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Original Article

The association and joint effect of serum cholesterol, glycemic status with the risk of incident cancer among middle-aged and elderly population in china cardiometabolic disease and cancer cohort (4C)-study

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Abstract: The associations between different combinations of metabolic abnormalities and the risk of all and site-specific cancers remain unclear. We aimed to estimate the association and interplay between serum cholesterol, glycemic status and risk of cancer in the China Cardiometabolic Disease and Cancer Cohort (4C)-Study, a nationwide, multicenter, prospective, population-based study. The investigation was performed in 137,884 participants during 2014-2016. Incident cancer was defined as the first occurrence of any type cancer of all sites during follow-up. After 510,164 person-years of follow-up, 1,710 were detected as incident cancer after exclusion of participants diagnosed as cancer within 6 months from baseline. A relatively low level of LDL cholesterol (<100 mg/dl) was related to a significant higher risk of incident cancer [1.20 (1.08-1.34); P=0.0007]. Diabetic individuals have a significantly higher risk of incident cancer, especially those with poorly glycemic control. Diabetic participants with both lower levels of LDL cholesterol and poorly glycemic control were at a higher risk of incident cancer [1.42 (1.10-1.81); P=0.006]. Our study showed a positive association of cancer risk with low-level LDL cholesterol and diabetes and found that participants with both lower levels of LDL cholesterol and poorly controlled diabetes had the higher risk of incident cancer, which indicates the compelling need of achieving glycemic control goal and maintaining appropriate LDL cholesterol levels.

Keywords: Cancer, cholesterol, diabetes, HbA1c, LDL

Introduction

Cancer is considered as a major threat to public health, and action needs to be taken on all fields of prevention. Findings from epidemiological study and experimental investigations have linked factors that may alter metabolic status, such as diet, smoking, and obesity, with an increased cancer risk [1-3]. Diabetes and higher levels of serum LDL cholesterol are believed to be major metabolic risk factors of several non-communicable chronic diseases, including stroke and coronary heart diseases [4-6]. However, the association between metabolic elements and cancer is complex and incongruous. Diabetes is a well-established risk factor for all cancer and several site-specific cancers [7-12]. On the other hand, hypercholesterolemia has been found of an incongruous association with cancer risk [13-16]. A few prospective epidemiological studies have detected that serum LDL cholesterol level is inversely associated with the risk of cancer, but these studies have been limited by some residual confounding factors, such as the use of lipid-lowering medication and findings from previous studies are inconsistent [13-18]. Moreover, the combination of glycemic status and serum cholesterol in the association of cancer is not well understood and nor do current recommendations on optimal management of these two factors with regard to cancer. To our knowledge, the associations between different combinations of metabolic abnormalities and the risk of all and site-specific cancers remain unclear.

Thus, the present study aimed to investigate the association and joint effect between serum cholesterol, glycemic status and the risk of incident cancer in middle-aged and elderly Chinese population.

Materials and methods

Study design

The China Cardiometabolic Disease and Cancer Cohort (4C)-Study is a nationwide, multicenter, prospective, population-based study that was designed to explore the associations of metabolic factors with clinical outcomes, including incident diabetes, cardiovascular events and cancer in middle-aged and elderly Chinese individuals [19]. The 4C study included 20 community sites, covering 16 provinces, autonomous regions, or municipalities of mainland China. We used data from this study of 193,846 individuals for this investigation. The study protocol and informed consent were approved by the Committee on Human Research at Rui-Jin Hospital Affiliated to the Jiao-Tong University School of Medicine. All participants signed the written informed consent.

Baseline data collection

At each study site, baseline data was collected according to a standardized protocol in examination centers at local health stations or community clinics in 2010-2011.

Using a standard questionnaire, trained staff collected information face-to-face about sociodemographic characteristics, history of diseases and medication, family history, and lifestyle factors (including current smoking status, current drinking status, physical activity, sedentary behavior and diet habits) [20] Height, weight and blood pressure were measured by the trained personnel using a standardized protocol.

