

Population-based cohort studies of type 2 diabetes and stomach cancer risk in Chinese men and women

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Key words

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Although positive associations have been found for diabetes and a number of cancer sites, investigations of stomach cancer are limited and the results lack consistency. In this prospective study we investigated the relationship between type 2 diabetes mellitus (T2DM) and stomach cancer risk in mainland China. We assessed the associations among T2DM, T2DM duration, and stomach cancer risk in two prospective population-based cohorts, the Shanghai Women's Health Study and the Shanghai Men's Health Study. Included in the study were 61 480 men and 74 941 women. Stomach cancer cases were identified through annual record linkage to the Shanghai Cancer Registry, and verified through home visits and review of medical charts. After a median follow-up of 7.5 years for the Shanghai Men's Health Study and 13.2 years for the Shanghai Women's Health Study, a total of 755 incident cases of stomach cancer (376 men and 379 women) were identified through to September 2013. Overall, we did not find any evidence that T2DM was associated with an increased risk of stomach cancer either in men (multi-adjusted hazard ratio = 0.83, 95% confidence interval, 0.59–1.16) or in women (multi-adjusted hazard ratio = 0.92, 95% confidence interval, 0.68–1.25). Our findings from two large prospective population-based cohorts suggest that T2DM was not associated with stomach cancer risk.

Approximately 952 000 new stomach cancer cases and 723 000 deaths from stomach cancer occurred in 2012, which account for 6.8% of the total cancer cases and 8.8% of total cancer deaths worldwide. Despite the fact that the incidence of and mortality from stomach cancer have declined markedly worldwide over the past decades, stomach cancer is still the third most common cause of cancer-related death in the world. It is also one of the most common cancers in China, ranking second only after lung cancer. The age-adjusted incidence and mortality rates were 22.7 per 100 000 and 17.9 per 100 000, respectively, in China in 2012.⁽¹⁾

The co-occurrence of diabetes and cancer has frequently drawn attention in clinical practice, and growing evidence suggests that diabetes and impaired glucose tolerance are possible risk factors for various types of cancers. Epidemiological studies have found that patients with diabetes are at increased risk of cancers of the liver, biliary tract, pancreas, colon, kidney, bladder, breast, and endometrium, but at a reduced risk of prostate cancer.⁽²⁾ Although numerous epidemiological studies have examined the association between diabetes and stomach cancer, the findings have been contradictory, as recent meta-analyses have concluded that the association is alternately neutral,⁽³⁾ marginal,⁽⁴⁾ and positive.^(5,6) The prevalence of diabetes has been rising rapidly worldwide, particularly in developing countries.⁽⁷⁾ In China, the age-standardized incidence rate of diabetes in 1994 was 2.4%, and it increased to 9.7% in 2007–

2008.^(8,9) To our knowledge, no prospective study has been carried out in China to evaluate the association of type 2 diabetes mellitus (T2DM) and stomach cancer.

In the present study, we investigated the association between T2DM and stomach cancer risk using data from the Shanghai Women's Health Study (SWHS) and the Shanghai Men's Health Study (SMHS), two large ongoing population-based prospective cohorts in Shanghai, China.

Materials and Methods

Study population. The details of the designs and methods used in this study have been described elsewhere.^(10,11) Briefly, for the SMHS, 61 480 men aged 40–75 years with no history of cancer at baseline were recruited in urban Shanghai from 2002 to 2006, with an overall study participation rate of 74.1%. For the SWHS, 74 941 women aged 40–70 years were recruited from 1996 to 2000, with an overall study participation rate of 92.7%. Participants were interviewed in person using a structured questionnaire to obtain information about demographic characteristics, lifestyles, dietary habits, medical history, occupational history, and physical activity habits. Anthropometric measurements, including current weight, height, and circumferences of the waist and hips, were also taken at baseline. The participants were followed up with home visits every 2–3 years to update exposure information

and to collect information on disease occurrence including cancers. For the SMHS, two in-person surveys, conducted from 2004 to 2008 and 2008 to 2011, have been completed with response rates of 97.6% and 94.9%, respectively. For the SWHS, four in-person surveys, conducted from 2000 to 2002, 2002 to 2004, 2004 to 2007, and 2007 to 2010, have been completed with response rates of 99.8%, 98.7%, 96.7% and 92.3%, respectively. All participants provided written informed consent, and this study was approved by the Institutional Review Boards of Shanghai Cancer Institute (China), National Cancer Institute (USA), and Vanderbilt University (USA).

