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ABO Blood Group and Diabetes Mellitus Influence the Risk for Pancreatic Cancer in a Population from China

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The mechanism by which diabetes mellitus (DM) impacts the association between ABO blood types and pancreatic cancer is unclear.

Material/Methods: A retrospective case-control study of 264 patients with pancreatic cancer and 423 age- and sex-matched individuals with nonmalignant diseases was performed to assess whether ABO blood group and DM jointly contribute to pancreatic cancer risk.

Results: A multivariate analysis with adjustments for risk factors revealed that blood type, chronic pancreatitis, and DM were significantly associated with increased pancreatic cancer risk. The estimated adjusted odds ratios (AORs with 95% confidence intervals [CIs]) were 2.130 (1.409–3.220) for blood type A, 2.383 (1.313–4.325) for blood type AB, 1.518 (1.012–2.276) for DM, and 10.930 (1.202–99.405) for chronic pancreatitis. Blood type A significantly modified the risk for pancreatic cancer in individuals with DM (AOR, 3.506; 95% CI, 1.659–7.409).

Conclusions: The risk for pancreatic cancer was associated with ABO blood type, DM, and chronic pancreatitis in a Chinese population. The risk was greatest for individuals with blood type A and DM.

MeSH Keywords: ABO Blood-Group System • Diabetes Mellitus • Pancreatic Neoplasms

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Background

Pancreatic cancer is ranked fifth among the most frequently diagnosed cancers and is the fourth most common cause of cancer-associated death worldwide [1]. Currently, surgical resection is the only treatment option for pancreatic cancer patients. Moreover, > 80% of patients present at an advanced incurable stage, with 5-year survival rates of approximately 5% [2]. To reduce the incidence and consequences of pancreatic cancer, risk factors that can be manipulated to prevent the disease need to be identified [3,4]. The known factors associated with pancreatic cancer include genetics [5], polymorphisms in the gene for somatostatin receptor 5 [6], alcohol intake [7], cigarette smoking [8], metabolic syndrome [9–12], chronic pancreatitis (CP) [13], chronic hepatitis B virus (HBV) infection [14,15], and having first-degree relatives with pancreatic cancer [16]. The relationship between diabetes mellitus (DM) and pancreatic cancer risk has been a topic of study since 1833 [17]. Epidemiologic evidence suggests that people with diabetes are at a significantly greater risk for developing pancreatic cancer [18].

ABO blood group antigens are present throughout the body on the surfaces of red blood cells. An association between blood type A and cancer was proposed on the basis of the observation that gastric cancer patients were more likely than control patients to have this blood type [19]. Recent studies have shown that blood group antigens influence pancreatic cancer risk [20–24]. However, there are few published studies examining the contribution of DM to this risk. The objective of this population-based case-control study was to precisely analyze the associations between blood antigen types and the development of pancreatic cancer in a Chinese population, with an emphasis on the contribution of DM.

Material and Methods

Patients and data collection

The medical records of 350 patients diagnosed with pancreatic cancer between January 2015 and July 2017 at The First Hospital of Jilin University (Changchun, China) were reviewed. In total, data from the complete medical records for 264 of these patients were included in the analysis. The control group comprised 423 age- and sex-matched inpatients with nonmalignant diseases. Data on potential pancreatic cancer risk factors (i.e., sex, age, history of smoking, family history of pancreatic cancer, presence of DM, presence of chronic HBV infection, presence of CP, history of alcohol drinking, and ABO blood group) were taken from the medical records.

The study protocol and recruitment of human study participants were approved by The Independent Institutional Review Board of The First Hospital of Jilin University (No. 2014-325). Written informed consent was obtained from each participant prior to enrollment.

Diagnosis of pancreatic cancer

The diagnosis of pancreatic cancer was confirmed on the basis of the results of histological examinations, endoscopic retrograde cholangiopancreatography, or the combination of clinical findings and the results from at least 2 imaging modalities [25].

Diagnosis of DM

A diagnosis of DM was determined on the basis of medical histories, antidiabetic therapy, or at least 1 of the following criteria: 1) fasting glucose concentrations ≥7.0 mmol/L; 2) random glucose concentrations ≥11.1 mmol/L; or 3) 2-hour postload plasma glucose ≥11.1 mmol/L [26].

Diagnosis of chronic HBV infection

Patients with persistent or intermittent elevations in alanine transaminase concentrations (≥2 times the upper normal threshold value) and elevated HBV DNA levels for ≥6 months were diagnosed with chronic HBV infections.