Fasting blood samples were collected to evaluate the levels of fasting glucose and cholesterol. All participants underwent a 75-g load OGTT, and OGTT postload plasma glucose level was obtained at 2 hours. Plasma glucose concentrations were evaluated at local hospitals using the glucose oxidase or hexokinase method and serum total cholesterol, LDL cholesterol, and HDL cholesterol were measured at the central laboratory using an auto-analyzer (ARCHITECT ci16200 analyzer, Abbott Laboratories, Illinois, USA). A Hemoglobin Capillary Collection System (HCCS, Bio-Rad Laboratories, CA, USA) was used to collect finger capillary whole blood and determined by high-performance liquid chromatography (VARIANT™ II Systems, BIO-RAD, Hercules, CA, USA).

According to the 2010 American Diabetes Association (ADA) criteria, diabetes was diagnosed at baseline if meeting at least one of the following criteria (1) Fasting plasma glucose (FPG) level of 126 mg/dL or higher, (2) OGTT 2-hour postload plasma glucose (PPG) level of 200 mg/dL or higher, or (3) HbA1c level of 6.5% or higher, or (4) A self-reported diagnosis by professionals. Prediabetes was defined as (1) FPG level between 100 mg/dL and 125 mg/dL,

(2) OGTT 2-hour PPG level between 140 mg/dL and 199 mg/dL, or (3) HbA1c level between 5.7% and 6.4%. Participants who had an FPG level <100 mg/dL and OGTT 2-hour PPG level <140 mg/dL and HbA1c level <5.7% were defined as normal glucose regulation (NGR).

Follow-up investigation and outcome assessment

The follow-up investigation was conducted during 2014-2016. If patients were hospitalized or visited an emergency department, their medical records were abstracted using a standard form that including inpatient record, pathology reports and their photocopies. Two members of the outcome adjudication committee who are masked to the baseline characteristics of participants verified each clinical event independently, and discrepancies were adjudicated by discussion involving other members of the committee. Incident cancer was defined as the first occurrence of any type of cancer at all sites during follow-up.

Statistical analyses

Baseline characteristics were summarized as the means (± standard deviation), medians (interquartile ranges) or proportions. One-way ANOVA was used to compare continuous variables and chi-square tests for categorical variables. The incidence rate of cancer with 95% CI was calculated per 1000 person-years with the number of persons with new-onset cancer during follow-up as the numerator and the total person-years as denominator. Participants with a diagnosis of cancer within 6 months from baseline were withdrawn to avoid the prediagnostic effect.

Cox proportional hazards models were used to investigate the associations of baseline cholesterol measures and glycemic status with subsequent incident cancer. Multivariate analyses were adjusted for potential confounders: age, sex, BMI, family history of cancer, smoking status, drinking status, education level, physical activity, consumption of vegetables and fruit, insulin therapy, lipid-lowering medication, diabetes status and systolic blood pressure. Potential nonlinear associations between the levels of LDL cholesterol and the incident cancer were examined with restricted cubic splines. All analyses were conducted by SAS version 9.2 (SAS Institute, Cary, NC), and a two-tailed test with $P<0.05$ was considered as statistically significant.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request; some restrictions will apply.

Results

General flowchart

The 4C study was conducted among 193,846 participants recruited from 20 community sites of 16 provinces in mainland China. The baseline survey was performed in 2010-2011. Of those participants, 23,606 individuals were lost to follow-up (12.18%) and 170,240 remained in the study. Among these 170,240, 2,798 with cancer at baseline were excluded and 24,572 participants without follow-up data on cancer status were also excluded. Participants with cholesterol or glucose measures missing at baseline were further excluded (n=4,639), and 347 were withdrawn because of a diagnosis of cancer within 6 months from baseline. Finally, 137,884 participants were included for the current analysis and the mean follow-up duration was 3.8 years (**Figure 1**).

Baseline characteristics

After 510,164 person-years of follow-up, 1,710 (1.24%) were detected as incident cancer based on their medical records (1.60% in men and 1.06% in women). The new-onset cancer mainly consisted of lung cancer (n=357), breast cancer (n=188), colorectal cancer (n=187), liver cancer (n=156) and stomach cancer (n=156). The baseline characteristics stratified by incident cancer status are shown in **Table 1**. Generally, participants with incident cancer were older, were more likely to be men, were current smokers and drinkers, and had significantly higher levels of systolic blood pressure, FPG, OGTT 2-hour PPG, and HbA1c and lower levels of LDL-cholesterol, HDL-cholesterol, total cholesterol ($P<0.05$). Additionally, higher levels of education, less consumption of vegetables and fruit and insulin therapy were associated