We excluded participants from this analysis if they: (i) had a previous diagnosis of cancer at baseline (not collected for men; $n = 1598$ for women); (ii) died of cancers of unknown primary site or without cancer diagnosis date ($n = 137$ for men; $n = 138$ for women); (iii) were lost to follow up ($n = 14$ for men; $n = 5$ for women); (iv) were diagnosed with cancer *in situ* or non-confirmed cancer ($n = 43$ for men; $n = 150$ for women); (v) lacked a diabetes diagnosis date (none for men; $n = 3$ for women); (vi) were younger than 20 years on the day of diabetes diagnosis to reduce potential bias from including patients with type 1 diabetes ($n = 2$ for men; $n = 3$ for women); or (vii) were diagnosed with stomach cancer before diabetes ($n = 1$ for men; $n = 2$ for women). After these exclusions, 61 283 men and 73 042 women were included in the current analysis.

Outcome ascertainment. The incident stomach cancer cases were defined as primary tumors with the International Classification of Diseases-9 codes of 151. All cases were identified through annual record linkage to the Shanghai Cancer Registry and Shanghai Municipal Registry of Vital Statistics. All possible cancer cases were further verified through home visits and further review of medical charts by clinical and/or pathological experts. Outcome data through to September 2013 were used for the current analysis.

Diabetes assessment. Self-reported diabetes was recorded on the baseline questionnaires (2002–2006 for the SMHS; 1996–2000 for the SWHS) and updated in each of the subsequent follow-up questionnaires (2004–2008 and 2008–2011 for the SMHS; 2000–2002, 2002–2004, 2004–2007, and 2007–2010 for the SWHS). During interviews, participants were asked whether they had ever been diagnosed with diabetes by a physician (yes/no), and the age at diagnosis was also collected. From the middle of the first follow-up for women, and for all subsequent surveys, all participants were additionally asked in what year and month and in which hospital their diabetes was diagnosed for the first time. To further confirm whether participants have ever been diagnosed with diabetes, individuals were asked if they met at least one of the following criteria: (i) fasting plasma glucose concentration ≥ 7 mmol/L or oral glucose tolerance test carried out in the doctor's office with a value ≥ 11.1 mmol/L on at least two separate occasions; and (ii) use of hypoglycemic medication (i.e., insulin or hypoglycemic agents).^(f2)

Covariates. Covariates were selected based on their potential role in modifying the association between T2DM and stomach cancer. All covariates were collected at baseline interview that are important in T2DM development, including age, education (\leq elementary school, middle school, high school, $>$ high school), income (low, low to middle, middle to high, high), total energy intake (kcal/day), physical exercise (MET h/week), fruit intake (g/day), vegetable intake (g/day), red meat intake (g/day), body mass index (BMI; kg/m²), ever smoke (yes/no), ever drink alcohol (%), ever drink tea (%), ever had

chronic gastritis (yes/no), and family history of stomach cancer (yes/no).

Statistical analysis. Age-adjusted and multivariate-adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox regression models with age as the timescale to evaluate the association of T2DM with the risk of stomach cancer. In the main analyses, T2DM (yes/no) and duration (no history of diabetes/diabetes diagnosed < 5 years prior to baseline/diabetes diagnosed ≥ 5 years prior to baseline) were modeled as a time-dependent exposure. For example, a person who was first diagnosed with T2DM in September 1998 would contribute person-time to the non-diabetic group from baseline interview to September 1998, and contribute person-time to the diabetic group afterward. We further stratified the data by age groups, smoking status, ever had history of gastritis, and BMI groups. To evaluate the potential effect for over diagnosis bias, we calculated age-adjusted incidence rates by different time intervals of follow-up (0–1, 1–3, ≥ 3 years) in the diabetes cohort and no-diabetes cohort, directly standardized by the entire cohort population. In further analyses, we excluded stomach cases that occurred within the first 2 years after baseline interview, included only those diagnosed with distal stomach cancer, and categorized the exposure solely on the status at baseline. All statistical analyses were carried out using SAS 9.2 (SAS Institute, Cary, NC, USA) and a two-sided P -value of 0.05 was considered statistically significant.