Statistical analysis

SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) was used to perform chi-squared tests comparing categorical variables and independent sample *t*-tests for comparing continuous variables from normally distributed data. All tests were 2-tailed. A multivariate logistic regression analysis was conducted to adjust for possible confounding effects among the variables. The adjusted odds ratios (AORs) and 95% confidence intervals (CIs) were calculated for these comparisons. A *P* value of <0.05 indicated statistical significance.

Results

Patient characteristics and blood group distribution

The baseline clinical and demographic characteristics of the patients are presented in Table 1. A total of 687 consecutive eligible patients were enrolled as cases or controls and were matched according to sex and age. The case group comprised 264 patients diagnosed with pancreatic cancer (151 male and 113 female patients). The median age was 64.0 years (55.3–72.0 years). The control group consisted of 423 hospital patients without malignant disease. This group was representative of patients in northeast China. The median age was 63.0 years (53.0–71.0 years), and 52% of the control group were male patients.

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Table 1. Baseline demographic and clinical characteristics of cases and controls.

Characteristic	Cases *N*=264		Controls *N*=423		*P* value
Sex					0.205
Female	113	(42.8)	202	(47.8)	
Male	151	(57.2)	221	(52.2)	
Age (years)	64.0	(55.3, 72.0)	63.0	(53.0, 71.0)	0.068
<60	92	(34.8)	170	(40.2)	0.352
60–69.9	92	(34.8)	131	(31.0)	
≥70	80	(30.3)	122	(28.8)	
History of smoking					0.970
No	215	(81.4)	344	(81.3)	
Yes	49	(18.6)	79	(18.7)	
Family history of pancreatic cancer					0.736
No	263	(99.6)	422	(99.8)	
Yes	1	(0.4)	1	(0.2)	
Diabetes mellitus					0.014
No	203	(76.9)	357	(84.4)	
Yes	61	(23.1)	66	(15.6)	
Chronic pancreatitis					0.002
No	256	(97.0)	422	(99.8)	
Yes	8	(3.0)	1	(0.2)	
Chronic hepatitis B infection					0.319
No	253	(95.8)	398	(94.1)	
Yes	11	(4.2)	25	(5.9)	
Alcohol drinking					0.426
No	230	(87.1)	377	(89.1)	
Yes	34	(12.9)	46	(10.9)	
ABO blood type					0.001
O	62	(23.5)	145	(34.3)	
A	95	(36.0)	106	(25.1)	
AB	31	(11.7)	31	(7.3)	
B	76	(28.8)	141	(33.3)	

Continuous variables are expressed as median (25^{th}, 75^{th} percentiles). Categorical variables are displayed as numbers and percentages.

There were statistically significant between-group differences in demographic characteristics, including the prevalence of DM, presence of CP, and distributions of the ABO blood types. A significantly larger proportion of pancreatic cancer patients were diagnosed with DM than control patients (23.1% versus 15.6%; *P*=0.014). CP was more prevalent in the pancreatic cancer patients than in the control patients (3.0% versus 0.2%; *P*=0.002). The distributions of the ABO blood groups differed significantly between the 2 groups (*P*=0.001). Ninety-five patients (36.0%) with pancreatic cancer were blood type A, whereas 106 patients (25.1%) of the control group were type A. The percentages of B and AB blood types in the patients with pancreatic cancer were 28.8% and 11.7%, respectively. In the control group, the percentages were 33.3% and 7.3%, respectively. All study patients were RhD positive.

There were no statistically significant between-group differences with regard to smoking or alcohol consumption, family history of pancreatic cancer, or the prevalence of chronic HBV infections.

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Table 2. Univariate and multivariate analyses of the demographic and clinical characteristics of patients with pancreatic cancer and the patients in the control group.

Variable	Univariate analysis			Multivariate analysis*		
	OR (95% CI)		*P* value	AOR (95% CI)		*P* value
History of smoking			0.970			
No	1					
Yes	0.992	(0.669–1.473)				
Family history of pancreatic cancer			0.736			
No	1					
Yes	1.605	(0.100–25.763)				
Diabetes mellitus			0.014			0.043
No	1			1		
Yes	1.625	(1.102–2.397)		1.518	(1.012–2.276)	
Chronic pancreatitis			0.002			0.034
No	1			1		
Yes	13.187	(1.640–106.051)		10.930	(1.202–99.405)	
Chronic hepatitis B infection			0.319			
No	1					
Yes	0.692	(0.335–1.431)				
Alcohol drinking			0.426			
Never	1					
Yes	1.101	(0.869–1.394)				
ABO blood type			0.001			0.001
O	1			1		
A	2.096	(1.396–3.147)	<0.001	2.130	(1.409–3.220)	<0.001
AB	2.339	(1.310–4.177)	0.004	2.383	(1.313–4.325)	0.004
B	1.261	(0.838–1.895)	0.266	1.301	(0.860–1.969)	0.213

OR – odds ratio; AOR – adjusted odds ration; CI – confidence interval. * Adjusted for sex, age, family history of pancreatic cancer, history of smoking, DM, chronic pancreatitis, chronic hepatitis B infection, alcohol drinking, and ABO blood type.