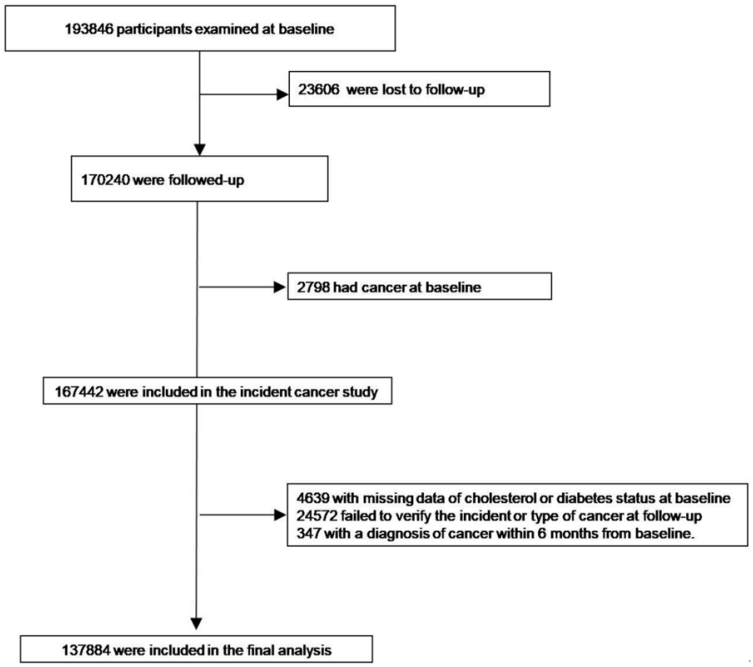

Figure 1. Participant Flow Diagram of the China Cardiometabolic Disease and Cancer Cohort (4C) Study.

with incident cancer (P<0.05). There was no significant difference for the use of lipid-lowering drugs between the two groups.

Association of serum cholesterol level with incident cancer

The HRs and 95% CIs for the association between serum cholesterol level with incident cancer are shown in **Table 2**. We stratified the participants according to their fasting total cholesterol level, LDL cholesterol and HDL cholesterol level at baseline into quartile groups. Multiple-adjusted hazard ratios of all incident cancer associated with serum cholesterol level based on their quartiles interval were 1.36 (1.18-1.55), 1.11 (0.97-1.28), and 1.03 (0.89-1.18) for LDL cholesterol; 1.07 (0.93-1.23), 0.98 (0.85-1.12), and 0.95 (0.82-1.10) for HDL cholesterol; and 1.41 (1.22-1.62), 1.28 (1.11-1.47), and 1.11 (0.96-1.28) for total cholesterol, respectively (**Table 2**). Furthermore, according to the guideline-recommended cut-off values, compared with higher levels of LDL cholesterol (≥130 mg/dl), lower LDL cholesterol (<100 mg/dl) was associated with an increased risk of incident cancer [<70 mg/dl: 1.48 (1.25-1.75); P<0.0001; 70-100 mg/dl: 1.21 (1.06-1.38); P=0.005], whereas no significantly elevated risk was observed for a moderate level of LDL cholesterol (100-130 mg/dl: 1.06 (0.93-1.20; P=0.39). A similar association was also detected for total cholesterol, but not for HDL-cholesterol.

Multivariable adjusted restricted cubic spline analyses suggested an association between incident cancer and LDL cholesterol as a continuous variable, regardless of the glycemic status. The findings suggested that risk of incident cancer may be lower with higher LDL cholesterol and the risk reduction may level off after 100-130 mg/dL (**Figure 2**).

Association of glycemic status with incident cancer

Table 3 shows the hazard ratios and 95% CIs for the association of glycemic status with incident cancer, which detected diabetes was an independent risk factor; but no statistically significant association was observed for prediabetes. In addition, diabetic participants with poorly glycemic control had a significantly higher risk of incident cancer [diabetes with HbA1c <7.0% vs. normal glucose regulation: 1.24 (1.04-1.50); diabetes with HbA1c ≥7.0% vs. normal glucose regulation: 1.34 (1.08-1.66)].

