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Prospective evaluation of type 2 diabetes mellitus on the risk of primary liver cancer in Chinese men and women

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Background: No prospective study has investigated the relationship between type 2 diabetes mellitus (T2DM) and the risk of primary liver cancer (PLC) in mainland China, and little is known about the effect of diabetes duration on PLC risk.

Design: Data from two population-based cohorts (the Shanghai Men's Health Study, SMHS, 2002–2006 and the Shanghai Women's Health Study, SWHS, 1996–2000) were thus used to assess the associations among T2DM, diabetes duration and PLC risk in Chinese population.

Results: During follow-up through 2009, 344 incident PLC cases were identified among 60 183 men and 73 105 women. T2DM is significantly associated with the increased risk of PLC in both men [hazard ratio (HR) = 1.63, 95% confidence interval (CI) 1.06–2.51] and women (HR = 1.64, 95% CI 1.03–2.61). The highest risk of incident liver cancer was observed in the first 5 years after diabetes diagnosis, and decreased substantially with the prolonged diabetes duration ($P_{\text{trend}} < 0.001$). No synergistic interaction in the development of PLC was found between diabetes and other known risk factors.

Conclusions: T2DM is associated with the increased risk of subsequent liver cancer within 5 years after diagnosis in Chinese population, suggesting that hyperinsulinaemia rather than hyperglycaemia is more likely to be a primary mediator for this association.

Key words: China, cohort study, primary liver cancer, type 2 diabetes

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introduction

Although a declining trend of primary liver cancer (PLC) morbidity and mortality was observed in several Chinese registry catchment populations over the last few decades [1, 2], the incidence rates in China are still among the highest worldwide. Recently, the prevalence of diabetes mellitus (DM) increased substantially in China, with the age-standardized rates from 2.4% in 1994 [3] to 9.7% in 2007–2008 [4], which may parallel a marked lifestyle transition [5]. Unlike the steady transition in most Western developed countries, these changes have occurred within a very short period in China [6].

Several cohort studies have investigated the association between type 2 diabetes mellitus (T2DM) and hepatocellular carcinoma (HCC) risk [7]. However, such an association has, to our knowledge, not previously been examined in detail in mainland China. Given the aforementioned increasing prevalence of DM in China, if such condition is associated even with a little increase in the risk of HCC, this will translate into important consequences for public health [8]. Moreover, several key questions regarding the association between T2DM and the risk of development of PLC still remained. First, a critical question, as suggested by the American Diabetes Association (ADA) and the American Cancer Society (ACS) [9], is whether the associations between diabetes and the risk of certain cancers are largely attributed to their co-risk factors such as obesity and physical inactivity. Second, although a positive link has been demonstrated for HCC in several prospective studies, these may reflect some degree of ‘reverse causality’ because in some cases diabetes might itself be a result of chronic liver diseases [10]. Third, because the over-detection bias (i.e. the increased detection around the time of T2DM diagnosis) may exist in the DM–cancer association study, which makes that newly diagnosed DM is more likely to be diagnosed with cancer [11], the effect of diabetes would be overestimated. Fourth, most of the pertinent studies only considered a single measurement of DM at baseline. This may have resulted in some underestimation of the true associations since the diabetes initially identified during the follow-up time were neglected. Finally, no prospective study has assessed the effect of diabetes duration on the liver cancer risk to our knowledge.

We thus investigated the association between T2DM and liver cancer risk using data from two large ongoing population-based prospective cohorts in Shanghai, one of the largest cities with a high incidence of liver cancer in China.

methods

study population

Participants in this study were selected from the 61 491 men of the Shanghai Men’s Health Study (SMHS) and 74 942 women of the Shanghai Women’s Health Study (SWHS). Details on the designs and methods used in these studies have been described elsewhere [12, 13]. Briefly, for the SWHS, 74 941 women aged 40–70 years old in Shanghai were recruited from 1996 to 2000, with an overall study participation rate of 92.7%. For the SMHS, 61 491 men aged 40–74 years old with no history of cancer were recruited in Shanghai from 2002 to 2006, with an overall study participation rate of 74.1%. Participants were interviewed in person using a

structured questionnaire to obtain information about demographic characteristics, lifestyle, 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 to 3 years to update exposure information and to learn of newly diagnosed cancers. For the SMHS, the first follow-up interview was conducted from 2004 to 2008 with a response rate of 97.6%. For the SWHS, the first, second and third follow-ups were conducted from 2000 to 2002, 2002 to 2004 and 2004 to 2007 with the corresponding response rates of 99.8, 98.7 and 96.7%, respectively. All participants provided written informed consent.

