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The association between fasting blood glucose and the risk of primary liver cancer in Chinese males: a population-based prospective study

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Background: To investigate the association between fasting blood glucose (FBG) levels and the risk of incident primary liver cancer (PLC) in Chinese males, a large prospective cohort was performed in the current study.

Methods: A total of 109 169 males participating in the routine checkups every two years were recruited in the Kailuan male cohort study since May 2006. Cox proportional hazards regression models and restricted cubic spline (RCS) were used to evaluate the association between levels of baseline FBG and the risk of incident PLC.

Results: Compared to the males with normal FBG ($3.9 \leqslant FBG < 6.1\,mmol\,l^{-1}$), the males with impaired fasting glucose (IFG: $6.1 \leqslant FBG < 7.0\,mmol\,l^{-1}$) and diabetes mellitus (DM: FBG $\geqslant 7.0\,mmol\,l^{-1}$) had a 60% (95% CI: 1.09–2.35) and a 58% (95% CI: 1.07–2.34) higher risk of incident PLC, respectively. Subgroup analysis found that IFG increased the risk of PLC among the non-smoker (HR = 1.73, 95% CI: 1.01–2.98) and current alcohol drinker (HR = 1.80, 95% CI: 1.03–3.16). While DM increased the risk of PLC especially among the males with normal BMI ($<25\,kg\,m^{-2}$) (HR = 1.76, 95% CI: 1.05–2.94) and the HBV negativity (HR = 1.89, 95% CI: 1.16–3.09), RCS analysis showed a positive non-linearly association between the FBG levels and the risk of PLC (p-overall = 0.041, p-non-linear = 0.049).

Conclusions: Increased FBG may be an important and potentially modifiable exposure that could have key scientific and clinical importance for preventing PLC development.

Primary liver cancer (PLC) is the fifth most common incident cancer and second most common cause of cancer death in males around the world. It is a major cancer especially in China where over 50% of the estimated 554 000 new cancer cases and 521 000 cancer deaths worldwide occurred in 2012, according to the estimation of GLOBOCAN series of the International Agency for Research on Cancer (IARC) (Ferlay *et al*, 2015).

Several studies have demonstrated that abnormal fasting blood glucose (FBG) levels were related to the risks of non-communicable diseases (Sarwar *et al*, 2010; Liao *et al*, 2015), including liver cancer which have been reported since 2005 (Han *et al*, 2017).

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However, a consensus regarding the association between FBG level and the risk of PLC has not been reached, leaving evidences to be further accumulated.

The recent study reported that FBG level has been steadily increasing in general population of China (Vaidya *et al*, 2016). The research on the association of PLC risk to FBG level might be helpful for identifying an important and potentially modifiable exposure of PLC, in additional to hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, and meaningful for preventing PLC development. Therefore, in the present study, we conducted a large cohort established in the Kailuan group and aim to explore the association between levels of FBG and risk of PLC in Chinese males.

MATERIALS AND METHODS

Study design and population. The data were obtained from a health examination of employees of the Kailuan Company in the city of Tangshan, Hebei Province, north of China. Tangshan is situated about 90 miles southeast of Beijing and represents the overall Chinese population from a socio-economic perspective (Xue *et al*, 2013; Wang *et al*, 2015). Over the past few decades, Kailuan Group has developed a comprehensive company managing coal production, machine manufacture, transportation, chemical production, education and health care, etc. Eleven hospitals are affiliated with the Kailuan Company and in charge of the every 2-year health examination of employees.

Participants who met the criteria as follows were enrolled in the present study: (1) males older than 18 years; (2) signing informed consent; (3) completing the questionnaire interview; (4) providing blood samples at baseline. In case of the potential survival bias, subjects who were diagnosed with any prevalent cancer before baseline checkup were excluded from the study.

The study was performed according to the guidelines of the Helsinki declaration and was approved by the Medical Ethics Committee of Kailuan General Hospital. Informed consent was obtained from all individual participants included in the study.