Joint effect of LDL cholesterol and glycemic status with incident cancer

We then examined whether combinations of baseline glycemic status and LDL cholesterol could predict the incidence of cancer. We found that the risk of incident cancer may be lower with higher LDL cholesterol and the risk reduction may level off after 100-130 mg/dl, especially in diabetic participants. **Table 3** shows the hazard ratios and 95% CI of the incident cancer according to several combinations of LDL cholesterol and glycemic status. Individuals with both lower levels of LDL cholesterol (<100 mg/dl) and poorly controlled diabetes (Diabetes with HbA1c ≥7.0%) were at higher risk of incident cancer than others [1.42 (1.10-1.81); P=0.006].

Table 1. Characteristics of the study population according to the incident cancer status

	All Cancer		
	Incident cancer (-)	Incident cancer (+)	*P* value
N, %	136,174 (98.76)	1,710 (1.24)	-
Age at recruitment, years	56.80 ± 9.10	61.84 ± 9.56	<0.0001
Male sex, n (%)	47,346 (34.77)	769 (44.97)	<0.0001
Education attainment (high school or above), n (%)	48,806 (36.78)	547 (32.81)	0.0008
Family history of cancer	14,772 (12.10)	179 (12.82)	0.41
BMI, kg/m^2	24.68 ± 3.61	24.61 ± 3.69	0.48
Systolic blood pressure, mmHg	133.59 ± 20.94	137.59 ± 21.77	<0.0001
Diastolic blood pressure, mmHg	78.57 ± 11.20	78.38 ± 11.40	0.49
Smoking status			
Never	104,301 (75.64)	1,201 (70.23)	<0.0001
Former	6,488 (4.76)	118 (6.90)	
Current	19,950 (14.65)	326 (19.06)	
Alcohol consumption			
Never	112,192 (82.39)	1,353 (79.12)	0.0003
Former	2,944 (2.16)	58 (3.39)	
Current	13,858 (10.18)	200 (11.70)	
Vegetables and fruit intake <4.5 cups/day, n (%)	74,256 (57.19)	1,020 (62.69)	<0.0001
Red meat intake, g/day	28.57 (7.14-58.81)	21.43 (0.00-57.14)	0.67
Fasting plasma glucose, mmol/L	5.97 ± 1.65	6.09 ± 1.84	0.003
2 h Postprandial plasma glucose, mmol/L	8.27 ± 3.86	9.04 ± 4.49	<0.0001
HbA1c, %	6.02 ± 1.03	6.12 ± 1.13	0.0001
LDL cholesterol, mg/dl	111.93 ± 33.95	108.67 ± 35.00	<0.0001
HDL cholesterol, mg/dl	51.91 ± 14.05	50.71 ± 14.42	0.0005
Total cholesterol, mg/dl	176.92 (83.26-230.95)	173.37 (82.37-262.98)	<0.0001
insulin therapy, n (%)	1,795 (1.32)	35 (2.05)	0.009
Lipid-lowering medications, n (%)	1,261 (0.93)	21 (1.23)	0.20

Association and joint effect between LDL cholesterol, glycemic status and site-specific cancers

When all site-specific cancers were evaluated, only digestive cancer was significantly associated with LDL cholesterol [LDL cholesterol <100 mg/dl vs. ≥100 mg/dl: 1.70 (1.41-2.05); P<0.0001]. Individuals with both lower levels of LDL cholesterol (<100 mg/dl) and poorly controlled diabetes (diabetes with HbA1c ≥7.0%) were at higher risks of digestive cancer than others [2.03 (1.39-2.96); P=0.0002]. The multivariable Cox regression revealed a similar relationship for incident colorectal cancer and liver risk. Those with both lower levels of LDL cholesterol and poorly controlled diabetes had an increased risk of pancreatic cancer than others [2.97 (1.08-8.17); P=0.03], whereas diabetic individuals had a higher risk of esophageal cancer [2.10 (1.09-4.07); P=0.03] (**Table 4**).

Discussion

The present study showed that relatively low LDL cholesterol was associated with the risk of incident cancer, whereas diabetes was significantly associated with the incident cancer in Chinese adults aged 40 years or older. Moreover, participants with both lower levels of LDL cholesterol and poorly controlled diabetes had the higher risk of incident cancer and this association seemed to be driven mainly by digestive cancer.

