperglycemia 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 favor cancer incidence and progression in diabetic patients. In addition, free fatty acids, interleukin-6, monocyte chemoattractant protein, plasminogen activator inhibitor-1, adiponectin, leptin, and tumor necrosis factor-α, which were produced by adipose tissue among T2D related obesity, may play an etiologic role in regulating malignant transformation or cancer progression [36].

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 diabetes were self-reported and a number of patients with diabetes did not know they had the disease [38], the misclassification of type 2 diabetes cannot be ruled out and could be non-differential, thus led to the underestimation of the true association. Nevertheless, we observed a high agreement between self-report data and data from medical records and laboratory test for T2D in a random sample of subjects 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 over-detection bias, given higher incidence rate of lung cancer in the first year following the diabetes index date compared to those without diabetes regardless of different time intervals of follow-up. However, the results were

unchanged in the analysis after excluding lung cancer cases occurred within the first 3 years after diabetes onset. Moreover, this potential 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 pharmacologic data on diabetes treatments, including hypoglycemic agents 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. Whereas this finding should be interpreted with cautions because the information for the history of hypoglycemic drug use were also on the basis of self-reported data in our study.

In summary, our cohort study indicated that type 2 diabetes is not associated with lung cancer risk. Future research to find other modifiable risk factors for lung cancer should be warranted.

Acknowledgements We would like to thank the participants of the Shanghai Men's Health Study and the Shanghai Women's Health Study for the invaluable contribution to this work.

Contributions YBX contributed to the conception and design of the study; YBX, HLL and YTG acquired data; WSY, YY and YBX performed the statistical analysis and the interpretation of results; WSY wrote the first draft; All authors contributed to the critical review of the manuscript and approved the final manuscript; The corresponding author (YBX) had full access to all of the data and the final responsibility for the decision to submit for publication.

Funding This work was supported by the US National Institutes of Health (grant number R37 CA070867 and R01 CA82729); the fund of Key Discipline and Specialty Foundation of Shanghai Municipal Commission of Health and Family Planning.

Competing interests None. The funding sponsor had no role in the study design, data collection, statistical analysis and result interpretation, as well as in the writing of the report and the decision to submit for publication. The corresponding author had full access to all data in the study and final responsibility for the decision to submit for publication.

Study approval Institutional review board.

Ethics approval IRBs of Vanderbilt University (USA) and Shanghai Cancer Institute (China).

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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)[1]

	Men		Women	
	No type 2 diabetes	Type 2 diabetes	No type 2 diabetes	Type 2 diabetes
Number of subjects	55311	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 (%)[2]				
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
Great 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[3]	4.75[3]
Physical activity (MET hours/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
Post-menopausal (%)	-	-	46.27	76.58
HRT use (%)	-	-	2.07	2.10

[1] Abbreviations: BMI, body mass index; DM, diabetes mellitus; MET, metabolic equivalents (1 MET-hr=15 minutes of moderate intensity activity); HRT, hormone replacement therapy. Continuous variables are presented as the mean (the standard deviation).

[2] Low: less than 10,000 Yuan per family per year for women and less than 1000 Yuan per person per month for men; Low to middle: 10,000 - 19,999 Yuan per family per year for women and 1000-3000 Yuan per person per month for men; Middle to high: 20,000-29,999 Yuan per family per year for women and 3000-5000 Yuan per person per month for men; High: greater

than 30,000 Yuan per family per year for women and more than 5000 Yuan per person per month for men.

[3] Due to small number of smokers among women, the number of current and former smokers was combined.

Table 2 Hazard ratios 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		
	No. of cases/person-years	HR (95%CI)	No. of cases/person-years	Age-adjusted HR (95%CI)	Multivariable-adjusted HR (95%CI) [1]
Men					
Entire cohort	450/354,902	1.00(referent)	42/28,825	0.80(0.58-1.10)	0.87(0.62-1.21)
Sensitivity analysis[2]	260/354,604	1.00(referent)	28/28,805	0.94(0.64-1.39)	1.10(0.73-1.64)
Women					
Entire cohort	469/801,158	1.00(referent)	56/72,600	0.88(0.66-1.18)	0.93(0.69-1.25)
Sensitivity analysis[2]	396/801,041	1.00(referent)	52/72,596	0.93(0.69-1.26)	0.99(0.72-1.34)

[1] 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).

[2] Analysis after excluding lung cancer cases occurred within the first 3 years after diabetes onset.

Table 3 Hazard ratios 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) [1]

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

[1] The adjusted covariates are as indicated in Table 1.

[2] 1st tertile: <0.878; 2nd tertile: 0.878-0.924; 3rd tertile: ≥0.924.

[3] A waist circumference≥ 85cm for men was defined as overweight and central adiposity.

[4] 1st tertile: <0.785; 2nd tertile: 0.785-0.831; 3rd tertile: ≥0.831.

[5] A waist circumference ≥80 cm for women was defined as overweight and central adiposity.

[6] Due to limited number of former smokers among women, the former and current smokers were combined.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Page	Recommendation
Title and abstract	1-3	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	3	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	6	Present key elements of study design early in the paper
Setting	6	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	6-7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	6-7	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	8	Describe any efforts to address potential sources of bias
Study size	6	Explain how the study size was arrived at
Quantitative variables	8	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	6-9	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	6-7	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	9	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders

		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	9	Report numbers of outcome events or summary measures over time
Main results	9	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	10	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	10	Summarise key results with reference to study objectives
Limitations	11-12	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	10-12	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	12	Discuss the generalisability (external validity) of the study results
Other information		
Funding	13	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.