Results

The distributions of selected baseline characteristics of the study subjects according to T2DM status are shown in Table 1. A total of 9.5% (5798) men and 10.2% (7416) women in the two cohorts had been diagnosed with T2DM at baseline or during follow-up periods. Compared to those without diabetes, both female and male diabetes patients were older and had a higher BMI, but were less likely to have a middle school education or greater, or to have a history of chronic gastritis. In addition, people diagnosed with T2DM had lower fruit consumption, red meat consumption, and total energy intake, but higher vegetable consumption than those not diagnosed with T2DM.

After a median follow-up of 7.5 years for the SMHS and 13.2 years for the SWHS, 755 incident cases of stomach cancer (376 men and 379 women) were identified in the two cohorts. For men, the age-standardized incidence rates (1/100 000 person-years) of stomach cancer were 0.00, 12.61, and 97.94 for 0–1, 1–3, and ≥ 3 years following the diabetes index date, respectively, in the diabetes cohort, and 9.17, 16.50, and 52.14 for 0–1, 1–3, ≥ 3 years since baseline interview, respectively, for the cohort without diabetes. For women, the age-standardized incidence rates (1/100 000 person-years) were 11.21, 5.87, and 116.00 for 0–1, 1–3, and ≥ 3 years following the diabetes index date, respectively, in diabetes members; and 5.21, 9.22, and 64.17 for 0–1, 1–3, ≥ 3 years since baseline interview, respectively, for non-diabetes members.

The associations of T2DM with risk of stomach cancer are presented in Table 2. Type 2 diabetes mellitus was not associated with the risk of developing stomach cancer in both cohorts (multi-adjusted HR = 0.83, 95% CI, 0.59–1.16 in men; multi-adjusted HR = 0.92, 95% CI, 0.68–1.25 in women). These null associations remained after excluding stomach cancer cases occurred within the first 2 years after baseline interview, including distal stomach cancer cases only, or assessing diabetes status at baseline only (Tables S1–S3).

Table 1. Characteristics of study participants according to type 2 diabetes mellitus (T2DM) status at baseline in the Shanghai Women's Health Study and Shanghai Men's Health Study

Baseline characteristic	Men			Women		
	No T2DM	T2DM	<i>P</i> -value	No T2DM	T2DM	<i>P</i> -value
No. of subjects	55 485	5798		65 626	7416	
Mean age at baseline, years	54.90 ± 9.63	59.66 ± 9.65	<0.0001	51.91 ± 8.91	57.78 ± 8.58	<0.0001
Education, %						
≤Elementary school	6.30	10.53		19.14	40.74	
Middle school	33.46	34.40		37.94	30.78	
High school	36.69	30.20		28.93	19.28	
≥Prof/Tech/College	23.55	24.87	<0.0001	13.99	9.20	<0.0001
Income, %†						
Low	55.24	54.33		15.58	20.75	
Low–middle	42.52	43.65		38.07	39.72	
Middle–high	1.86	1.71		28.47	24.75	
High	0.38	0.31	0.3000	17.88	14.78	<0.0001
Physical exercise, MET h/week	59.54 ± 34.10	60.35 ± 35.57	0.1000	106.9 ± 45.34	103.3 ± 43.49	<0.0001
Total energy intake, kcal/day	1918.2 ± 484.5	1822.7 ± 481.7	<0.0001	1680.3 ± 401.5	1645.4 ± 438.3	<0.0001
Fruit intake, g/day	155.9 ± 126.1	110.8 ± 119.2	<0.0001	272.0 ± 178.4	199.2 ± 176.9	<0.0001
Vegetable intake, g/day	341.4 ± 190.2	367.8 ± 216.2	<0.0001	295.6 ± 168.9	304.6 ± 185.5	<0.0001
Red meat intake, g/day	63.60 ± 44.75	60.18 ± 44.65	<0.0001	51.38 ± 36.53	47.92 ± 37.53	<0.0001
BMI, kg/m ²	23.61 ± 3.06	24.80 ± 3.06	<0.0001	23.78 ± 3.31	26.06 ± 3.71	<0.0001
Ever smoke, %	70.23	63.73	<0.0001	2.57	4.63	<0.0001
Ever drink alcohol, %	34.05	30.36	<0.0001	2.29	1.87	0.0200
Ever drink tea, %	66.98	68.64	0.0100	30.05	28.60	0.0100
Ever had chronic gastritis, %	15.36	12.97	<0.0001	19.83	17.93	<0.0001
Family history of stomach cancer, %	6.31	7.32	0.0030	5.81	6.07	0.3700

†Low, <10 000 yuan per family per year for women and <1000 yuan per person per month for men; Low–middle, 10 000–19 999 yuan per family per year for women and 1000–3000 yuan per person per month for men; Middle–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. BMI, body mass index; MET, metabolic equivalent.