Despite the controversial results, there is a growing of evidence linking cholesterol to cancer risk [13-18]. A study from Korea showed total cholesterol levels were positively associated with breast cancer in women and prostate and colon cancer in men, and inversely associated with liver and stomach cancer [14]. Another study of European populations indicat-

Table 2. Incidence rate and adjusted hazard ratios for incident cancer in participants according to serum lipids level

	No. of person-years	No. of events	Incidence, per 1000 person-year	Unadjusted		Adjusted*	
				HR (95% CI)	*P* value	HR (95% CI)	*P* value
LDL cholesterol, mg/dl							
Groups according to quartile range							
Q1	125,709	501	4.0	1.24 (1.09-1.42)	0.001	1.36 (1.18-1.55)	<0.0001
Q2	125,408	415	3.3	1.04 (0.91-1.20)	0.54	1.11 (0.97-1.28)	0.14
Q3	124,192	394	3.2	0.998 (0.87-1.15)	0.97	1.03 (0.89-1.18)	0.53
Q4	125,818	400	3.2	1.00 (ref.)	-	1.00 (ref.)	-
Groups according to guideline-recommended cut-off values							
<70	49,510	212	4.3	1.34 (1.13-1.57)	<0.0001	1.48 (1.25-1.75)	<0.0001
70-100	140,767	504	3.6	1.13 (0.99-1.28)	0.06	1.21 (1.06-1.38)	0.005
100-130	173,255	559	3.2	1.02 (0.90-1.16)	0.77	1.06 (0.93-1.20)	0.39
≥130	137,596	435	3.2	1.00 (ref.)	-	1.00 (ref.)	-
HDL cholesterol, mg/dl							
Groups according to quartile range							
Q1	128,941	497	3.9	1.12 (0.99-1.28)	0.08	1.07 (0.93-1.23)	0.34
Q2	124,383	416	3.3	0.997 (0.87-1.14)	0.97	0.98 (0.85-1.12)	0.73
Q3	125,296	396	3.2	0.95 (0.83-1.09)	0.49	0.95 (0.82-1.10)	0.49
Q4	122,508	401	3.3	1.00 (ref.)	-	1.00 (ref.)	-
Groups according to guideline-recommended cut-off values							
<40	97,621	371	3.8	1.11 (0.98-1.24)	0.09	1.07 (0.95-1.21)	0.25
≥40	403,507	1,339	3.3	1.00 (ref.)	-	1.00 (ref.)	-
Total cholesterol, mg/dl							
Groups according to quartile range							
Q1	127,116	493	3.9	1.28 (1.12-1.47)	0.0003	1.41 (1.22-1.62)	<0.0001
Q2	125,136	446	3.6	1.19 (1.04-1.37)	0.01	1.28 (1.11-1.47)	0.0007
Q3	123,868	399	3.2	1.08 (0.94-1.25)	0.27	1.11 (0.96-1.28)	0.16
Q4	125,008	372	3.0	1.00 (ref.)	-	1.00 (ref.)	-
Groups according to guideline-recommended cut-off values							
<150	77,273	310	4.0	1.27 (1.11-1.45)	0.0006	1.39 (1.20-1.59)	<0.0001
150-<200	214,085	750	3.5	1.13 (1.01-1.25)	0.03	1.18 (1.06-1.31)	0.003
≥200	209,769	650	3.1	1.00 (ref.)	-	1.00 (ref.)	-

*Adjusted for age, sex, BMI, family history of cancer, smoking, drinking, education status, physical activity, consumption of vegetables and fruit, insulin therapy, lipid-lowering medication, diabetes status and systolic blood pressure.

ed that HDL cholesterol is inversely associated with colorectal cancer risk and no relationship was detected for LDL cholesterol [15]. In addition, the association is often confounded and the role of lipid-lowering medication and baseline health status in causation is questionable [17, 18]. In our study, an inverse association for LDL cholesterol with all cancer incidence is observed, even after adjusting for lipid-lowering medication. There was a strong association of incident cancer with colorectal cancer and liver cancer; whereas a borderline significant relationship was detected for pancreatic cancer.

The mechanisms through which low LDL cholesterol levels could lead to an increased risk of cancer are still unclear. Actually, cholesterol is believed to play a role in several biochemical pathways of cancer initiation or progression, such as steroid hormone synthesis and vitamin D [21, 22]. Previous experimental studies showed that cancer cells have higher levels of cholesterol-rich lipid rafts in the plasma membrane, which may be relevant to cancer cell survival [23, 24]. Moreover, evidence is emerging that cholesterol related to the regulation of immune cell function, by improving their antitumor activity and activating immune signalling, which may provide novel insights into the role of cholesterol in the development of cancer [25-27].