Exposure assessment and laboratory tests. Face-to-face interviews were performed by trained physicians or nurses for all subjects using standardised questionnaires to collect information of potential risk factors at baseline entry. Smoking was defined as tobacco smoking at least one cigarette per week for more than 6 months. Alcohol drinking was defined as drinking at least once per month for more than 6 months. Body weight and height were measured while participants were wearing light clothes without shoes, and the body-mass index (BMI) was calculated according to the equation that BMI = weight (kg)/height (m^2).

The morning fasting venous blood of all subjects were obtained to detect HBsAg and FBG. The enzyme-linked immunosorbent assay for HBsAg (SHANGHAI KEHUA BIO-ENGINEERING, KHB) was applied to detect HBsAg quantitatively. All of the tests were conducted in the central laboratory of the Kailuan General Hospital by standard operating procedure. We divided baseline FBG levels into four categories according to WHO standard: Low FBG (LFBG, $<3.9\,mmol\,l^{-1}$), the normal ($3.9-<6.1\,mmol\,l^{-1}$), impaired fasting glucose (IFG, $6.1-<7.0\,mmol\,l^{-1}$) and diabetes mellitus (DM, $\geqslant 7.0\,mmol\,l^{-1}$) (WHO, 1999).

Outcome ascertainment. We followed participants beginning at the baseline examination and ending at occurrence of cancer, death, or 31 December 2013, whichever event came first. Incident cancer cases in the cohort were collected by tracking subjects when they participated in the every 2-year routine health examination until 31 December, 2013. In addition, medical records from Tangshan medical insurance system and death certificates from Kailuan social security system were checked yearly to get outcome information that may have been missed. Moreover, the outcome information was further confirmed by checking discharge summaries from the 11 affiliated hospitals where participants were treated and diagnosed once a year (Wang *et al*, 2015).

The diagnosis of incident liver cancer was confirmed by medical records review by clinical experts. Information of pathological diagnosis, imaging diagnosis (including ultrasonography, computerised tomographic scanning and magnetic resonance imaging), blood biochemical examination and alpha fetoprotein test was collected for the incident PLC cases assessment. Cancers were coded according to the International Classification of Diseases, Tenth Revision (ICD–10) and PLC was coded as C22.

Statistical analysis. Categorical variables were described by percentages and compared using the Chi-square test. Cox proportional hazards regression models adjusted for suspected confounders were used to calculate HRs and 95% confidence intervals (CI) for baseline FBG levels and incident PLC, with adjustments for age group (10-year interval), education level (illiterate or primary school, junior high school, senior high school, and college and above), income status (<500 yuan per month, 500–1000 yuan per month, and >1000 yuan per month), HBV infection status (HBsAg negative/positive), BMI (continuous variable), frequency of smoking (non-smoker, ex-smoker, <1 cigarette per day, and $\geqslant 1$ cigarette per day), and frequency of alcohol drinking (never and past drinker, <1 time per day, and $\geqslant 1$ time per day). Subgroup analyses were performed by HBsAg status, BMI, cigarette smoking status and alcohol drinking status. The restricted cubic spline (RCS) analysis was used in the multivariate Cox proportional hazard model to explore the association between continuous FBG and PLC in the study (Desquilbet and Mariotti, 2010). Addictive model was applied to evaluate the synergisms between FBG level and HBsAg infection (de Jager *et al*, 2011). Synergism index (S) and its 95% CI were calculated to assess the deviation of the addictive model of no interaction: $S = (HR11\text{-}1)/[(HR01 + HR10)\text{-}2]$. As the value of S equal to unity represented additivity, value greater than unity was interpreted as super additivity and synergism (Rothman, 1976; Lundberg *et al*, 1996). As a sensitivity analysis, we further excluded 5420 participants who took antidiabetic medications, including oral antidiabetics use and insulin use, and 85 participants who occurred PLC within the first 2 years after entry to the cohort. The data management and all analyses were conducted using SAS statistical software, version 9.4 (SAS Institute). $P<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of participants. Total of 109 169 males were recruited in this study with the mean age of 51.33 years. The prevalence of IFG ($6.1\leqslant FBG<7.0\,mmol\,l^{-1}$) and DM ($FBG\geqslant 7.0\,mmol\,l^{-1}$) was 9.15% and 8.64% among the males, respectively. Selected baseline characteristics of participants in the Kailuan male cohort were listed in Table 1. The rate of current smoking and alcohol drinking were 42.13% and 45.46%, respectively, as well as the prevalence of HBsAg was 3.21% among the population. The FBG levels were higher in older males ($\geqslant 50$ years) and among those who with lower education level (Illiterate or primary school) and $BMI\geqslant 25.0\,kg\,m^{-2}$, compared with younger males (<50) and those with higher education level ($P<0.001$) and lower BMI ($P<0.001$) (Table 1).