We excluded participants from this analysis if they: (i) had a previous diagnosis of cancer at baseline (none for men and $n = 1579$ for women), (ii) were younger than 20 years on the day of DM diagnosis to reduce potential bias from including patients with type 1 diabetes ($n = 3$ for men and $n = 4$ for women), (iii) died of cancers of unknown primary site or without diagnosis date ($n = 133$ for men and $n = 135$ for women), (iv) had missing data for any of the covariates of interest ($n = 1170$ for men and $n = 117$ for women) and (v) was diagnosed with PLC before the diagnosis of diabetes ($n = 2$ for both men and women). After exclusion, 60 183 men and 73 105 women were included in current analysis.

DM assessment

Self-reported DM 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 DM had been diagnosed since the most recent survey. In the current study, a case of T2DM was considered to be confirmed if the participant reported having been diagnosed with type 2 diabetes and met at least one of the following criteria: (i) fasting plasma glucose concentration ≥ 7 mmol/l on two separate occasions, (ii) plasma glucose concentration ≥ 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.

outcome ascertainment

The incident liver cancer cases were defined as a primary tumour with an International Classification of Diseases (ICD)-9 code of 155, and were identified through annual record linkage to the Shanghai Cancer Registry, Shanghai Municipal Registry of Vital Statistics, and Shanghai Resident Registry. 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, 2009 for both men and women was used for the current analysis.

statistical analysis

Age-adjusted and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox regression models with age as the time scale to estimate the associations of T2DM with the risk of PLC.

T2DM (yes/no) and duration were modelled as a time-dependent exposure, meaning that information on T2DM reported in questionnaire n was used to prospectively categorize participants for the period between the

completion of questionnaires n , and $n + 1$, and the risk time was allocated to the corresponding groups. In the SWHS, for example, a participant who first reported having T2DM in 2001 would contribute person-time to the non-diabetes group from 1996 to 2000, whereas from 2001 onward, this participant would contribute person-time to the diabetes group.

Covariates were selected based on their potential to confound or modify the association between T2DM and PLC. All covariates were modelled using baseline values. The covariates included in the multivariate-adjusted models were age (<50, 50–60, ≥60 years), 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), occupation [housewife (women only), manual, clerical and professional], ever smoking (yes/no), ever alcohol drinking (yes/no), family history of cancer (yes/no), total energy intake (kcal/day, quartiles), fruit intake (g/day, quartiles), vegetable intake (g/day, quartiles), total physical activity [PA; standard metabolic equivalents (METs) as MET-h/day in quartiles; 1 MET-h = 15 min of moderate intensity activity], history of hepatitis/chronic liver disease (yes/no), hormone replacement therapy (HRT; yes/no for women only), menopausal status (pre- and post-menopausal for women only). We also tested for potential interactions between DM and age, income, education, occupation, BMI, history of hepatitis/chronic liver disease, alcohol drinking, physical activity and smoking.

In sensitivity analyses, we repeated the analysis after excluding PLC cases occurred within 1 year after the onset of diabetes to reduce the potential bias of reverse causality. Considering that diabetes might itself be a result of chronic liver diseases, we further repeated the analysis after excluding the participants whose diagnosis of chronic liver diseases is before the diagnosis of diabetes. Given the possible changes in weight after DM diagnosis, we repeated the analysis using the BMI at the age of 20 years to replace the BMI at baseline in the models. We also restricted the analysis in subjects who are of normal body weight ($18.5 \leq \text{BMI} < 24$) and have regular physical exercise to examine whether the association between T2DM and PLC could attribute to their shared risk factors (obesity and physical inactivity).

To evaluate the potential effect for over-detection bias, 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 PLC, and were directly standardized by the entire cohort population.