Previous population studies have suggested that people with diabetes are at an increased

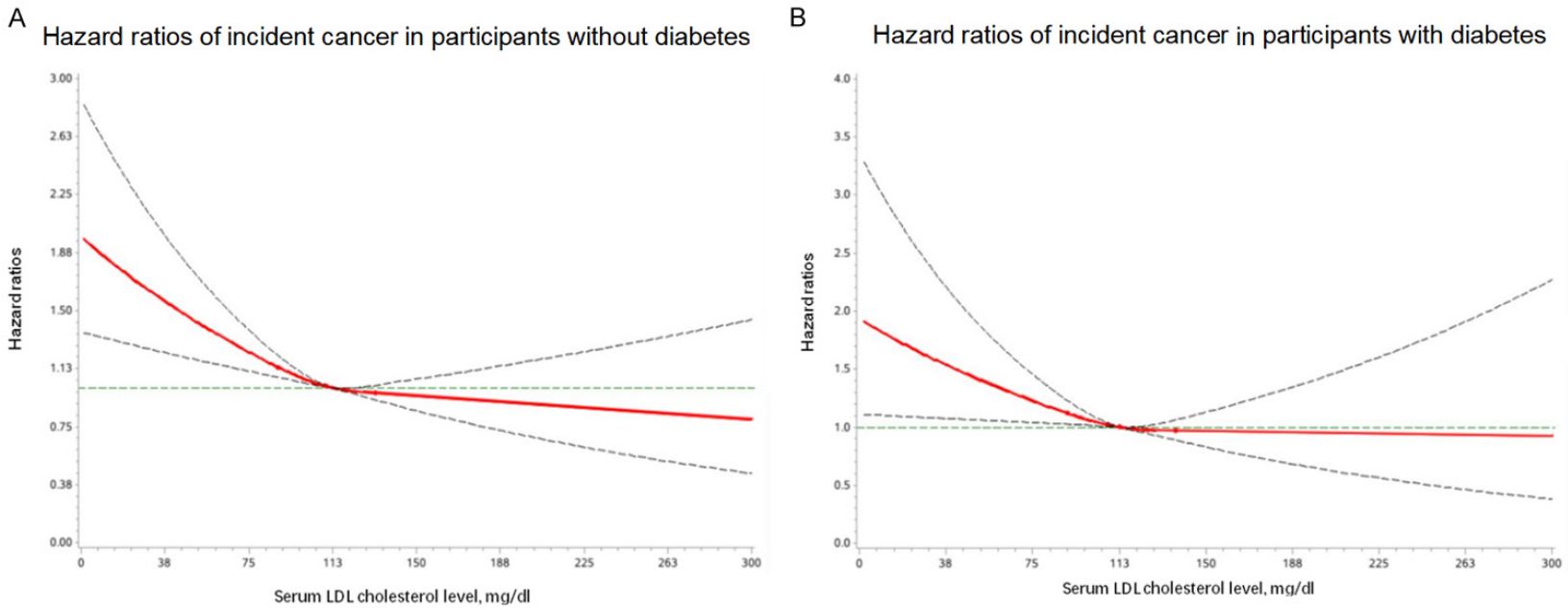

Figure 2. Hazard ratios and 95% CIs for combination of LDL cholesterol and diabetic status in relation to incident cancer. A. Multivariable-adjusted hazard ratios of incident cancer in participants without diabetes. B. Multivariable-adjusted hazard ratios of incident cancer in participants with diabetes. The solid lines are multivariate-adjusted hazard ratios and the dashed lines indicate 95% confidence intervals derived from restricted cubic spline regression. Four knots were located at the 25%, 50%, and 75% percentiles for serum LDL cholesterol. The Cox regression was adjusted for age, sex, BMI, family history of cancer, smoking, drinking, education status, physical activity, consumption of vegetables and fruit, insulin therapy, lipid-lowering medication, and systolic blood pressure at baseline.