The association between FBG level and PLC risk. By 31 December 2013, a total of 267 newly diagnosed primary liver cancer cases with 659 232.27 person years accumulated with a median follow-up of 6.89 years in the Kailuan male cohort. The

Table 1. Baseline characteristics of males in the Kailuan cohort by fasting blood glucose level, 2006–2013

Characteristics	Total no. (%)	FBG (mmol l^{-1}) LFBG (FBG < 3.9) no. (%)	3.9 ⩽ FBG < 6.1 no. (%)	IFG (6.1 ⩽ FBG < 7.0) no. (%)	DM (7.0 ⩽ FBG) no. (%)	χ^2	*P*-value
Age (year)							
<40	20211 (18.51)	365 (1.81)	18287 (90.48)	1090 (5.39)	469 (2.32)	1684.19	<0.0001
40–49	23968 (21.95)	338 (1.41)	19455 (81.17)	2252 (9.40)	1923 (8.02)		
50–59	37851 (34.67)	852 (2.25)	29137 (76.98)	4020 (10.62)	3842 (10.15)		
⩾60	27139 (24.86)	929 (3.42)	20390 (75.13)	2627 (9.68)	3193 (11.77)		
Education							
Illiterate or primary school	12285 (11.55)	483 (3.93)	9141 (74.41)	1322 (10.76)	1339 (10.90)	369.42	<0.0001
Junior high school	70662 (66.43)	1508 (2.13)	56063 (79.34)	6630 (9.38)	6461 (9.14)		
Senior high school	14718 (13.84)	319 (2.17)	12265 (83.33)	1204 (8.18)	930 (6.32)		
College and above	8710 (8.19)	144 (1.65)	7524 (86.38)	593 (6.81)	449 (5.15)		
Income (yuan per month)							
<500	25222 (24.80)	587 (2.33)	19952 (79.11)	2569 (10.19)	2114 (8.38)	3.46	0.18
500–1000	56024 (55.08)	1364 (2.43)	44923 (80.19)	4807 (8.58)	4930 (8.80)		
>1000	20463 (20.12)	424 (2.07)	16421 (80.25)	1934 (9.45)	1684 (8.23)		
HBsAg status							
Negative	95090 (96.79)	84 (2.66)	2524 (80.08)	293 (9.30)	251 (7.96)	1.51	0.22
Positive	3152 (3.21)	2313 (2.43)	75909 (79.83)	8631 (9.08)	8237 (8.66)		
BMI (kg m^{-2})							
BMI < 18.5	2646 (2.44)	138 (5.22)	2252 (85.11)	138 (5.22)	118 (4.46)	923.06	<0.0001
18.5 ⩽ BMI < 25.0	63107 (58.12)	1591 (2.52)	51777 (82.05)	5137 (8.14)	4602 (7.29)		
25.0 ⩽ BMI < 30.0	37749 (34.77)	674 (1.79)	29073 (77.02)	4043 (10.71)	3959 (10.49)		
BMI ⩾ 30.0	5071 (4.67)	69 (1.36)	3726 (73.48)	600 (11.83)	676 (13.33)		
Frequency of smoking							
Non-smoker	52999 (53.76)	1093 (2.06)	42212 (79.65)	4826 (9.11)	4868 (9.19)	71.44	<0.0001
Ex-smoker	4061 (4.12)	129 (3.18)	3129 (77.05)	409 (10.07)	394 (9.70)		
<1 cigarette per day	2875 (2.92)	57 (1.98)	2342 (81.46)	256 (8.90)	220 (7.65)		
⩾1 cigarette per day	38656 (39.21)	1003 (2.59)	31099 (80.45)	3588 (9.28)	2966 (7.67)		
Frequency of alcohol drinking							
Never and past drinker	58194 (54.53)	1394 (2.40)	45947 (78.95)	5197 (8.93)	5656 (9.72)	152.00	<0.0001
<1 time per day	26383 (24.72)	509 (1.93)	21827 (82.73)	2263 (8.58)	1784 (6.76)		
⩾1 time per day	22133 (20.74)	556 (2.51)	17466 (78.91)	2334 (10.55)	1777 (8.03)		