In testing of the proportional hazard assumption by creating interaction of DM and a logarithm of time in the model, we found no violation of proportionality. Statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC) and a two-sided P value of 0.05 was considered statistically significant.

results

Table 1 shows baseline characteristics of participants with and without T2DM. Compared with men and women without T2DM at baseline, participants with T2DM were older, more obese and had more history of hepatitis or chronic liver disease, less physical activity, more total energy and vegetable intake, less fruit intake and alcohol drinking.

During a median follow-up of 5.5 years in the SMHS and 11.2 years in the SWHS, 344 (204 for men and 140 for women) incident cases were documented. Table 2 shows the standardized incidence rates (per 100 000 person-years) of PLC in the T2DM and control cohorts throughout the entire follow-up. In the first year following the diabetes index date, the age-adjusted incidence rates for men and women were all lower in the diabetic cohort (11.10/100 000 person-years for

men and 8.80/100 000 person-years for women), compared with those without diabetes regardless of different time intervals of follow-up.

Table 3 presents the associations between T2DM and the risk of PLC. Among men, pre-existing diabetes is associated with a 63% (95% CI: 1.06–2.51) higher risk of incident liver cancer compared with non-diabetes. When considering major potential confounders (i.e. chronic liver disease and alcohol drinking), the positive association remained but not statistically significant. However, the significantly positive association cannot be reversed in other sensitivity analyses among men. Among women, pre-existing diabetes is associated with a 64% (95% CI: 1.03–2.61) higher risk of incident liver cancer. Because of only one case in the diabetic group who had a normal body weight and regular exercise at baseline, the results regarding this sensitivity analysis were not shown; whereas in other sensitivity analyses, the pertinent results cannot alter the main finding. There was no significant interaction between type 2 diabetes and age, income, education, occupation, BMI, history of hepatitis/chronic liver disease, alcohol drinking, physical activity and smoking either in men or in women (data not shown).

The association between T2DM duration and PLC risk is shown in Table 4. The highest risk of incident PLC was observed in the first 5 years following the diabetes index date with the HRs of 4.79 (95% CI: 2.23–10.29) among men and 79.70 (95% CI: 35.07–181.05) among women, and decreased substantially with diabetes duration ($P_{\text{trend}} < 0.001$).

discussion

This is the first population-based prospective investigation on the association between type 2 diabetes and PLC in the mainland China. We found that DM is an independent risk factor for PLC with a modest elevated risk of 63% and 64% for men and women, respectively, and such risk is correlated with a short diabetes duration. Given the high prevalence and incidence of diabetes and PLC in the general population in China, the observed association has both clinical and public health importance.

The adjusted HR for developing PLC in diabetics in this analysis is close to 1.65, which is lower than the risk observed in other earlier prospective studies. In our recent meta-analysis of prospective cohort studies through January, 2011 [7], DM is significantly associated with 87% and 88% increased risk of HCC incidence and mortality, respectively. In more recent prospective investigations in Taiwan, however, the relative risk of liver cancer was found to be 1.67 (95% CI 1.39–2.01) with a sample size of 985 815 participants [14], and 1.73 (95% CI 1.47–2.03) with a sample size of 96 745 participants [15], which are in accordance with the current analysis. No synergistic effect on the development of liver cancer has been found between DM and BMI, history of hepatitis/chronic liver disease, alcohol drinking, physical activity and smoking in the present study, although previous studies have reported that chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections [15–17], alcohol use [18, 19], cirrhosis [15, 20] could modify the association of DM with the development of HCC.

Table 1. Baseline characteristics by type 2 diabetes status in the Shanghai Men's Health Study SMHS, (2002–2006) and the Shanghai Women's Health Study (SWHS, 1996–2000)