Table 3. Incidence rate and adjusted hazard ratios for incident cancer in participants according to glycemic status and LDL cholesterol

	No. of person-years	No. of events	Incidence, per 1000 person-year	Unadjusted		Adjusted*	
				HR (95% CI)	*P* value	HR (95% CI)	*P* value
Groups according to glycemic status							
NGR	109,627	315	2.9	1.00 (ref.)	-	1.00 (ref.)	-
Prediabetes	268,649	845	3.1	1.12 (0.98-1.27)	0.09	0.99 (0.86-1.16)	0.94
Diabetes with HbA1c <7.0%	74,010	322	4.4	1.54 (1.32-1.80)	<0.0001	1.24 (1.04-1.50)	0.02
Diabetes with HbA1c ≥7.0%	48,842	228	4.7	1.65 (1.39-1.95)	<0.0001	1.34 (1.08-1.66)	0.007
Groups according to combination of glycemic status and LDL cholesterol							
Group 1: LDL cholesterol <100 mg/dl							
Group 1 vs. others	190,277	716	3.8	1.17 (1.06-1.29)	0.002	1.20 (1.08-1.34)	0.0007
Group 2: Diabetes							
Group 2 vs. others	105,017	482	4.6	1.48 (1.33-1.65)	<0.0001	1.31 (1.15-1.49)	<0.0001
Group 3: Diabetes with LDL cholesterol <100 mg/dl							
Group 3 vs. others	37,392	200	5.3	1.64 (1.41-1.90)	<0.0001	1.40 (1.18-1.65)	<0.0001
Group 4: Diabetes with HbA1c ≥7.0% and LDL cholesterol <100 mg/dl							
Group 4 vs. others	14,983	85	5.7	1.69 (1.36-2.10)	<0.0001	1.42 (1.10-1.81)	0.006

NGR, normal glucose regulation. *Adjusted for age, sex, BMI, family history of cancer, smoking, drinking, education status, physical activity, consumption of vegetables and fruit, insulin therapy, lipid-lowering medication, and systolic blood pressure.

risk for incident cancer and related mortality. Current evidence from the China Kadoorie Biobank (CKB) has also demonstrated a positive relationship between diabetes and an increased risk of site-specific cancers such as colorectal, liver and pancreatic [28-31]. Actually, our study is the first study that evaluates diabetes in China using the latest diabetes diagnosis criteria in a nationwide, multicenter, population-based, prospective cohort study. All glycemic indicators for the diagnosis of diabetes (FPG, OGTT-2 hour PPG, and HbA1c) were employed, which provided a comprehensive evaluation of diabetes in Chinese population and reflected a precise relationship of diabetes with cancer risk. We found that diabetes was significantly associated with risk of total cancer and several site-specific cancers such as colorectal, liver, and esophageal cancer.

As important manifestations of the metabolic syndrome, hypercholesterolemia and diabetes are often co-occurring. Given the proposed potentiation of the development of atherosclerotic cardiovascular disease, LDL cholesterol has been considered a principal target of lipid-lowering therapy, especially in diabetic participants. The ACC/AHA 2013 guideline lowered the threshold level of LDL cholesterol for initiating statin therapy from 100 mg/dl to 70 mg/dl in population with a very high risk of cardiovascular disease [32-34]. Apparently, the association of LDL cholesterol level with cancer is inconsistent with that for cardiovascular diseases. Our population study showed that the risk of incident cancer was inversely related to LDL cholesterol level, especially in the lower range (<100 mg/dl). These findings suggest an awareness of striking a balance to avoid too low LDL cholesterol levels as for cancer, yet to still provide benefit for cardiovascular diseases.

As a high-risk group for cardiovascular disease, diabetic patients have a more stringent goal for LDL cholesterol in clinical guidelines. According to the ACC/AHA 2018 guideline, adults of 40 to 75 years of age with diabetes mellitus should initiate a moderate-intensity statin regimen, and a high-intensity statin therapy may be recommended if multiple risk factors exist [35]. In our study, the diabetic subjects who had lower levels of LDL cholesterol (<100 mg/dl) had an increased risk of incident cancer and those with poorly glycemic control conferred higher cancer risk. The synergistic effects of these two conditions highlight the need for clinicians to evaluate lipid-lowering targets and achieve glycemic control goals in the clinical routine among diabetic patients.