Table 2. Hazard ratios (HRs) for the association between type 2 diabetes mellitus (T2DM) and stomach cancer

Population	No T2DM		T2DM		
	Cases, <i>n</i>	HR (95% CI)	Cases, <i>n</i>	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)†
All	664/1 258 950	1.00 (ref.)	91/134 728	0.90 (0.72–1.13)	0.88 (0.70–1.10)
Women	329/848 845	1.00 (ref.)	50/92 640	0.98 (0.73–1.33)	0.92 (0.68–1.25)
Men	335/410 105	1.00 (ref.)	41/42 088	0.88 (0.64–1.22)	0.83 (0.59–1.16)
≤65 years old	412/1 077 067	1.00 (ref.)	47/97 048	0.96 (0.71–1.31)	0.94 (0.69–1.29)
>65 years old	252/181 884	1.00 (ref.)	44/37 680	0.86 (0.62–1.18)	0.78 (0.56–1.10)
Never smoker	407/951 864	1.00 (ref.)	68/103 937	1.05 (0.81–1.36)	1.01 (0.77–1.32)
Ever smoker	257/307 078	1.00 (ref.)	23/30 792	0.67 (0.44–1.03)	0.63 (0.41–1.00)
No gastritis	513/1 025 809	1.00 (ref.)	76/112 326	0.94 (0.74–1.20)	0.90 (0.70–1.16)
History of gastritis	151/233 141	1.00 (ref.)	15/22 402	0.76 (0.45–1.30)	0.79 (0.46–1.35)
BMI ≤ 24	343/706 940	1.00 (ref.)	30/44 428	0.89 (0.61–1.29)	0.85 (0.57–1.26)
BMI > 24	321/552 010	1.00 (ref.)	61/90 300	0.91 (0.69–1.20)	0.89 (0.67–1.18)

†Adjusted for age, sex, education, income, body mass index (BMI), chronic gastritis, family history of stomach cancer, physical exercise, total energy intake, ever smoke, ever drink tea, ever drink alcohol, vegetable intake, red meat intake, and fruit intake. CI, confidence interval; HR, hazard ratio; ref., reference.

We carried out stratified analyses to determine if T2DM and stomach cancer risk differ by gender, age groups, smoking status, ever had history of gastritis, and BMI groups. Results from subgroup analyses did not appreciably alter the main results.

When examining the exposure as duration of diabetes prior to baseline, we did find a suggestion of an increased risk of stomach cancer for individuals diagnosed with T2DM ≥5 years prior to baseline, particularly for the traditionally low-risk groups for stomach cancer of never smokers, and individuals

without a history of gastritis, but after adjustment for potential confounders these associations did not reach statistical significance (Table S4).

Discussion

In these two large cohort studies, we did not observe a statistically significant association between T2DM and risk of stomach cancer in Chinese men and women. To our knowledge,

this is the first attempt to evaluate stomach cancer risk in relation to T2DM in mainland China.

It has shown that diabetes and cancer are more frequently diagnosed within the same individual than would be expected by chance, even after adjusting for age.⁽¹³⁾ Although the underlying biology of this linkage remains unclear, several possible mechanisms have been proposed. Hyperinsulinemia may lead to cancer through insulin's effect on its cognate receptor and the insulin-like growth factor system, and the effects of insulin and insulin-like growth factor I on cancer development and progression have been shown in animal and human studies.⁽¹⁴⁾ Hyperglycemia may cause dysregulation of energy balance, impair the effect of ascorbic acid on the intracellular metabolism, and reduce the effectiveness of the immune system, which could favor cancer during the onset and progression in diabetic patients.⁽¹⁵⁾ In addition, common risk factors such as obesity also could modulate energy balance, calorie restriction, growth factors, multiple signaling pathways, and inflammatory processes.⁽¹⁶⁾