Baseline Characteristics	Men			Women		
	No type 2 DM	Type 2 DM	P value	No type 2 DM	Type 2 DM	P value
Number of subjects	55 551	4632		66 821	6284	
Mean age at baseline (years)	54.90 ± 9.63	60.49 ± 9.71	<0.001	51.94 ± 8.91	58.30 ± 8.34	<0.001
Education level (%)						
≤Elementary school	6.31	11.44	<0.001	19.28	43.14	<0.001
Middle school	33.54	33.51		37.94	29.25	
High school	36.66	29.47		28.86	18.44	
≥Prof/Tech/College	23.50	25.58		13.92	9.17	
Income (%) ^a						
Low	12.88	9.22	<0.001	15.58	21.45	<0.001
Low-middle	77.46	80.87		38.08	39.82	
Middle-high	8.90	9.24		28.47	24.40	
High	0.76	0.67		17.87	14.34	
Occupation (%)						
Housewife	–	–		0.34	0.64	
Professional	25.79	31.91		29.98	23.87	
Clerical	21.90	22.50		20.80	20.32	
Manual worker	52.31	45.53	<0.001	49.87	56.17	<0.001
BMI kg/m ²	23.64 ± 3.07	24.62 ± 3.04	<0.001	23.82 ± 3.33	26.00 ± 3.76	<0.001
<18.5 (%)	4.50	1.53		3.58	1.30	<0.001
18.5–24.0 (%)	50.76	43.11		51.81	29.06	
24.0–28.0 (%)	37.02	41.52		33.84	42.39	
>28 (%)	7.72	13.84	<0.001	10.77	27.24	
Ever smokers (%)	70.39	62.09	<0.001	2.58	4.73	<0.001
Physical excise (MET h/week) ^b	59.58 ± 34.05	61.06 ± 35.82	0.005	106.97 ± 45.30	102.50 ± 43.31	<0.001
Ever alcohol intake (%)	34.10	29.51	0.028	2.29	1.88	0.036
Total energy intake (kcal/day) ^b	8031.30 ± 2031.00	7487.00 ± 1936.60	<0.001	7034.10 ± 1681.40	6846.70 ± 1841.90	<0.001
Fruit intake (g/day) ^b	155.25 ± 125.35	98.64 ± 110.66	<0.001	272.07 ± 178.36	187.92 ± 175.22	<0.001
Vegetable intake (g/day) ^b	341.22 ± 190.13	367.14 ± 218.26	<0.001	291.93 ± 168.31	305.87 ± 188.78	<0.001
History of hepatitis/chronic						
Liver disease (%)	2.71	4.10	<0.001	2.51	3.25	0.001
Family history of cancer (%)	28.42	29.90	0.016	26.49	26.65	0.771
Post-menopausal (%)	–	–	–	46.25	76.58	<0.001
HRT use (%)	–	–	–	2.07	2.10	0.870

^aLow: <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.

^bContinuous variables are presented as the mean ± standard deviation.

BMI, body mass index; DM, diabetes mellitus; MET, metabolic equivalents (1 MET-h = 15 min of moderate intensity activity); HRT, hormone replacement therapy;

In sensitivity analyses, we found a positive and similar diabetes–liver cancer association in alcohol never-users and in subjects free of chronic liver disease among women (Table 3), thus ruling out a possibility that the modest diabetes–liver cancer association represents residual confounding by alcohol or chronic HBV/HCV infection on liver cancer risk. However, such an association was not statistically significant but positive in male gender, which could be partly due to the limited cases and a consequence of insufficient power in these sensitivity analyses among men (Table 3).

Previous studies have suggested that the sedentary lifestyle and high BMI are associated with both diabetes [21–23] and liver cancer [24–26]. As proposed by ADA and ACS [9], we then restricted the analysis in subjects who are of normal body

weight and have regular physical exercise at baseline, and yielded the positive link, ruling out the possibility that the association between diabetes and liver cancer is caused by their shared risk factors (obese and physical inactivity). Despite the possible changes in body weight after the diabetes diagnosis [27], the results from the models using the BMI at the age of 20 years were similar to the results from the analysis using the BMI at baseline. A cohort study [11] conducted in British Columbia found that the elevated risk of some cancers in diabetics may be partly due to the increased detections around the time of diabetes diagnosis, practically in the first 3 months following the diabetes index date with a cancer incidence rate (per 1000 person-years) of 35.35 in diabetic group, compared with 14.13 in non-diabetics. In our study, the increased

Table 2. Standardized incidence rates (per 100 000 person-years) for primary liver cancer (PLC) in type 2 diabetes and control cohorts, the Shanghai Men's Health Study (SMHS, 2002–2006) and the Shanghai Women's Health Study (SWHS, 1996–2000)^a