Abbreviations: BMI = body mass index; DM = diabetes mellitus; FBG = fasting blood glucose; IFG = impaired fasting glucose; LFBG = low fasting blood glucose.

percentage of diagnosis of PLC by pathology and imaging tests were 21.72% (58/267) and 47.94% (128/267), respectively. Among the 186 cases with either pathological or imaging diagnosis, there were 164 (88.17%) cases of hepatocellular carcinoma (HCC), 20 (10.75%) cases of intrahepatic cholangiocarcinoma (ICC) and 2 (1.08%) uncertified cases.

The males with IFG and the DM were associated with a 56% (95% CI: 1.08–2.24) and a 51% (95% CI: 1.03–2.20) higher risk of incident PLC, compared with the subjects with normal FBG, respectively (Table 2). After adjustment of age, education level, income level, HBsAg infection, BMI, and frequency of smoking and alcohol drinking, significantly higher risk of PLC was found related to IFG (HR = 1.60, 95% CI: 1.09–2.35) and DM (HR = 1.58, 95% CI: 1.07–2.34).

Subgroup analyses showed that the IFG increased the risk of incident PLC especially in the non-smoker (HR = 1.73, 95% CI: 1.01–2.98), current drinker (HR = 1.80, 95% CI: 1.03–3.16). While DM could increase the risk of PLC incidence, especially in the males who were HBsAg-negative (HR = 1.89, 95% CI: 1.16–3.09) and with normal weight (HR = 1.76, 95% CI: 1.05–2.94) (Table 2).

The RCS model showed a positive dose-response but non-linear association between the level of FBG and the PLC risk among the subject (*P*-overall = 0.041, *p*-non-linear = 0.049) (Figure 1). As the 20th quintile of FBG (4.6 mmol l^{-1}) was chosen to be the reference, the HRs of PLC related to FBG levels rise sharply and then steadily when FBG levels was over 7.0 mmol l^{-1}.

Interaction analysis between the levels of FBG HBV infection status. The independent and joint effects of FBG levels and HBV infection on the risk of PLC were analysed. The males with HBsAg positivity had a significantly higher risk of PLC (HR = 31.73, 95% CI: 24.39–41.28) than the males with HBsAg negativity. However, there was no evidence of interaction effect between FBG levels and HBsAg infection status, considering that the estimated synergism index was not statistically significant (IFG: S = 1.59, 95% CI = 0.70–2.15; DM: S = 1.11, 95% CI = 0.53–2.06). Additionally, the interaction effects between FBG levels and smoking (IFG: S = 1.01, 95% CI = 0.29–3.52, DM: S = 1.18, 95% CI = 0.30–3.84), drinking (IFG: S = 1.89, 95% CI = 0.06–27.49, DM: S = 0.85, 95% CI = 0.05–16.24) and BMI ⩾ 25.0 kg m^{-2} (IFG: S = 1.19, 95% CI = 0.20–5.76, DM: S = 0.71, 95% CI = 0.14–5.20) were not significant.