Strengths and limitations

The major strength of this analysis lies in the large number of participants with comprehensive measurements of cholesterol and glycemic

Table 4. Incidence rate and adjusted hazard ratios for site-specific cancer according to glycemic status and LDL cholesterol

	No. of events	LDL cholesterol <100 mg/dl vs. others		Diabetes vs. others		Diabetes with LDL cholesterol <100 mg/dl vs. others		Diabetes with HbA1c ≥7.0% and LDL cholesterol <100 mg/dl vs. others	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Digestive organs									
Total	614	1.70 (1.41-2.05)	<0.0001	1.62 (1.31-2.01)	<0.0001	2.03 (1.57-2.62)	<0.0001	2.03 (1.39-2.96)	0.0002
Colorectal Cancer	187	1.47 (1.06-2.04)	0.02	1.68 (1.16-2.43)	0.006	2.42 (1.58-3.73)	<0.0001	1.82 (0.89-3.70)	0.10
Liver Cancer	156	2.13 (1.50-3.03)	<0.0001	2.15 (1.47-3.16)	<0.0001	2.97 (1.97-4.50)	<0.0001	3.59 (2.07-6.21)	<0.0001
Stomach Cancer	156	1.02 (0.71-1.46)	0.92	0.95 (0.60-1.50)	0.82	0.54 (0.26-1.14)	0.11	0.73 (0.26-2.05)	0.54
Pancreatic Cancer	68	1.58 (0.89-2.80)	0.12	1.06 (0.52-2.16)	0.88	1.69 (0.75-3.78)	0.20	2.97 (1.08-8.17)	0.03
Esophageal cancer	47	1.69 (0.91-3.15)	0.10	2.10 (1.09-4.07)	0.03	1.96 (0.87-4.41)	0.10	0.52 (0.07-3.98)	0.52
Other sites other than digestive organs									
Total	1096	1.03 (0.90-1.18)	0.65	1.19 (1.01-1.40)	0.03	1.13 (0.91-1.41)	0.27	1.16 (0.84-1.61)	0.37
Lung Cancer	357	1.03 (0.81-1.30)	0.84	1.12 (0.84-1.49)	0.44	1.18 (0.81-1.72)	0.38	1.36 (0.78-2.34)	0.28
Female breast Cancer	188	0.79 (0.56-1.11)	0.17	1.26 (0.82-1.96)	0.29	1.17 (0.64-2.14)	0.62	1.57 (0.69-3.56)	0.28
Thyroid Cancer	108	0.83 (0.54-1.28)	0.40	0.99 (0.55-1.78)	0.98	0.78 (0.31-1.99)	0.61	0.81 (0.19-3.49)	0.78
Endometrial Cancer	77	0.88 (0.53-1.45)	0.61	1.26 (0.67-2.37)	0.48	0.89 (0.34-2.35)	0.81	0.74 (0.17-3.30)	0.69
Haematological Malignancies	59	1.15 (0.64-2.06)	0.64	1.38 (0.69-2.74)	0.36	1.69 (0.75-3.82)	0.21	0.38 (0.05-2.94)	0.38
Cervical Cancer	52	0.98 (0.54-1.76)	0.93	0.47 (0.14-1.51)	0.20	1.05 (0.30-3.65)	0.94	1.92 (0.40-9.17)	0.41

HRs were adjusted for age, sex, BMI, family history of cancer, smoking, drinking, education status, physical activity, consumption of vegetables and fruit, insulin therapy, lipid-lowering medication, and systolic blood pressure.

biomarkers, all measured at the same clinical laboratory. To our best knowledge, this is the first large-sample prospective study on cancer risk with detailed information on cholesterol and glucose biomarkers in a Chinese population.

Our study has several limitations. First, the study participants were only followed-up for an average of 3.8 years. This relatively short follow-up duration limited the number of clinical events and influenced the study's statistical power for several site-specific cancers. However, we have observed 1,710 incident cancer cases. Second, 12.18% of study participants were lost to follow-up in this study. Rural-urban migration and urban redevelopment in China contributed to this loss-to-follow-up. Finally, the potential existence of precancerous conditions or prediagnostic cancer may influence the cholesterol levels and lead to bias in the study. Nevertheless, this study was conducted in the general population after excluding participants with cancer diagnosed within the first 6 months after the baseline investigation.

Conclusions

In summary, our study showed a positive association of cancer risk with low-level LDL cholesterol and diabetes, which lends support to the postulation that a lower level of LDL cholesterol may confer a higher cancer risk. These findings indicate the compelling need of achieving glycemic control goal among diabetic patients and maintaining appropriate LDL cholesterol levels to provide benefit for cancer, as well as cardiovascular diseases in clinical practice.

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Disclosure of conflict of interest

None.

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