ABO blood group, DM, and pancreatic cancer risk

Univariate analysis revealed that DM and CP were significantly more prevalent in pancreatic cancer patients than in the control group. The ABO blood type distributions differed significantly between the 2 groups (Table 2).

A multivariate analysis was performed to assess pancreatic risk factors (i.e., sex, age, smoking, alcohol consumption, family history of pancreatic cancer, DM, chronic HBV infection, CP, and ABO blood type). The independent factors most strongly associated with pancreatic cancer after adjusting for potential confounding variables were DM, CP, and ABO blood type. DM was associated with a nearly 2-fold greater risk of pancreatic cancer (AOR [95% CI], 1.518 [1.012–2.276]), whereas a 10-fold greater risk was found for those with CP (10.930 [1.202–99.405]).

Compared to those with blood type O, patients with the A blood type were at a 2-fold greater risk for pancreatic cancer (2.130 [1.409–3.220], $P<0.001$). Multivariate analysis also revealed a significant association between pancreatic cancer and AB blood type (2.383 [1.313–4.325], $P=0.004$). We found that blood type B was not significantly associated with a risk for pancreatic cancer (1.301 [0.860–1.969], $P=0.213$).

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Table 3. Associations between diabetes mellitus and A blood group with the odds of having pancreatic cancer.

Blood type/DM	Cases (*N*=264)	Controls (*N*=423)	Univariate analysis		Multivariate analysis*	
	N (%)	N (%)	OR (95% CI)	*P*	AOR (95% CI)	*P*
Non-A/No	130 (49.2)	263 (62.2)	1	0.001	1	0.003
Non-A/Yes	39 (14.8)	54 (12.8)	1.461 (0.920–2.320)	0.108	1.328 (0.825–2.138)	0.243
A/No	73 (27.7)	94 (22.2)	1.571 (1.084–2.277)	0.017	1.535 (1.054–2.235)	0.025
A/Yes	22 (8.3)	12 (2.8)	3.709 (1.780–7.728)	<0.001	3.506 (1.659–7.409)	0.001

OR – odds ratio; AOR – adjusted odds ration; CI – confidence interval. * Adjusted for sex, age, family history of pancreatic cancer, history of smoking, chronic pancreatitis, chronic hepatitis B infection, and alcohol drinking.

Blood type A, DM, and pancreatic cancer risk

Because the results indicated that DM and the A blood type were major risk factors associated with pancreatic cancer, we further analyzed the associations among these factors (Table 3). We adjusted for age, sex, history of smoking, family history of pancreatic cancer, chronic HBV infection, CP, and alcohol consumption. Compared with patients without DM and a blood type other than A, those with blood type A but without DM had greater odds of having pancreatic cancer (AOR [95% CI], 1.535 [1.054–2.235]). The risk was greatest for individuals with blood group A and DM (3.506 [1.659–7.409], *P*=0.001). The risk for pancreatic cancer was not significant for patients with DM and a blood type other A (1.328 [0.825–2.138], *P*=0.243).

Discussion

Our hospital-based case-control study revealed statistically significant associations between ABO blood type and pancreatic cancer risk in a Chinese population. Specifically, there was a significantly higher risk for developing pancreatic cancer in Chinese patients with the A or AB blood types than for those with type O. These results are similar to those from studies of gastric cancer, hepatocellular carcinoma, and epithelial ovarian cancer [27–29].

The results of the Risch et al. study performed in China suggested that the A blood type is the primary independent risk factor for pancreatic cancer development [24]. In a study of 339 432 patients, Sun and colleagues [30] found an increased pancreatic cancer risk for patients with non-O blood types. A similar case-control study of 753 Korean patients diagnosed with pancreatic cancer and 3012 healthy controls revealed that those with non-O blood types were at a greater risk for developing pancreatic cancer than those with the O blood type [31]. However, there are some studies indicating that blood type is not associated with an increased risk of pancreatic cancer [3,32].