Sensitivity analysis. After excluding males with antidiabetic medications use history ($n = 5420$), we found that compared with the males with normal FBG, the males with IFG (HR = 1.65, 95% CI: 1.11–2.45) still had an increased risk of all incident PLC cancers. In addition, excluding participants who occurred PLC within the first 2 years after entry to the cohort, there was still a positive association of the risk of PLC related to DM (HR = 1.62, 95% CI: 1.02–2.59; Table 3). The results of sensitivity analyses concerning the major potential confounders cannot alter the main findings.

Table 2. The association between fasting blood glucose and primary liver cancer risk in males, Kailuan cohort, 2006–2013

	FBG (mmol l^{-1})			
	LFBG (FBG < 3.9)	3.9 ⩽ FBG < 6.1	IFG (6.1 ⩽ FBG < 7.0)	DM (7.0 ⩽ FBG)
All				
P-Ys (case)	15 833.64 (8)	527 887.20 (194)	59 726.03 (34)	55 785.40 (31)
Crude HR (95% CI)	1.36 (0.67–2.75)	ref	1.56 (1.08–2.24)	1.51 (1.03–2.20)
HR[a] (95% CI)	0.99 (0.46–2.12)	ref	1.60 (1.09–2.35)	1.58 (1.07–2.34)
HBsAg status				
HBsAg negative				
P-Ys (case)	15 062.26 (5)	484 834.83 (96)	54 856.21 (17)	51 590.99 (21)
Crude HR (95% CI)	1.66 (0.67–4.07)	ref	1.57 (0.94–2.63)	2.06 (1.28–3.30)
HR[a] (95% CI)	1.24 (0.45–3.40)	ref	1.54 (0.90–2.64)	1.89 (1.16–3.09)
HBsAg positive				
P-Ys (case)	529.90 (3)	15 678.51 (88)	1796.76 (16)	1489.53 (10)
Crude HR (95% CI)	0.84 (0.26–2.76)	ref	1.62 (0.95–2.76)	1.21 (0.63–2.33)
HR[a] (95% CI)	0.65 (0.18–2.27)	ref	1.66 (0.95–2.88)	1.19 (0.62–2.31)
BMI				
Normal weight (BMI < 25 kg m^{-2})				
P-Ys (case)	11 144.98 (7)	330 722.45 (124)	32 403.54 (18)	28 619.49 (18)
Crude HR (95% CI)	1.63 (0.76–3.49)	ref	1.49 (0.91–2.44)	1.68 (1.02–2.75)
HR[a] (95% CI)	1.23 (0.53–2.84)	ref	1.57 (0.93–2.65)	1.76 (1.05–2.94)
Overweight (25 kg m^{-2} ⩽ BMI)				
P-Ys (case)	4688.66 (1)	197 164.74 (70)	27 323.49 (16)	27 165.92 (13)
Crude HR (95% CI)	0.60 (0.08–4.34)	ref	1.65 (0.96–2.84)	1.34 (0.74–2.43)
HR[a] (95% CI)	0.45 (0.06–3.25)	ref	1.66 (0.94–2.92)	1.36 (0.75–2.47)
Smoking status				
Non-smoker				
P-Ys (case)	6924.40 (4)	254 950.66 (84)	28 629.89 (17)	28 806.75 (15)
Crude HR (95% CI)	1.70 (0.63–4.65)	ref	1.82 (1.08–3.07)	1.58 (0.91–2.73)
HR[a] (95% CI)	1.15 (0.36–3.68)	ref	1.73 (1.01–2.98)	1.60 (0.92–2.79)
Ever smoker				
P-Ys (case)	7675.53 (4)	224 991.50 (96)	26 116.30 (15)	21 731.60 (16)
Crude HR (95% CI)	1.22 (0.45–3.31)	ref	1.35 (0.78–2.33)	1.73 (1.02–2.93)
HR[a] (95% CI)	0.92 (0.34–2.53)	ref	1.49 (0.86–2.58)	1.55 (0.89–2.69)
Alcohol drinking status				
Never and past drinker				
P-Ys (case)	8745.80 (5)	276 421.56 (115)	30 677.33 (17)	33 251.66 (19)
Crude HR (95% CI)	1.36 (0.56–3.33)	ref	1.34 (0.80–2.22)	1.38 (0.85–2.24)
HR[a] (95% CI)	1.09 (0.40–2.98)	ref	1.44 (0.85–2.45)	1.60 (0.97–2.62)
Current drinker				
P-Ys (case)	6979.69 (3)	242 026.90 (76)	28 078.41 (17)	21 581.50 (12)
Crude HR (95% CI)	1.35 (0.43–4.28)	ref	1.95 (1.15–3.29)	1.74 (0.95–3.20)
HR[a] (95% CI)	0.88 (0.27–2.88)	ref	1.80 (1.03–3.16)	1.54 (0.81–2.94)