	Men		Women	
	Cases	Incidence rate	Cases	Incidence rate
Diabetics	26	77.63	25	22.78
0–1 year since index date of diabetes	1	11.10	1	8.80
1–3 years since index date of diabetes	10	100.54	4	19.53
>3 years since index date of diabetes	15	85.26	20	25.45
Non-diabetics	178	59.59	115	15.93
0 to 1 year since baseline interview	34	61.63	11	16.85
1–3 years since baseline interview	64	58.33	26	19.40
>3 years since baseline interview	80	58.86	78	14.92

^aThe incidence rates for liver cancer were directly standardized by the entire cohort population.

ascertainment in diabetics is unlikely to occur among persons with T2DM, given the lower incidence rates of PLC in the diabetic cohort within the first year after the diabetes diagnosis, compared with those without diabetes regardless of different time intervals of follow-up (Table 2). However, the small number of PLC cases among subjects with diabetes is a limitation that may undermine the likelihood of these results.

In addition to over-detection bias, another concern is the methodological issues related to reverse causality. Patients with chronic liver diseases or cirrhosis frequently develop impaired glucose tolerance or overt diabetes [10], making it difficult to determine whether a direct relationship exists between diabetes and cancer. Because the positive links between DM and PLC risks were observed in the analysis after exclusion of PLC cases that occurred within the first year after diabetes onset, and in the analysis after excluding the participants diagnosed with chronic liver diseases before the diagnosis of DM, this reverse causality is less likely to explain the current DM–PLC association.

Our study is the first prospective investigation regarding the association between the diabetes duration and PLC risk, and found that the positive link between diabetes and PLC was correlated with the short diabetes duration, which supports the insulin–cancer hypothesis [28–30] that hyperinsulinaemia

Table 3. Hazard ratios (HRs) for the association between type 2 diabetes and primary liver cancer (PLC), the Shanghai Men's Health Study (SMHS, 2002–2006) and the Shanghai Women's Health Study (SWHS, 1996–2000)

	No type 2 DM		Type 2 DM		
	No. of cases/person-years	HR (95%CI)	No. of cases/person-years	Age-adjusted HR (95%CI)	Multivariable-adjusted HR (95%CI) ^b
Men					
Total ^a	178/303 796	1.00 (referent)	26/24 895	1.58 (1.04–2.40)	1.63 (1.06–2.51)
Model 1 ^b	144/303 778	1.00 (referent)	25/24 894	1.83 (1.19–2.82)	1.85 (1.18–2.80)
Model 2 ^c	178/303 796	1.00 (referent)	20/24 022	1.27 (0.79–2.02)	2.02 (1.24–3.28)
Model 3 ^d	33/52 048	1.00 (referent)	9/5315	2.41 (1.14–5.09)	2.71 (1.23–5.98)
Model 4 ^e	155/263 720	1.00 (referent)	22/20 715	1.60 (1.02–2.52)	1.57 (0.99–2.52)
Model 5 ^f	59/91 301	1.00 (referent)	9/9616	1.50 (0.73–3.05)	1.46 (0.69–3.12)
Model 6 ^g	117/295 656	1.00 (referent)	15/23 893	1.29 (0.75–2.22)	1.40 (0.79–2.46)
Women					
Total ^a	115/738 447	1.00 (referent)	25/67 247	1.86 (1.19–2.92)	1.64 (1.03–2.61)
Model 1 ^b	104/738 441	1.00 (referent)	24/67 246	1.96 (1.23–3.11)	1.70 (1.05–2.74)
Model 2 ^c	115/738 447	1.00 (referent)	22/65 167	1.67 (1.04–2.68)	1.76 (1.06–2.90)
Model 3 ^e	78/643 751	1.00 (referent)	15/ 51 374	2.13 (1.21–3.76)	1.86 (1.04–3.34)
Model 4 ^f	114/732 667	1.00 (referent)	24/66 144	1.81 (1.15–2.87)	1.59 (0.99–2.55)
Model 5 ^g	95/732 940	1.00 (referent)	21/67 131	1.74 (1.06–2.84)	1.59 (0.96–2.64)

^aThe entire cohort;

^bAnalysis after excluding liver cancer cases occurred within the first year after diabetes onset;