However, the underlying biological mechanism of the associations between ABO blood types and cancers has not been explained in detail [33]. The mechanism might involve a modulation of host inflammatory processes associated with ABO blood type, which might promote cancer progression and metastasis [3,34,35]. Single nucleotide polymorphisms of the genes encoding ABO antigens are linked to the plasma levels of E-selectin [36,37], P-selectin [38], soluble intercellular adhesion molecule 1 (sICAM-1) [39,38], and tumor necrosis factor alpha. These proteins are adhesion molecules required for the recruitment of immune cells and thus mediate the systemic inflammatory response. These findings suggest a direct role of ABO blood type-related genes in tumor initiation and malignancy, supporting the proposed association of ABO blood type and cancer cell survival.

Alternatively, the association might involve ABO glycosyltransferase enzymes, which participate in malignant cell immunosurveillance as well as cellular membrane signaling modifications and intercellular adhesion during tumorigenesis [40–43]. A dysregulation of these enzymes might enable the progression and spread of carcinoma [44,45] in a manner similar to the mechanism by which ABO glycosyltransferases are associated with risk of venous thromboembolism, i.e., via the regulation of the plasma levels of circulating von Willebrand factor [46,47]. The von Willebrand factor modulates the tumorigenesis-related processes of apoptosis and angiogenesis, adding further interest to this mechanism [48].

Our results and the results of other studies suggest an association of non-O blood types, especially type A, with more aggressive tumor development and progression. Patients with blood type A have significantly lower serum levels of sICAM-1 than blood type O patients. sICAM binds to the ICAM ligands on circulating cells to prevent the attachment of lymphocytes to endothelial cells [49,38], and numerous diseases are associated with lower serum levels of sICAM, including cancers [50,51]. For example, the A and B antigens increase the basal apoptosis resistance of colon adenocarcinoma cells in rats, suggesting these antigens might enable cancer cells to escape from immune surveillance [52].

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We also found that among patients with DM, the A blood type significantly modified the risk for developing pancreatic cancer. The reason might be that both are risk factors for the development of pancreatic cancer. However, the potential relationship between blood type and DM should be considered. Individuals with blood types other than type O are at greater risk for type 2 DM [53]. The mechanism might be associated with the aforementioned markers, such as von Willebrand factor and ICAM-1, which have close relationships with ABO blood type and are associated with an increased risk for type 2 DM [54,55]. The ABO blood group is among the genetic factors influencing the composition of the intestinal microbiota [56], thereby affecting energy balance, glucose metabolism, and low-grade inflammation [57]. Further research is necessary to characterize the potential mechanisms by which the A blood type and DM jointly promote the development of pancreatic cancer.

There is increasing interest in determining the relationship between CP and pancreatic cancer, because inflammation is implicated in cancer development [13]. In this study, we confirmed that CP and pancreatic cancer are significantly associated, regardless of other factors such as smoking or alcohol consumption. This finding is consistent with the findings from previous studies [13,58,59]. A meta-analysis of 22 studies found an increased relative risk (13.3) for developing pancreatic cancer in patients with CP [60]. The Fourth International Symposium of Inherited Diseases of the Pancreas classifies CP as a moderate (5-fold to 10-fold) risk factor for the development of pancreatic cancer [59]. The mechanisms remain unclear even though a number of cellular and genetic mechanisms (prolonged inflammation, genetic susceptibility, alcohol abuse, and smoking) have been identified [61–64]. The results of our study indicated that the association between smoking and pancreatic cancer was not statistically significant. One possible explanation is that the patients in the control group in our study were not healthy, and so smoking might have been a risk factor for disease in this group.

This study had some limitations. First, the number of cases included in our study population was small. These numbers were affected by our desire to include complete information, such as ABO blood type, which prevented analyses of the type and duration of CP. Second, all cases in our study were RhD positive, and so we could not analyze the effects of Rh blood group on pancreatic cancer risk. Third, the hospital is a homogenous cohort of individuals belonging to the same ethnicity (Han Chinese). There are 91% Han Chinese in northeast China which is similar with the entire country population. Such a homogenous population could minimize potential confounding findings but may limit the generalizability of our study findings to other populations with more diverse prevalence of exposures. Moreover, this is a retrospective case-control study, the direct causal relationship between joint ABO blood type and DM and the risk of pancreatic cancer will need to be confirmed by a large population-based prospective cohort study. Our study is also limited by not having information on care managers, which could be an effect modifier in the management of DM and might further affect the relationship between DM and risk of pancreatic cancers [65].

Conclusions

We found that in a Chinese population, an individual's ABO blood type and the presence of DM and CP influence their risk for developing pancreatic cancer. We found that patients with the A blood type who also had DM had greater odds of having pancreatic cancer. Further research is needed to confirm our results and to identify the mechanisms by which the A blood type and DM jointly contribute to the risk of the development of pancreatic cancer.

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