Abbreviations: BMI = body mass index; CI = confidence interval; DM = diabetes mellitus; FBG = fasting blood glucose; HR = hazard ratio; IFG = impaired fasting glucose; LFBG = low fasting blood glucose; ref = reference group.

[a]Adjusted for age (10-year interval), education level (illiterate or primary school, junior high school, senior high school, and college and above), income status (< 500 yuan per month, 500–1000 yuan per month, > 1000 yuan per month), HBsAg infection status (negative and positive), BMI, frequency of smoking (non-smoker, ex-smoker, < 1 cigarette per day, ⩾1 cigarette per day, frequency of alcohol drinking (never and past drinker, < 1 time per day, ⩾1 time per day).

DISCUSSION

In this large prospective cohort study among Chinese males, we found that FBG levels are modestly associated with increased risk of PLC, which could be modified by HBsAg infection, BMI, tobacco smoking and alcohol drinking status. In addition, FBG level was non-linearly related to PLC risk among target males. To our knowledge, this is the first prospective study to explore the association between the FBG level and the risk of PLC among general males in mainland China.

Findings that high FBG level was associated with a statistically significantly increased risk of primary liver cancer in males of this study are in line with observations in the exiting four prospective cohort studies as follows. The prospective cohort study in Korea found that FBG level of 6.1–6.9 mmol l^{-1} and 7.0–7.7 mmol l^{-1} for males might increase the risk of liver cancer incidence (HR = 1.16, 95% CI: 1.07–1.27; HR = 1.45, 95% CI: 1.24–1.70) referred to FBG < 5.0 mmol l^{-1} (Jee *et al*, 2005). Compared to the group of FBG < 5.6 mmol l^{-1} category, a study observed that the risk of HCC in Japanese men and women was 75% higher in those with FBG ⩾ 5.6 mmol l^{-1} (Inoue *et al*, 2009), while the study based on Korean Multi-Center Cancer Cohort showed that DM increased two-fold risk of liver cancer (Gwack *et al*, 2007). The study conducted in 140 000 adults in Austria demonstrated a strong association between high level of FBG and risk of liver cancer in males (6.1 ⩽ FBG < 6.9 mmol l^{-1}: HR = 3.50, 95% CI: 1.28–9.60; FBG ⩾ 7.0 mmol l^{-1}: HR = 4.58, 95% CI: 1.81–11.62), in comparison with FBG between 4.2 and 5.2 mmol l^{-1} (Rapp *et al*, 2006). However, no association was found among 578 700 Europeans (Borena *et al*, 2012), and among the HBV carriers in Taiwan after adjustment of insulin (Chao *et al*, 2011).