We previously studied the associations between T2DM and some common cancers in this same population. For example, we found an increased risk of primary liver cancer among T2DM patients in SWHS and SMHS, but failed to find any significant relationship between T2DM and lung cancer in these two cohorts.^(12,17) Although a possible association between diabetes and an increased risk of stomach cancer has been examined in numerous studies, the findings have been inconsistent. The two most recent meta-analyses (comprising approximately 20 studies each) found that while the majority of the studies found null associations, with significant heterogeneity, taken together there is a 10–18% increase in odds for gastric cancer among patients with diabetes, particularly for women and those with longer follow-up.^(8,9)

However, there are a number of individual investigations that have found an inverse association between diabetes and stomach cancer risk. Results from a large cohort of US veterans showed that men with diabetes had a borderline significant reduced risk of stomach cancer (adjusted relative risk = 0.95, 95% CI, 0.89–1.02), and this association was more pronounced in black veterans (adjusted relative risk = 0.85, 95% CI, 0.75–0.96).⁽¹⁸⁾ The same trend of significant inverse association was also found in a case-control study in northern Italy and in a nationwide population-based cohort in Taiwan.^(19,20) Another National Health Insurance Research Database in Taiwan observed a significantly lower incidence (odds ratio = 0.63) of stomach cancer during the first 5 years after diabetes diagnosis, but a greater risk (odds ratio = 1.76) for the past 5 years after diabetes diagnosis.⁽²¹⁾ Some studies found diabetes was positively associated with risk of stomach cancer. Research of a Japanese population-

based cohort indicated that a higher level of hemoglobin A1c (6.0–6.9% and >7.0% groups) was associated with an increased risk of stomach cancer compared with the 5.0–5.9% group, and subjects who were *Helicobacter pylori* positive with modest (5.3–5.8 mmol/L) and high (>5.8 mmol/L) fasting plasma glucose levels or had both high hemoglobin A1c levels (>6.0%) and *H. pylori* infection had significantly elevated cancer risk.^(22,23) Additionally, a Japan public health center-based prospective study found borderline significant increases in stomach cancer risk both in male and female diabetes patients after adjusting for age, study area, history of cerebrovascular disease, history of ischemic heart disease, smoking, ethanol intake, BMI, leisure time physical activity, green vegetable intake, and coffee intake.⁽²⁴⁾

Null associations were reported in a retrospective cohort study in Israel,⁽²⁵⁾ in Taiwan's National Health Research Institutes database study,⁽²⁶⁾ in the population of Tayside Health Board in Scotland,⁽²⁷⁾ in a population-based cohort in Austria,⁽²⁸⁾ and in a pooled analysis of eight cohort studies in Japan.⁽²⁹⁾ Possible reasons for inconsistent results are different study population, sample size, and confounding adjustment. In our study, we failed to find any significant association between T2DM and stomach cancer risk, even though we had a large study population examined prospectively and were able to adjust for numerous potential confounders.

Strengths of our study include the population-based cohort design, large sample size, high response rates of follow up (over 96% for in-person home visits), and the use of updated diabetes status. There are several limitations to this study that should be noted. Although other validation studies^(30–32) indicated that the self-reported diabetes was reasonably accurate and could provide a useful assessment for broad measures of diabetes in the two cohorts, the misclassification of T2DM cannot be ruled out, as a number of patients might not know they had diabetes, and thus could lead to the underestimation of the true association. Other limitations of this study include the lack of information on antidiabetic pharmacological therapy and *H. pylori* infection status, which may in turn directly or indirectly promote or inhibit cancer progression. For instance, patients who used metformin only showed a lower incidence of gastric cancer than those who did not use metformin, and significance was more obvious in patients who used metformin for more than 3 years.⁽³³⁾

In summary, our two cohort studies indicate that T2DM is not associated with stomach cancer risk in Chinese men and women in urban Shanghai, consistent with the generally null findings from research in other populations.

Disclosure Statement

The authors have no conflict of interest.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Table S1. Hazard ratios (HRs) for the association between type 2 diabetes mellitus and stomach cancer, after excluding cancer cases that occurred within the first 2 years after baseline interview.

Table S2. Hazard ratios (HRs) for the association between type 2 diabetes mellitus and distal stomach cancer.

Table S3. Hazard ratios (HRs) for the association between baseline identified type 2 diabetes mellitus and stomach cancer.

Table S4. Hazard ratios (HRs) for the association between type 2 diabetes mellitus and stomach cancer, stratified by years from type 2 diabetes onset to baseline.