^cAnalysis after excluding participants whose diagnosis of chronic hepatitis/chronic liver diseases was before diabetes diagnosis;

^dAnalysis in those who are of normal body weight ($18.5 \leq$ body mass index, BMI, < 24) and have regular exercise within past 5 years at baseline;

^eAnalysis using BMI at age 20 years to replace the BMI at baseline;

^fAnalysis within subjects who were alcohol never-users at baseline;

^gAnalysis within subjects who were free of chronic hepatitis/chronic liver diseases at baseline;

^hAdjusted for age, birth cohort, education, income, BMI, occupation, ever smoking, ever alcohol drinking, family history of cancer, total energy intake, fruit intake, vegetable intake, total physical activity, history of chronic hepatitis or chronic liver disease, hormone replacement therapy (HRT, women only) and menopausal status (women only).

CI: confidence interval; HR: hazard ratio.

Table 4. Hazard ratios (HRs) for the association between type 2 diabetes duration and primary liver cancer (PLC), the Shanghai Men's Health Study (SMHS, 2002–2006) and the Shanghai Women's Health Study (SWHS, 1996–2000)^a

	Men		Women	
	No. of cases/person-years	Multivariable-adjusted HR (95%CI) ^b	No. of cases/person-years	Multivariable-adjusted HR (95%CI) ^b
Duration of type 2 DM (years)				
No type 2 DM	178/303 796	1.00 (referent)	115/738 447	1.00 (referent)
<5	7/3718	4.79 (2.23–10.29)	12/4014	79.70 (35.07–181.05)
5 to 10	10/ 10 446	1.58 (0.82–3.03)	8/24 824	4.22 (2.03–8.73)
≥10	9/10 731	1.07 (0.54–2.13)	4/31 472	0.46 (0.18–1.14)
P _{trend}		<0.001		<0.001

^aModels exclude participants with an unknown duration of diabetes.

^bThe adjusted covariates are as indicated in Table 3.

CI: confidence interval; HR: hazard ratio.

combined with insulin resistance, rather than hyperglycaemia, is a primary mediator for the DM–HCC association. Because beta-cells in the pancreas are expected to produce lower insulin plasma levels compared with their earlier stage of diabetes, it is reasonable to observe an inverse association between diabetes duration and cancer development if hyperinsulinaemia plays a key role in this association.

Strengths of the current study include the population-based prospective cohort design, large sample size and verified cancer outcomes. In addition, taking into account the variation of diabetes status during the follow-up period strengthened the association. However, several limitations should be noted. First, our study is lacking laboratory test on the hepatitis virus infection status which is assumed to be a potential confounder; therefore, we can only use the self-reported data on chronic hepatitis or chronic liver disease (yes/no); whereas the misclassification of chronic hepatitis or liver diseases could not be ruled out. Second, T2DM is self-reported and many patients with type 2 diabetes did not know they had the disease [31]; likewise, the misclassification of exposure may exist and would be nondifferential, leading to the underestimation of the observed association. However, previous studies [32, 33] regarding the validation of self-reported T2DM showed that a self-reported history of diabetes may be reasonably accurate and could provide a useful estimate for broad measures of population prevalence; moreover, our previous meta-analysis [7] found that pooled analysis on studies using medical records as a means of DM ascertainment yielded similar results to studies using self-report data to determine the DM status. Third, due to the limited number of outcomes (only 51 liver cancer cases) among people with type 2 diabetes, the play of chance in the results could not be ruled out. Other limitations in our study include the lack of pharmacologic data on diabetes treatments, including hypoglycaemic agents use and degree of glucose control.

In conclusion, our study suggested that type 2 diabetes is an independent risk factor for PLC in Chinese men and women. Although with a modest association, the finding will translate into important consequence for the prevention of liver cancer given the increasing prevalence of diabetes in China.

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disclosure

The authors have declared no conflicts of interest.

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Adherence to treatment guidelines for primary sarcomas affects patient survival: a side study of the European CONnective Tissue Cancer NETwork (CONTICANET)

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Background: The impact of adherence to clinical practice guidelines (CPGs) for loco-regional treatment (i.e. surgery and radiotherapy) and chemotherapy on local disease control and survival in sarcoma patients was investigated in a European study conducted in an Italian region (Veneto).

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