Several possible mechanisms might explain the association between high FBG and increasing risk of PLC. Basic research found

that high glucose concentration was capable of accelerating tumourigenesis in humans though its damage to DNA (Pereira *et al*, 2013). Hyperglycaemia and its related conditions, such as chronic oxidative stress and the accumulation of advanced glycation end-products, might act as carcinogenic factors (Abe and Yamagishi, 2008; Qiao *et al*, 2016). Additionally, glucose catabolism could promote the proliferation of cancer cells by triggering quiescence exit (Laporte *et al*, 2011), insulin resistance, as well as stimulating insulin-like growth factor I (IGF -1) (Pollak, 2008; Rajpathak *et al*, 2009) and Erk1/2 phosphorylation (Zhang *et al*, 2015). Meanwhile, high glucose exposure also enhances the adhesion, migration and invasion of ICC cells via STAT3 activation (Saengboonmee *et al*, 2016).

The prevalence of HBsAg was 3.21% in the present study, which was similar to the HBsAg prevalence (< 4%) among north Chinese reported previously (Yin *et al*, 2010). As it has been reported widely that HBsAg has a very close linkage with HCC or liver cancer incidence (Lin and Kao, 2013; Yang *et al*, 2016), our study also proved the significant association between HBV positivity and the risk of PLC (HR = 31.73, 95% CI: 24.39–41.28). The obesity was also reported to be closely associated with glucose concentration (Fu *et al*, 2013; Ek *et al*, 2015) and liver cancer, which was attributed to insulin resistance and IGF-1 regulating. Furthermore, IARC has classified cigarette smoking as a causal risk factor for liver cancer since 2004 (IARC, 2014), considering the DNA damaging effect of several compounds in tobacco smoking and the response of liver plays in the metabolism of these compounds (Staretz *et al*, 1997; Christmann and Kaina, 2012). Therefore, when these established risk factors play a leading role in the development of PLC, the effect of FBG might be weakened. However, for the HBV negative, non-smokers and the males with normal weight, the increases of FBG showed a significant effect on the development of PLC. The results of the present study showed that increased FBG might be an important and potentially modifiable exposure that could have key scientific and clinical importance for preventing PLC development, in addition to HBV vaccination, tobacco control and keep healthy weight.

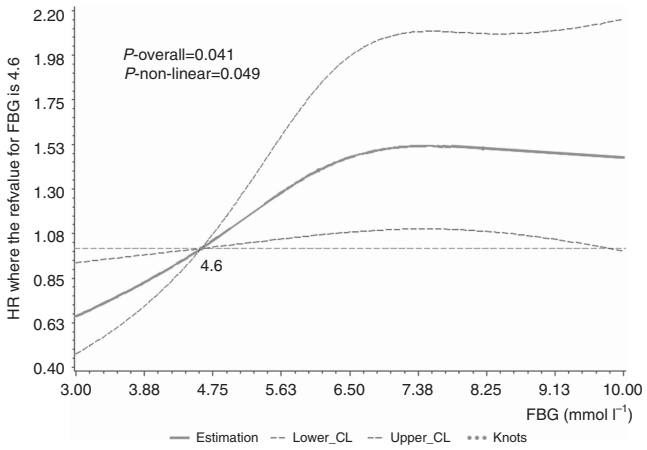

Figure 1. Cubic spline graph of the adjusted HR (represented by solid line) and 95% CI (represented by the dotted lines) for the association between FBG and risk of male primary liver cancer in Kailuan cohort, 2006–2013. Knots: 4.6, 6.1, and 8.2 (95th) of the distribution of fasting blood glucose concentration (mmol l^{-1}); Referent: 4.6 mmol l^{-1}, 20th of the distribution of fasting blood glucose concentration.

Alcohol drinking may increase 87% risk of liver cancer incidence (Pei *et al*, 2008), and attribute to 15.7% of liver cancer deaths in Chinese population (Fan *et al*, 2013). Studies have suggested that increased FBG was independent risk factor of the development of fibrosis in alcohol-related hepatic disease because insulin resistance appeared to be a central pathophysiologic feature (Raynard *et al*, 2002). Besides, it has been reported that alcohol consumption might exacerbate the effect of DM on the development of HCC (Balbi *et al*, 2010; Raff *et al*, 2015). Consequently, our finding that increased PLC risk related to evaluated FBG especially among current drinkers was consistent with the studies above.

There are several strengths and limitations that should be noted when interpreting the results of our study. The major limitation of our study was the follow-up time (~7.67 years) was relatively short, which precluded an evaluation of analysis by subtypes of PLC, for example, ICC and HCC, due to small case numbers. Another limitation is the information collection for potential risk factors of PLC was not detailed enough such as the lack of the amount of cigarette smoking and alcohol drinking, which leads to the impossibility to assess the confounders more precisely. HCV was not detected in the study, however, which plays a little less effect on PLC development in Chinese than in other Asian population (de Martel *et al*, 2015). The most important strength of our study is that it was a large population-based prospective cohort study, which minimises the possibility that the associations observed in our study are due to early disease effects compared with retrospective studies; though as noted, future analyses will be needed to rule out this possibility. In addition, strengths of our study included a high participation (78.60%), high percentage of collection of blood samples (99.16%) and almost 100% follow-up rate among the study population for well-organised 2-year health examination of employees, and comprehensive health system including medical records, death certificates and health insurance in City of Tangshan. Moreover, the detection of FBG centralised at

Table 3. Sensitivity analysis of the association between fasting blood glucose and primary liver cancer risk in males, Kailuan cohort, 2006–2013

	FBG (mmol l^{-1})			
	LFBG (FBG < 3.9)	3.9 ⩽ FBG < 6.1	IFG (6.1 ⩽ FBG < 7.0)	DM (7.0 ⩽ FBG)
Analysis after excluding males with antidiabetic medication use history				
P-Ys (case)	15 686.77 (8)	521 623.49 (194)	54 899.16 (34)	33 464.84 (31)
Crude HR (95% CI)	1.37 (0.68–2.78)	ref	1.60 (1.10–2.33)	1.46 (0.90–2.38)
HR[a] (95% CI)	0.99 (0.46–2.12)	ref	1.65 (1.11–2.45)	1.61 (0.98–2.66)
Analysis after excluding participants who occurred PLC within the first 2 years after entry to the cohort				
P-Ys (case)	15 830.69 (5)	527 828.17 (134)	59 716.97 (22)	55 777.53 (21)
Crude HR (95% CI)	1.19 (0.49–2.90)	ref	1.46 (0.93–2.30)	1.49 (0.94–2.35)
HR[a] (95% CI)	0.99 (0.40–2.44)	ref	1.47 (0.91–2.37)	1.62 (1.02–2.59)

Abbreviations: CI = confidence interval; DM = diabetes mellitus; FBG = fasting blood glucose; HR = hazard ratio; IFG = impaired fasting glucose; LFBG = low fasting blood glucose; PLC = primary liver cancer; ref = reference group.
[a]Adjusted for age (10-year interval), education level (illiterate or primary school, junior high school, senior high school, and college and above), income status (< 500 yuan per month, 500–1000 yuan per month, > 1000 yuan per month), HBsAg infection status (negative and positive), BMI, frequency of smoking (non-smoker, ex-smoker, < 1 cigarette per day, ⩾1 cigarette per day, frequency of alcohol drinking (never and past drinker, < 1 time per day, ⩾1 time per day).

the central laboratory of Kailuan hospital (Wang *et al*, 2015), minimising the detection bias.

In summary, our study provides further evidence that higher level of FBG is modestly and non-linearly associated with increased risk of PLC in Chinese males. The findings indicate that the FBG surveillance could be one of the scientific and important ways to identify the high-risk population of PLC. The well control of FBG might be served as a possible primary prevention for further decrease of PLC among the Chinese males who experienced the national vaccination since 1990s and just in the time of steadily increasing of FBG in general Chinese population.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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